TECHNICAL SUPPORT DOCUMENT FOR CANCER POTENCY FACTORS

APPENDIX B.

Chemical-specific summaries of the information used to derive unit risk and cancer potency values.

ACETALDEHYDE

CAS No: 75-07-0

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	44.05
Boiling point	20.5° C
Vapor pressure	740 mm
Conversion factor	1 ppm = 1.8 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor	2.7 E-6 $(\mu g/m^3)^{-1}$
Slope Factor	1.0 E-2 $(mg/kg\text{-}day)^{-1}$

[Calculated from rat nasal tumor incidence data (Wouterson *et al.*, 1986) by OEHHA (1993) using a linearized, time-dependent multistage procedure.]

III. CARCINOGENIC EFFECTS

Human Studies

Bittersohl (1974) conducted a morbidity survey to study the incidence of total cancer in an aldol and aliphatic aldehyde factory in the German Democratic Republic (GDR). The work force in this factory was potentially exposed to a product primarily consisting of acetaldol (70)% combined with smaller, but variable, amounts of acetaldehyde; butylaldehyde; crotonaldehyde; "large" condensed aldehydes such as hexatrial, hexatetral, and ethylhexal; traces of acrolein; and 20 to 22% water. The observation period extended from 1967 to 1972. The study cohort consisted of 220 people, approximately 150 were employed for more than 20 years. Acetaldehyde concentrations were found to range from 0.56 to 1 ppm.

Nine cases of cancer (five squamous cell carcinomas of the bronchi, two squamous cell carcinomas of the mouth cavity, one adenocarcinoma of the stomach, and one adenocarcinoma of the cecum) were identified in male workers during the 6-year study period. An incidence rate of 6,000 per 100,000 population (9 cases/150 individuals employed for more than 20 years) for total cancer was calculated for this study cohort, compared to 1,200 per 100,000 in the general population. All cases had a history of smoking.

This study had the following major methodological limitations: the incidence rate was not age adjusted; concurrent exposure to other chemicals and cigarette smoke occurred; duration of exposure was short; a small number of subjects was studied; and information on subject selection, age, and sex distribution was lacking. Because of the limitations, the International Agency for Research on Cancer (IARC, 1985) considered this study to be inadequate to evaluate the carcinogenicity of acetaldehyde.

Animal Studies

Rats

Woutersen *et al.* (1984, 1986) exposed groups of 105 male and female SPF-Wistar rats to atmospheres containing acetaldehyde concentrations of 0, 750, 1500, or 3000/1000 ppm (0, 1350, 2700 or 5400/1800 mg/m^3, respectively), 6 hours/day, 5 days/week for up to 28 months. The highest concentration was gradually decreased from 3000 ppm (days 0 to 141) to 1000 ppm (from day 313 forward) because of severe growth retardation, loss of body weight, and early mortality.

Treatment-related nonneoplastic histopathological lesions were observed in the nose, larynx, and lungs, with the most severe lesions seen in the nose and in the vocal cord region of the larynx. Nasal tumors observed were mainly squamous cell carcinomas and adenocarcinomas originating from the respiratory and olfactory epithelium, respectively. Tumor incidences are listed in Table 1. The incidences of adenocarcinomas were significantly ($p < 0.01$) higher in both sexes of rats at all exposure concentrations when compared to controls. Squamous cell carcinomas were significantly ($p < 0.01$) increased in males in the mid- and high-dose groups and in females in the high-dose group. No laryngeal or lung tumors were seen in male rats and tumors observed in the other organs of treated rats were comparable to those in the controls. The presence of nasal tumors at all exposure levels suggested that the latency period for nasal tumor induction was independent of the acetaldehyde concentration. The authors concluded that under the conditions of this study, acetaldehyde was carcinogenic to the nasal mucosa of rats.

Table 1: Nasal tumor incidence in male and female Wistar rats exposed to acetaldehyde by inhalation (Woutersen *et al.*, 1986)

Sex	Exposure Concentration (ppm)	Nasal Tumor Incidence
males	0	1/49
	750	17/52
	1500	41/53
females	0	0/50
	750	6/48
	1500	36/53

In an extension of the above study, Woutersen and Feron (1987) examined the process of regeneration of damaged nasal mucosa in rats exposed to acetaldehyde at concentrations as described above for 52 weeks. Animals were sacrificed after a recovery period of 26 weeks. The number of nasal tumors observed was almost the same as in the lifetime study, which indicated that proliferative epithelial lesions of the nose may develop into tumors even without continued acetaldehyde exposure.

Hamsters

Feron *et al.* (1982) exposed groups of male and female Syrian golden hamsters to room air (0 ppm) or to decreasing concentrations of acetaldehyde. The initial concentration was 2500 ppm (4500 mg/m^3), which was gradually decreased (between weeks 9 and 44) to 1650 ppm (2970 mg/m^3) 6 hours/day, 5 days/week for 52 weeks. Acetaldehyde-induced nonneoplastic lesions were seen in the nose, larynx, and trachea. Tumors were seen in both the nose (adenoma, adenocarcinoma, and anaplastic carcinoma) and the larynx (carcinoma *in situ*, squamous cell carcinoma, and adenosquamous carcinoma). The tumor incidences were 2/27 (7%) and 6/23 (26%) in males and 1/26 (4%) and 4/26 (20%) in females for the nose and larynx, respectively; no nasal or laryngeal tumors were observed in the controls. Only the increases in laryngeal tumors were statistically significant ($p < 0.05$) compared to controls. Under the conditions of this study, acetaldehyde was considered to be carcinogenic in male and female hamsters.

In a second part of the above study (Feron, 1979), groups of male Syrian golden hamsters were exposed by inhalation to 0 or 1500 ppm (2700 mg/m^3) acetaldehyde vapor 7 hours/day, 5 days/week for 52 weeks. The animals also received a concurrent, weekly intratracheal instillation of 0, 0.625, 0.125, 0.225, 0.5, or 1 mg benzo[a]pyrene (BaP) in saline for the same duration. Simultaneous exposure to acetaldehyde and BaP induced marked nonneoplastic lesions in the nasal cavity and trachea which disappeared after the 26-week recovery period. No respiratory tract tumors were seen in hamsters exposed to acetaldehyde alone. Various types of benign and malignant respiratory tract tumors were found in male hamsters treated with BaP or BaP plus acetaldehyde. The results of this study indicated no evidence for carcinogenicity of acetaldehyde and limited evidence of co-carcinogenicity. This study had a number of methodological limitations such as the exposure level exceeding the maximum tolerated dose (MTD).

Feron *et al.* (1982) repeated the above study using male and female Syrian golden hamsters. Some of the animals were also treated with subcutaneous injections of 0.0625% diethylnitrosamine (DENA) once every 3 weeks. The enhancing effect of BaP-initiated respiratory tract tumor formation observed in this study was similar to that observed in the previous study (Feron, 1979). There was no evidence that acetaldehyde exposure increased the incidence or affected the type of DENA-induced tumors in any part of the respiratory tract. Based upon these findings, the authors concluded: "acetaldehyde is an irritant as well as a carcinogen to the nose and larynx with a weak initiating and a strong 'promoting' (co-carcinogenic) activity."

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The IARC concluded that there is inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of acetaldehyde (IARC, 1985). Therefore IARC classified acetaldehyde as class 2B, a possible human carcinogen. The U.S. EPA, using the guidelines for Carcinogen Risk Assessment, has classified acetaldehyde as a Group B2 probable human carcinogen, based on sufficient evidence of carcinogenicity in animals and inadequate evidence in humans (IRIS, 1997). OEHHA staff concurred that acetaldehyde is a potential human carcinogen.

OEHHA staff have used the rat nasal tumor data from the Woutersen *et al.* (1986) inhalation study and hamster laryngeal tumor data from the Feron *et al.* (1982) inhalation study to assess the cancer potency with the multistage model. Acetaldehyde tumors occurred in the nasal area for rats and in the larynx for hamsters. While it is assumed that the respiratory tract is the only organ affected by acetaldehyde, tumors in the nose in rats and in the upper larynx of hamsters do not directly mean that only tumors in the nose or larynx would occur in humans. Unlike the rodents, humans are not obligate nose breathers. Thus, the entire human respiratory tract, including the lung, may be at risk for cancer induction by acetaldehyde.

Methodology

Data from the Woutersen *et al.* (1986) inhalation study were used to calculate cancer risk from the male and female rat nasal carcinoma incidence. Three types of nasal tumors were observed: squamous cell carcinomas, adenocarcinomas, and carcinomas *in situ*. OEHHA staff used only 49-53 (out of 55) animals of each group that were examined for nasal changes in the quantitative risk assessment. Doses were converted to an equivalent continuous dose (US EPA, 1987; IRIS, 1997), because the animals were exposed for only 6 hours/day, 5 days/week. Because of the excessive morbidity with the animals exposed at the highest concentration (3000 ppm) and the eventual lowering of the concentration to 1000 ppm, data from this group were not used in deriving the cancer potency.

Using the computer program GLOBAL86 (Howe *et al.*, 1986), a linearized, time-independent multistage procedure was fit to the nasal carcinoma dose-response data. The male rat nasal tumor data yielded a maximum likelihood estimate (MLE) for q_1 of 1.6×10^{-8} ppb^{-1}, and an Upper 95% Confidence Limit (UCL) on q_1 (q_1*) of 3.2×10^{-6} ppb^{-1}. The female rat data yielded a somewhat lower risk with a q_1* equal to 9.3×10^{-7} ppb^{-1}. For acetaldehyde, 1 ppb = 1.8 $\mu g/m^3$. Using the latter units, the MLE for q_1 equals 8.8×10^{-9} $(\mu g/m^3)^{-1}$ and the 95% UCL for q_1 (q_1*) equals 1.8×10^{-6} $(\mu g/m^3)^{-1}$ for the male rat data.

The following scaling factors are used for scaling from animals to humans: 1.5 for the 400 g male rat and 1.6 for the 250 g female rat, assuming 70 kg body weight for both human sexes. Using these scaling factors, risk values of 1.6×10^{-6} ppb^{-1} from female rat data and 4.8×10^{-6} ppb^{-1} from male rat data were obtained.

For rat nasal carcinomas, contact scaling factors were obtained: 5.6 for a 400 g male rat and 6.5 for a 250 g female rat, again assuming both human sexes have 70 kg body mass. The resultant risks of 6.3×10^{-6} ppb^{-1} for female rats and 2.7×10^{-5} ppb^{-1} for male rats would be used only to predict nasal or respiratory system cancers.

In the case of acetaldehyde, a best value of 2.7×10^{-6} $(\mu g/m^3)^{-1}$ (4.8×10^{-6} ppb^{-1}) was chosen from the range. The value was obtained from the male rat (more sensitive to tumor induction than the female rat) data using an interspecies surface area correction factor of body weight to the 2/3 power.

V. REFERENCES

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ACETAMIDE

CAS No: 60-35-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	59.07
Boiling point	222 °C
Melting point	81 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 2.416 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.0 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 7.0 E-2 $(mg/kg\text{-}day)^{-1}$
[Male Fischer 344 rat liver tumor data (Fleischman *et* al., 1980), contained in Gold *et al.* database (1990), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of acetamide on humans are known to exist.

Animal Studies

Dessau and Jackson (1955) exposed 5 Rockland albino rats to acetamide by gavage (4 g/kg body weight/day in distilled water) for 205 days. One animal developed an hepatocellular adenoma.

Male Wistar rats (25/group) were fed diet containing 0, 1.25, 2.5 or 5% acetamide for 1 year (Jackson and Dessau, 1961). One rat/group was sacrificed at monthly intervals; the remaining animals were sacrificed at 1 year. Liver tumors (described as trabecular carcinomas or adenocarcinomas) were seen in 0/25, 4/24, 6/22 and 1/18 animals from the control, low, medium and high dose groups. In the same study, a group of 50 male Wistar rats were fed a diet containing 5% acetamide for 1 year. One animal was killed weekly for 26 weeks, after which 1 animal was killed every other week. Liver tumors (trabecular carcinomas or adenocarcinomas) were observed in 4/48 animals treated for 38-42 weeks, compared to 0/43 in controls.

Male Wistar rats were fed control diet (15 animals), or diets containing 2.5% acetamide (40 animals), 2.5% acetamide + 5.6% L-arginine L-glutamate (40 animals), or 5.6% L-arginine L-glutamate (15 animals) for 1 year. Hepatomas were observed in 2/8 animals fed acetamide alone and killed after 1 year; 7/16 animals fed acetamide alone for 1 year followed by control diet for 3 months also developed liver tumors. In contrast, 1/11 animals fed diet containing acetamide + L-arginine L-glutamate for 1 year developed hepatomas, and 1/19 animals fed diet containing

acetamide + L-arginine L-glutamate for 1 year followed by control diet for 3 months developed hyperplastic liver nodules, but not tumors. No liver tumors were noted in either the control or 5.6% L-arginine L-glutamate treatment groups (Weisburger *et al*., 1969).

Fleischman *et al*.(1980) fed male and female C57BL/6 mice (50/sex/group) and Fischer 344 rats (50/sex/group) a diet containing 1.18% (mice) or 2.36% (mice, rats) acetamide for 365 consecutive days; animals were then fed a control diet for an additional 4 months. Male mice demonstrated a treatment-related increase in hematopoietic tumors, primarily malignant lymphomas; tumor incidence was 7/50 and 7/46 for the low and high dose groups, respectively, compared to 0/95 for the pooled (male and female) control group. Neoplastic nodules and hepatocellular carcinomas were observed in both male and female rats. However, the incidence, speed of onset and frequency of metastases were greater in males (Fleischman *et al*., 1980). No liver tumors were noted in control animals. Incidence data for hepatocellular carcinomas in F344 rats, the most sensitive species tested, are given in Table 1.

Table 1: Incidence of hepatocellular carcinomas in F344 rats treated with acetamide by dietary administration (Fleischman *et al*., 1980).

Dietary Concentration (%)	Average Dose[1] (mg/kg-day)	Tumor Incidence[2]	
		Male	Female
0	0	0/50	0/49
2.36	710	41/47	33/48

1. Doses as reported by Gold *et al*. (1984).

2. Decreased survival of treatment group according to Gold *et al*. (1990) (56% survival at study termination compared to 86% for controls); potency may be an underestimate (Cal/EPA, 1992).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The carcinogenicity bioassay by Fleischman *et al*. (1980) indicated that acetamide causes hematopoietic tumors in male C57BL/6 mice, and hepatocellular carcinomas in male and female Fischer 344 rats. Rats were more sensitive than mice, and male rats were more sensitive than female rats in this study; therefore, the male Fischer 344 rat liver tumor data was used as the basis of a cancer potency factor.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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ACRYLAMIDE

CAS No: 79-06-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	71.08
Boiling point	125°C at 25 mm Hg
Melting point	84.5
Vapor pressure	0.007 mm Hg at 25°C
Air concentration conversion	1 ppm = 2.91 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 4.5 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated by US EPA/IRIS (1988, 1993) from female Fischer 344 rat tumor data (central nervous system, mammary and thyroid glands, uterus, oral cavity) (Johnson *et al*., 1986) using a linearized multistage procedure, extra risk; adopted by CDHS/RCHAS (1990).]

III. CARCINOGENIC EFFECTS

Human Studies

US EPA (1993) reviewed a study of cancer mortality in workers exposed to acrylamide by Collins (1984). Data from a long duration exposure group (10 individuals) and a short duration/intermittent exposure group (52 individuals) was analyzed using a standardized proportional mortality ratio (SPMR) procedure. No excess mortality for all types of cancer combined was noted in either group. Mortality from lung and central nervous system cancer appeared to be slightly elevated. However, the SPMRs were not significantly different from expected values, due to small group size. US EPA (1993) also noted additional study limitations including underrepresentation of the potential at-risk worker population, incomplete cause of death ascertainment, and incomplete exposure data.

Sobel *et al*. (1986) studied the mortality experience of 371 workers (365 white males, 6 white females) employed in acrylamide monomer production and polymerization operations at the Michigan Division of the Dow Chemical Company from 1955 through 1979. Vital status followup was performed from the date of the first potential exposure to December 31, 1982. Mortality comparisons were made between the cohort and United States white male mortality rates; comparisons were made with a subcohort of workers previously exposed to organic dyes both included and excluded. Slight excesses of mortality from all cancers (11 observed/7.9 expected), digestive tract cancer (4 observed/1.9 expected) and respiratory tract cancer (4 observed/2.9 expected) were observed in the total cohort; these excesses were not observed when the organic dye exposure subcohort was excluded. The authors concluded that the study did not support a relationship between acrylamide exposure and general or specific cancer mortality. However, US EPA (1988) considers this study insufficient to assess the carcinogenicity of acrylamide in humans

because of small cohort size, multiple chemical exposures, limited followup, and short exposure duration (167 cohort members had < 1 year of employment; 109 had 1-4 years of employment).

Animal Studies

Bull *et al*. (1984a) exposed female Sencar mice and male and female A/J mice to acrylamide. Female Sencar mice (40/treatment group) were exposed to 0, 12.5, 25.0 or 50.0 mg/kg body weight acrylamide by gavage, intraperitoneal injection or dermal application. Doses were administered 6 times over a 2 week period; total doses were 0, 75, 150 and 300 mg/kg. Acrylamide was dissolved in distilled water for gavage and intraperitoneal injection administration, and in ethanol for dermal application. Two weeks after the cessation of acrylamide exposure, 1.0 µg 12-*O*-tetradecanoyl-phenol-13-acetate (TPA) dissolved in 0.2 ml acetone was applied to the shaved back of each animal 3 times/week for 20 weeks. A promotion control group was included which received 300 mg/kg acrylamide followed by dermal applications of 0.2 ml acetone on the same treatment schedule and duration as the animals receiving TPA. All animals were sacrificed at 52 weeks, and were evaluated for the presence of skin tumors. Male and female A/J mouse (40/sex/treatment group) acrylamide exposures were conducted at laboratories of the US EPA (Cincinnati, OH) and the Medical College of Ohio (Toledo, OH) (MCO) . Animals exposed at US EPA received acrylamide dissolved in distilled water by gavage 3 times/week for 8 weeks at doses of 0, 6.25, 12.5 or 25 mg/kg. Animals exposed at MCO initially received acrylamide by intraperitoneal injection 3 times/week for 8 weeks at doses of 0, 1, 3, 10, 30 or 60 mg/kg; however, peripheral neuropathy and decreased survival forced treatment termination on the 60 mg/kg group after the 11th injection. An untreated control group was also included. Animals were sacrificed after either 7 months (US EPA) or 6 months (MCO) and examined for lung adenomas. Acrylamide induced skin tumors (squamous cell papillomas and carcinomas) in TPA-promoted female Sencar mice in a dose-dependent manner when administered by gavage, intraperitoneal injection or dermal application. Acrylamide did not induce skin tumors by any route of administration in animals not receiving TPA. Tumor incidence data from female Sencar mice exposed to acrylamide are listed in Table 1.

The incidence of lung adenomas in both male and female A/J mice exposed to acrylamide by either gavage or intraperitoneal injection was significantly increased in a dose-related manner (Bull *et al*., 1984a). Tumor incidence data for animals treated by intraperitoneal injection is listed in Table 2; numerical tumor incidence data for animals exposed to acrylamide by gavage was not listed.

Acrylamide dissolved in water was administered by gavage (0, 75, 150 or 200 mg/kg body weight, divided into 6 equal portions) to female ICR-Swiss mice (40 animals/treatment group) over a 2 week period (Bull *et al*., 1984b). Two weeks after the last acrylamide exposure, the animals were exposed 3 times/week to dermal applications of 2.5 µg TPA for 20 weeks. Another group of 20 animals were exposed to a total dose of 300 mg/kg acrylamide, but received dermal applications of acetone alone. All animals were sacrificed after 52 weeks. Acrylamide caused a significant dose-related increase in the incidence of skin tumors (papillomas and carcinomas combined). The incidence in animals also receiving TPA was 0/35, 4/34, 4/32 and 13/32 (number of animals with tumors/number of animals examined) for the control, low, mid and high dose groups, respectively; the skin tumor incidence in animals receiving 300 mg/kg acrylamide but not TPA was 10/36. Acrylamide-treated animals also demonstrated a significant dose-related increase in the incidence

of lung tumors (alveolar and bronchiolar adenomas and carcinomas). The incidence in animals also receiving TPA was 4/36, 8/34, 6/36 and 11/34 for the control, low, mid and high dose groups, respectively; the lung tumor incidence in animals receiving 300 mg/kg acrylamide but not TPA was 14/36.

Table 1. Skin tumor (squamous cell papillomas and carcinomas) incidence in female Sencar mice exposed to acrylamide (Bull *et al*., 1984a)

Total administered dose[1] (mg/kg body weight)	Route of administration	TPA[2]	Tumor incidence
0	gavage	+	2/40
75		+	12/40
100		+	23/40
300		+	30/40
300		-	0/20
0	intraperitoneal injection	+	0/40
75		+	10/40
100		+	13/40
300		+	21/40
300		-	0/20
0	dermal	+	7/40
75		+	4/40
100		+	11/40
300		+	18/40
300		-	0/20

1. The exposure duration was less than lifetime (2 weeks); the total administered dose listed was not adjusted to reflect a less-than-lifetime exposure.
2. TPA = 12-*O*-tetradecanoyl-phenol-13-acetate

Table 2. Lung adenoma incidence in male and female A/J mice exposed to acrylamide by intraperitoneal injection (Bull *et al*., 1984a)

Dose level[1] (mg/kg body weight)	Percent of animals with tumors	
	males	females
0	13	8
1	50	35
3	38	53
10	59	79
30	93	93

1. The exposure duration was less than lifetime (8 weeks); the dose level listed was not adjusted to reflect a less-than-lifetime exposure.

Robinson *et al*. (1986) exposed female SENCAR, BALB/c, A/J and ICR-Swiss mice (60 mice/strain/treatment group) to a single 50 mg/kg body weight dose of acrylamide by intraperitoneal injection; 2 days later 40 of the 60 mice in each treatment group received 1.0 µg (SENCAR), 2.5 µg (A/J and ICR-Swiss) or 5.0 µg (BALB/c) TPA in 0.2 ml acetone applied dermally 3 times/week for 20 weeks. The remaining 20 mice/strain/treatment group received acetone alone for the same treatment schedule and duration. All animals were sacrificed at 40 weeks, and were only examined for the number of skin papillomas and lung adenomas/animal. Acrylamide induced a significant increase in the number of skin papillomas and lung adenomas per animal in SENCAR mice receiving TPA treatment. The total number of animals bearing tumors was not listed. No significant increase in either tumor type was noted in the other mouse strains tested; tumor data for the animals receiving acrylamide but not TPA was not reported.

Male and female Fischer 344 rats (90/sex/treatment group) were exposed to acrylamide in drinking water for 2 years (Johnson *et al*., 1986). Acrylamide water concentrations were adjusted to provide dosages of 0, 0.01, 0.1, 0.5 or 2 mg/kg body weight/day. Interim sacrifices (10 animals/sex/treatment group) were performed at 6, 12 and 18 months. A maximum tolerated dose (MTD) was achieved based on decreased weight gain, increased mortality during the last 4 months of the study and the appearance of several toxic effects (including peripheral nerve degeneration) in the 2 mg/kg/day group. Increases in the incidences of a number of tumor types were observed in the 2.0 mg/kg/day exposure group animals. An increased incidence of thyroid gland-follicular epithelium tumors was observed in both males and females. In females, increased tumor incidences were noted in the mammary glands, central nervous system, oral tissues, uterus and clitoral gland. An increased incidence of scrotal mesothelioma was noted in males, in both the 2.0 and 0.5 mg/kg/day exposure group; additionally, although not statistically significant, the incidence of scrotal mesothelioma in the 0.1 mg/kg/day group was greater than either the control group or historical control incidences. Male rats in the 2.0 mg/kg/day exposure group also had a significant increase in adrenal pheochromocytomas, and an increased incidence of central nervous system tumors when compared to historical controls but not when compared to concurrent controls. Tumor incidence data is listed in Table 3.

Table 3. Acrylamide-induced tumor incidences in male and female Fischer 344 rats (Johnson *et al*., 1986)

Administered dose (mg/kg/day)	Human equivalent dose[1] (mg/kg/day)	Tumor type	Tumor incidence	
			males	females
0	0	combined central nervous system (CNS), mammary gland, oral cavity, thyroid gland, uterus[2]	NA	13/60
0.01	0.001		NA	18/60
0.1	0.015		NA	14/60
0.5	0.076		NA	21/60
2.0	0.305		NA	46/60
0	0	adrenal pheochromacytomas[3]	3/60	NA
0.01	0.001		7/60	NA
0.1	0.015		7/60	NA
0.5	0.076		5/60	NA
2.0	0.305		10/60	NA
0	0	central nervous system[4]	5/60	1/60
0.01	0.001		2/60	2/60
0.1	0.015		0/60	1/60
0.5	0.076		3/60	1/60
2.0	0.305		8/60	9/60
0	0	oral cavity[5]	6/60	0/60
0.01	0.001		7/60	3/60
0.1	0.015		1/60	2/60
0.5	0.076		5/60	3/60
2.0	0.305		6/60	8/60
0	0	mammary gland[6]	NA	2/60
0.01	0.001		NA	2/60
0.1	0.015		NA	1/60
0.5	0.076		NA	5/58
2.0	0.305		NA	8/61
0	0	scrotal mesotheliomia	3/60	NA
0.01	0.001		0/60	NA
0.1	0.015		7/60	NA
0.5	0.076		11/60	NA
2.0	0.305		10/60	NA
0	0	thyroid[7]	1/60	1/58
0.01	0.001		0/58	0/59
0.1	0.015		2/59	1/59
0.5	0.076		1/59	1/58
2.0	0.305		7/59	5/60
0	0	uterine adenocarcinomas	NA	1/60
0.01	0.001		NA	2/60
0.1	0.015		NA	1/60
0.5	0.076		NA	0/59
2.0	0.305		NA	5/60

Table 3 (continued). Acrylamide-induced tumor incidences in male and female Fischer 344 rats (Johnson *et al*., 1986)

1, 2. As calculated by US EPA (1988).
3. Benign and malignant.
4. Tumors of glial origin or glial proliferation suggestive of early tumor.
5. Squamous cell papillomas and carcinomas.
6. Adenomas and adenocarcinomas.
7. Males: follicular adenomas; females: follicular adenomas and adenocarcinomas.
NA not available

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The studies by Bull *et al*. (1984a, 1984b), Robinson *et al*. (1986) and Johnson *et al*. (1986) indicate that acrylamide is capable of acting as both an initiator and a complete carcinogen in animals. However, only the Johnson *et al*. (1986) study contained a data set suitable for generating a cancer potency factor. Female Sencar mice developing tumors after exposure to acrylamide in the study by Bull *et al*. (1984a) were also additionally exposed to TPA; animals not exposed to TPA did not develop skin tumors. Female A/J mice exposed in that study to acrylamide by either gavage or intraperitoneal injection developed an increased incidence of lung adenomas without requiring TPA exposure. However, the animals were not evaluated for tumor types other than lung adenomas, and numerical tumor incidence data for animals exposed to acrylamide by gavage was not listed. Also, the exposure and observation durations for animals exposed by gavage (8 weeks and 7 months, respectively) and by intraperitoneal injection (8 weeks and 6 months, respectively) were short. Female ICR-Swiss mice exposed to acrylamide by gavage in the study by Bull *et al*. (1984b) were generally also exposed to TPA; only one exposure group was included which received acrylamide (300 mg/kg) but not TPA. Additionally, the exposure duration was only 2 weeks and the exposure duration was less than lifetime (52 weeks). In the study by Robinson *et al*. (1986), all animals for which tumor incidence data was reported were exposed to TPA as well as acrylamide. Animals in the Johnson *et al*. (1986) study were exposed to acrylamide alone for the lifetime of the animals, and were comprehensively examined for tumors. For these reasons, tumor incidence data from the Johnson *et al*. (1986) study was used to derive a cancer potency factor for acrylamide.

Methodology

As recommended in the US EPA Guidelines for Carcinogen Risk Assessment (1986), US EPA (1988) pooled tumor incidence data from different tumor sites, under the consideration that risk numbers derived from site-specific tumor incidence data potentially may not be predictive of, and may in fact underestimate, "whole-body" risks that are determined using the pooled individual animal data. The dose-response curves for each sex based on the pooled tumor incidence (benign and malignant) constituted the data sets of choice for risk assessment. Tumors at a particular site were added into the pool only when the tumor site had statistically significantly increased incidence at least at the high dose level (treated vs. control). The female rat was considered to be

the more sensitive sex, as there were significantly increased tumor incidences at a greater number of sites than in the males; the female rat tumor data was therefore used as the basis of a risk estimate. A linearized multistage procedure (GLOBAL 83) was used to calculate a cancer potency factor (q_1^*) from the female rat tumor incidence data. Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors, using the relationship ($q_{human} = q_{animal} * (bw_h / bw_a)^{1/3}$), where q_{human} is the human potency, q_{animal} is the animal potency, and bw_h and bw_a are the human and animal body weights, respectively. Body weight values used for humans and rats were 70 kg and 0.2 kg, respectively. No exposure route adjustment was made to the risk estimates because data exists which indicates that the pharmacokinetics and tissue distribution of acrylamide were not significantly affected by the dose administered or the route of administration (Dearfield *et al*., 1988). US EPA calculated a cancer potency value (q_{human}) of 4.5 E+0 $(mg/kg\text{-}day)^{-1}$. A unit risk factor was then calculated from the cancer potency factor by OEHHA/ATES using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day. The unit risk should not be used if the air concentration exceeds 8 $\mu g/m^3$, as above this concentration the unit risk may not be appropriate.

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ACRYLONITRILE

CAS No: 107-13-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	53.06
Boiling point	77.3°C
Melting point	-82°C
Vapor pressure	100 mm Hg at 23°C
Air concentration conversion	1 ppm = 2.2 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.9 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.0 E+0 $(mg/kg\text{-}day)^{-1}$
[Human respiratory tract cancer incidence data (O'Berg, 1980), relative risk model (US EPA, 1983), reevaluated by CDHS/RCHAS (1988).]

III. CARCINOGENIC EFFECTS

Human Studies

Cancer incidence and mortality in a cohort of 1345 male workers exposed to acrylonitrile at a E.I. du Pont de Nemours and Co., Inc. textile plant in Camden SC was studied by O'Berg (1980). The study cohort was identified as having had potential exposure to acrylonitrile in the period between plant startup in 1950 and 1966. The 1966 cutoff date allowed for a 10-year follow-up through the end of 1976. Worker exposure levels were assessed qualitatively by the author and a committee of six DuPont employees with long-term experience in the acrylonitrile exposure area; plant environmental monitoring data was not available for the 1950-1966 period. High, moderate and low exposure categories were established. The U.S. Environmental Protection Agency (US EPA) (1983) noted that DuPont representatives agreed that 5, 10 and 20 ppm might be used to represent the low medium and high exposure classification levels. Expected numbers of cancer cases and deaths were calculated from both DuPont corporate data and from the 1969-1971 National Cancer Institute survey data set. However, the author only listed the results of cancer incidence and mortality calculations using the DuPont "control" data set as the source of the expected numbers of cancer cases and mortality; US EPA (1983) stated that the presentation of results based on this control cohort only would ignore the possible effects of other chemicals on the company control cohort. Exposed workers demonstrated 25 cases of all types of cancer, with 20.5 expected. Of these cases, 8 were lung cancer versus 4.4 expected. For workers employed during plant startup (1950-1952) and exposed for at least 6 months, 8 cases of lung cancer were noted vs. 2.6 expected ($p < 0.01$). Most of this excess occurred during the latest followup period (1970-1976) (6 cases of lung cancer vs. 1.5 expected, $p < 0.01$). Total cancer cases in this period were also significantly increased (17 observed, 5.6 expected, $p < 0.01$). Also, a trend was observed correlating increased cancer risk with increased severity of exposure. Workers in the moderate exposure group with a

probable latent period of at least 15 years exhibited 13 cases of cancer of all types vs. 5.5 expected, and 5 cases of lung cancer vs. 1.4 expected ($p < 0.05$).

One potential confounding factor in this study is the lack of controls for tobacco smoking. US EPA (1983) investigated the possible impact of smoking on lung cancer incidence in the O'Berg (1980) study. DuPont provided additional data on 32 of 36 cancer cases reported on in the plant under study (some cases were not in the study cohort) and on smoking data for a matched group of non-cancer cases. Of the 32 cancer cases for which smoking data was available, 22 were cancer types other than lung, and 16 of the non-lung cancer cases (73%) were smokers. Of the matched noncancer controls, 25 (69%) were smokers. US EPA estimated that 70% of the plant population were smokers and 30% nonsmokers, and of the smoker population, 50% were "moderate" smokers and 20% were "heavy" smokers. Based on the assumption that the relative risk of lung cancer for nonsmokers, moderate, and heavy smokers is 1, 10 and 20, respectively, US EPA adjusted the number of expected lung cancer cases in the study cohort to reflect the smoking prevalence data. The number of expected lung cancer cases after adjustment for smoking is 1.61 cases. This is about 15% higher than the 1.4 cases expected without considering smoking differences; however, this adjustment did not substantially alter the significance of the increased prevalence of lung cancer in the workers exposed to acrylonitrile. US EPA (1983) concluded that the observations by O'Berg (1980) of a statistically significant excess of lung cancer in acrylonitrile-exposed workers constitutes significant evidence that acrylonitrile is likely to be a human carcinogen.

A followup to the O'Berg (1980) study was conducted by O'Berg *et al*. (1985). Observations of cancer incidence and mortality for the study cohort of 1345 DuPont workers exposed to acrylonitrile was extended through 1981 for mortality and through 1983 for cancer incidence. Exposed workers demonstrated 43 cases of all types of cancer, with 37.1 expected. Of these cases, 10 were lung cancer versus 4.4 expected. These rates were in excess but were not statistically significant. Additionally, prostate cancer rates were significantly elevated, with 6 cases observed compared to 1.8 cases expected ($p < 0.05$).

Theiss *et al*. (1980) (reviewed by US EPA, 1983) conducted a cohort mortality study of 1469 workers from 12 factories owned by the BASF company in the Federal Republic of Germany (FRG). BASF purchased acrylonitrile during the study period in order to produce styrene-acrylonitrile and acrylonitrile-butadiene-styrene polymers in addition to organic intermediate products. Processing methods differed between factories, and worker exposure data was not available. The study population was defined as all workers employed for over 6 months in acrylonitrile processing from the time of first use of acrylonitrile (approximately 1956) to the study cut-off date of May 15, 1978. The cohort included 1081 German workers and 338 workers of other nationalities. Followup was 98% complete on the German workers, but only 56% complete on the foreign workers. Expected deaths were calculated from mortality rates for the city of Ludwigshafen, the state of Rheinhessen-Pfalz, and the FRG as a whole. An elevated risk of cancer (all types) mortality was noted in the study cohort (27 observed, 20.5 expected based on FRG mortality rates). The study cohort also demonstrated a significantly elevated risk of lung cancer (11 observed, 5.65 expected based on FRG rates, $p < 0.05$; 5.92 expected based on Rheinhessen-Pfalz rates, $p < 0.05$). An excess significant risk of lung cancer remained after 78 cohort members from one factory who reported "contact with other substances since proven to be carcinogenic" were removed from the calculations (9 observed, 4.37 expected based on FRG mortality rates, $p <$

0.05); additionally, a significant excess risk of lymphatic cancer was seen (4 observed, 1.38 expected based on FRG mortality rates, $p < 0.05$).

US EPA (1983) noted that the members of the study cohort were exposed to a number of other carcinogens, including vinyl chloride, and distillation residues including polycyclic aromatic hydrocarbons, cadmium, ß-napthylamine, dimethyl sulfate and epichlorohydrin. Additionally, tobacco smoking was a potential confounding factor; all lung cancer cases were smokers. However, US EPA also noted that the lung cancer risk associated with exposure to acrylonitrile estimated from this study could actually be an underestimate of the actual risk because 1) combining workers from 12 factories between which acrylonitrile exposure levels varied could have lend to an underestimate of risk due to the inclusion of unexposed or minimally exposed workers; 2) the "healthy worker" effect could have resulted in an underestimate of risk; 3) followup on the relatively youthful cohort was insufficient, and did not allow sufficient latency in the cohort segments most at risk - only 447.1 person-years were accumulated in members over 64 years of age and 4) underascertainment of vital status (12% of the study cohort were lost to followup) may have resulted in an undercount of observed deaths. US EPA concluded that it was possible that exposure to acrylonitrile might be related to the excess risk of lung cancer demonstrated by the study cohort of Theiss *et al*. (1980).

Werner and Carter (1981) studied the mortality of 1111 men who worked in acrylonitrile polymerization and acrylic fiber production (6 plants, located in England, Northern Ireland, Scotland and Wales) from 1950 to 1968; surveillance was continued to the end of 1978. An excess of total cancer deaths was noted (21 observed, 18.6 expected) but was not statistically significant. Expected deaths were calculated from mortality rates from England and Wales combined. Only 68 deaths from all causes had occurred as of the end of 1978; 72.4 were expected. An excess of deaths from all types of cancer combined was noted (21 observed, 18.6 expected), but this excess was not statistically significant. Significant increases in deaths due to stomach cancer were noted in all age groups combined (5 observed, 1.9 expected, $p < 0.05$), with deaths in the 55-64 age group comprising the largest portion of those deaths (3 observed, 0.7 expected, $p < 0.05$). A statistically significant elevated risk of lung cancer was also noted in the 15-44 age group (3 observed, 0.7 expected, $p < 0.05$), but not in other age groups or in all age groups combined. The authors note the lack of acrylonitrile exposure data, including potential differences in exposure levels between the 6 plants surveyed. US EPA (1983) also notes the relatively short followup in the cohort subgroup which would be expected to have incurred the greatest risk, the 158 men having the earliest exposure (during the 1950-1958 period). US EPA (1983) concluded that because of the relative youth of the cohort resulting in a small number of expected deaths, the lack of followup, and the lack of control for smoking, the findings of this study are only suggestive.

A cohort mortality study of 327 white male workers employed for 2 or more years between January 1, 1940 and July 1, 1971 at a rubber manufacturing plant in Akron OH who were potentially exposed to acrylonitrile was conducted by Delzell and Monson (1982). Acrylonitrile exposure levels were not reported. Cause-specific expected deaths were calculated based on both U.S. age and calendar specific white male mortality and mortality rates for other rubber workers from the same city; however, most results reported in this study used expected deaths calculated using U.S. white male mortality rates. An excess risk of lung cancer mortality was observed when either U.S. mortality rates (9 observed, 5.9 expected) or Akron rubber industry mortality rates (9 observed,

4.7 expected) were used to calculate expected lung cancer deaths. Workers employed for 5-15 years and followed for at least 15 years demonstrated a significantly increased risk of lung cancer (4 observed, 0.8 expected, $p < 0.01$). Cohort members could potentially have been exposed to other chemicals used in the same area (butadiene, styrene, vinyl pyridine). Also, smoking controls were not included. However, US EPA (1983) commented that the possibility that the excess risk of lung cancer demonstrated in this study was due to acrylonitrile exposure could not be dismissed.

Chen *et al*. (1987) examined cancer incidence and mortality in a cohort of 1083 male employees at a E.I. du Pont de Nemours and Co., Inc. textile plant in Waynesboro, VA who were potentially exposed to acrylonitrile in the period 1944-1970. Worker exposure levels were assessed by an Exposure Classification Committee consisting of seven DuPont employees with long-term experience in the acrylonitrile exposure area; plant environmental monitoring data was not available for the 1944-1970 period. High, moderate and low exposure categories were established. Expected numbers of deaths were calculated from both U.S. and DuPont mortality rates; however, the authors only listed the results of cancer incidence and mortality calculations using the DuPont "control" data set as the source of the expected numbers of cancer cases and mortality. No significant increase in incidence was noted for either all types of cancer (37 observed, 36.5 expected) or lung cancer (5 observed, 6.9 expected). However, a significant increase in the incidence of prostate cancer (5 observed, 1.9 expected) was noted; of these, 4 occurred in the 1975-1983 period (0.9 expected).

US EPA (1983) also reviewed several unpublished studies of cancer mortality and/or morbidity potentially caused by acrylonitrile (Kiesselbach *et al*., 1980; Zack, 1980; Gaffey and Strauss, 1981; Herman, 1981; Stallard, 1982). These studies indicated no cancer increase in workers potentially exposed to acrylonitrile. However, US EPA concluded that due to design and methodological deficiencies including short followup, small cohort size and young cohort age, "none of these studies can be cited as adequate evidence that acrylonitrile is not carcinogenic".

Animal Studies

Maltoni *et al*. (1977) (reviewed by US EPA, 1983) exposed male and female Sprague-Dawley rats (30/sex/exposure group) to 0, 5, 10, 20 or 40 ppm acrylonitrile by inhalation for 4 hours/day, 5 days/week for 12 months. The animals were then maintained for the remainder of their lifetime. Slight increases in the incidence of the following tumor types were noted: mammary gland tumors in males and females, nonglandular forestomach tumors in males and skin tumors in females. Tumor incidence data are listed in Table 1.

The authors claimed that these results indicated a "border-line carcinogenic effect". US EPA (1983) noted that low sensitivity of this study due to the low concentrations of acrylonitrile used and the short duration of acrylonitrile exposure (12 months). Additionally, male and female Sprague-Dawley rats (40/sex/group) were exposed to 0 or 5 mg/kg body weight acrylonitrile by gavage 3 times/week for 52 weeks.

Table 1. Tumor incidence in male and female Sprague-Dawley rats exposed to acrylonitrile by inhalation (Maltoni *et al*., 1977)

Tumor type	Tumor incidence Acrylonitrile concentration (ppm)				
	0	5	10	20	40
mammary tumors (females)	5/30	10/30	7/30	10/30	7/30
mammary tumors (males)	1/30	0/30	1/30	4/30	4/30
nonglandular forestomach papillomas (males)	0/30	1/30	2/30	0/30	3/30
skin carcinomas (females)	0/30	4/30	1/30	1/30	1/30

On spontaneous death, a moderate increase in the incidence of female rat mammary gland tumors and nonglandular forestomach tumors was noted. US EPA (1983) commented that although the observation period was relatively short (52 weeks) and only a single dose level was used, this study provides additional evidence for the carcinogenicity of acrylonitrile.

A three-generation reproductive study on the effect of acrylonitrile exposure in male and female Charles River rats [CRL:COBS CD (SD) BR] was conducted by Litton-Bionetics, Inc. for the Chemical Manufacturers Association (Beliles *et al*., 1980; reviewed by US EPA, 1983). The rats and their offspring were exposed to drinking water containing 0, 100 or 500 ppm acrylonitrile starting 15 days post-weaning and were mated after 100 days. After delivery of two litters, the animals were exposed to acrylonitrile for approximately 45 weeks. After exposure, all animals in generations F_0, F_1b and F_2b were sacrificed and examined histologically. Second-generation rats in the 500 ppm exposure group demonstrated a significant increase in the incidence of astrocytomas and Zymbal gland tumors. Tumor incidence data are listed in Table 2.

Table 2. Tumor incidence data in Charles River rats during a three-generation reproductive study (Beliles *et al*., 1980)

Tumor type	Generation	Tumor incidence Acrylonitrile dose (ppm)		
		0	100	500
astrocytomas	F_0	0/19	1/20	2/25
	F_1b	0/20	1/19	4/17
	F_2b	0/20	1/20	1/20
Zymbal gland	F_0	0/19	0/20	1/25
	F_1b	0/20	2/19	4/17
	F_2b	0/20	0/20	3/20

Bio/Dynamics Inc. conducted a study on the toxicity and carcinogenicity of acrylonitrile in Sprague-Dawley rats (Bio/Dynamics, 1980a) for the Monsanto Company (St. Louis, MO); the results of this study were subsequently submitted to the US EPA by the Monsanto Company on June 30, 1980. Male and female Sprague-Dawley rats (100/sex/treatment group) were exposed to acrylonitrile in drinking water at concentrations of 0,1, and 100 ppm. Interim sacrifices (10/sex/treatment group) were conducted at 6, 12 and 18 months. The study was terminated at less than 2 years because of low survival rates; males were sacrificed at 22 months and females were

sacrificed at 19 months. Statistically significant increases were noted in the incidence of astrocytomas of the brain and spinal cord, adenomas and carcinomas of the Zymbal gland, and nonglandular forestomach squamous cell papillomas and carcinomas in males and females of the 100 ppm group. Tumor incidence data are listed in Table 3.

Table 3. Tumor incidences in male and female Sprague-Dawley rats exposed to acrylonitrile in drinking water (Bio/Dynamics, 1980a)

Tumor type	Dose level (ppm)	Tumor incidence	
		males	females
brain astrocytomas	0	2/98	0/99
	1	3/95	1/100
	100	23/97	32/97
spinal cord astrocytomas	0	NA	0/96
	1	NA	0/99
	100	NA	7/98
Zymbal gland carcinomas	0	1/100	0/99
	1	0/91	0/95
	100	14/93	7/98
nonglandular forestomach papillomas/carcinomas	0	3/98	1/100
	1	3/98	4/99
	100	12/97	7/99

NA - not analyzed

A similar study was conducted by Bio/Dynamics Inc. on the toxicity and carcinogenicity of acrylonitrile in Fischer 344 rats (Bio/Dynamics, 1980b) for the Monsanto Company (St. Louis, MO); the results of this study were subsequently submitted to the US EPA by the Monsanto Company on December 12, 1980. Male and female Fischer 344 rats (100/sex/acrylonitrile treatment group; 200/sex/control group) were exposed to acrylonitrile in the drinking water at concentrations of 0,1, 3, 10, 30 and 100 ppm. Interim sacrifices (10/sex/acrylonitrile treatment group; 20/sex/control group) were conducted at 6, 12 and 18 months. The study was designed to be 24 months in duration; however, because of poor survival, all females were sacrificed at 23 months. Males were continued on study until 26 months, when survival rates comparable to females were achieved. Statistically significant increases were noted in the incidence of astrocytomas of the brain and spinal cord in males (30 and 100 ppm groups) and females (10, 30 and 100 ppm group), adenomas and carcinomas of the Zymbal gland in males (30 and 100 ppm groups) and females (10, 30 and 100 ppm groups), and nonglandular forestomach squamous cell papillomas and carcinomas in males (3, 10 and 30 ppm groups) and females (30 ppm group). Tumor incidence data are listed in Table 4.

Table 4. Tumor incidences in male and female Fischer 344 rats exposed to acrylonitrile in drinking water (Bio/Dynamics, 1980b)

Tumor type	Dose level (ppm)	Tumor incidence	
		males	females
brain astrocytoma	0	2/200	1/199
	1	2/100	1/100
	3	1/100	2/101
	10	2/100	4/95*
	30	10/99*	6/100*
	100	21/99*	23/98*
spinal cord astrocytoma	0	1/196	1/197
	1	0/99	0/97
	3	0/92	0/99
	10	0/98	1/92*
	30	0/99	0/96
	100	4/93*	1/91
Zymbal gland[1]	0	2/189	0/193
	1	1/97	0/94
	3	0/93	2/92
	10	2/88	4/90*
	30	7/94*	5/94*
	100	16/93*	10/86*
nonglandular forestomach[2]	0	0/199	1/199
	1	1/100	1/100
	3	4/97*	2/100
	10	4/100*	2/97
	30	4/100*	4/100*
	100	1/100	2/97

* Statistically significant at $p < 0.05$

Male and female Sprague-Dawley rats (Spartan strain) (100/sex/group) were exposed to acrylonitrile by gavage at dose levels of 0, 0.1 and 10 mg/kg-day, 5 days/week in a study conducted by Bio/Dynamics Inc. for the Monsanto Company (St. Louis, MO) (Bio/Dynamics, 1980c). Study termination was originally planned for 24 months; however, because only 10 and 13 high dose males and females, respectively, were still alive at 20 months, all surviving animals in all groups were killed during the 20th month to ensure that at least 10 animals/sex/group were available for histopathological examination. Interim sacrifices were performed at 6, 12 and 18 months (10 animals/sex/group). Statistically significant increases in tumor incidence were noted in the following tumor types: brain astrocytomas and Zymbal gland squamous cell carcinomas (high dose males and females), stomach papillomas and carcinomas and intestinal tumors (high dose males), and mammary gland tumors (high dose females). Tumor incidence data are listed in Table 5.

Table 5. Tumor incidence in male and female Sprague-Dawley rats (Spartan strain) exposed to acrylonitrile by gavage (Bio/Dynamics, 1980c)

Tumor type	Sex	Tumor incidence Dose level (mg/kg-day)		
		0	0.10	10.0
brain astrocytoma	male female	2/100 1/99	0/97 2/100	16/98 17/100
spinal cord astrocytoma	male female	0/94 0/100	0/93 0/95	1/97 1/99
Zymbal gland squamous cell carcinomas	male female	1/96 0/85	0/93 0/94	10/96 9/94
stomach papillomas/carcinomas	male female	2/99 2/99	6/97 4/99	40/99 17/99
Intestine	male female	0/100 NA	1/100 NA	6/100 NA
mammary gland	male female	NA 7/101	NA 6/100	NA 22/101

Dow Chemical Company (Midland, MI) performed a study in which male and female Sprague-Dawley rats (48 animals/sex/acrylonitrile exposure group; 80 animals/sex/control group) were exposed to acrylonitrile in drinking water for 2 years (Quast *et al*., 1980a). For the first 21 days of the study, the concentrations used were 0, 35, 85 and 210 ppm; the two higher concentrations were subsequently raised to 100 and 300 ppm. Animals at the highest 2 concentrations demonstrated treatment-related toxicity after 9 months. The mean administered doses of acrylonitrile were calculated to be 0, 3.42, 8.53 and 21.18 mg/kg-day for males and 4.36, 10.76 and 24.97 mg/kg-day for females for the 35, 100 and 300 ppm exposure groups, respectively. All surviving animals were sacrificed at 24 months. Statistically significant increases in tumor incidence were noted for the following tumor types: central nervous system tumors (astrocytomas, gliomas) in males and females (all treatment groups), Zymbal gland adenomas and carcinomas in females (all treatment groups) and males (300 ppm group), nonglandular forestomach squamous cell papillomas and carcinomas in males (all treatment groups) and females (100, 300 ppm groups), tongue squamous cell papillomas and carcinomas in males (all treatment groups) and females (100, 300 ppm groups), mammary gland tumors (benign and malignant) in females (35, 100 ppm groups), and small intestine cystadenocarcinomas in females (100, 300 ppm). Tumor incidence data are listed in Tables 6 and 7.

Table 6. Tumor incidence in male Sprague-Dawley rats exposed to acrylonitrile in drinking water (Quast *et al*., 1980a)

Tumor type	Tumor incidence Acrylonitrile dose level (ppm)			
	0	35	100	300
brain and/or spinal cord[1]	1/80	12/47	22/48	30/48
Nonglandular forestomach[2]	0/80	3/46	23/48	39/47
tongue[2]	1/75	2/7	4/9	5/40
Zymbal gland carcinomas	3/80	4/47	3/48	15/48

1. Benign and/or malignant
2. Squamous cell papillomas and/or carcinomas

Table 7. Tumor incidence in female Sprague-Dawley rats exposed to acrylonitrile in drinking water (Quast *et al*., 1980a)

Tumor type	Tumor incidence Acrylonitrile dose level (ppm)			
	0	35	100	300
brain and/or spinal cord[1]	0/80	17/48	22/48	24/48
mammary gland[1]	57/80	42/48	42/48	35/48
Nonglandular forestomach[2]	1/80	1/47	12/48	30/48
small intestine[3]	0/80	1/7	4/11	4/48
tongue[2]	0/78	1/5	2/3	12/45
Zymbal gland carcinomas[4]	1/80	5/48	8/48	18/48

1. Benign and/or malignant
2. Squamous cell papillomas and/or carcinomas
3. Mucinous cystadenocarcinomas
4. Adenomas and carcinomas

Male and female Sprague-Dawley rats (Spartan substrain; 100 animals/sex/exposure group) were exposed to acrylonitrile by inhalation in a study conducted by Dow Chemical Company for the Chemical Manufacturers Association (Quast *et al*., 1980b). Study animals were exposed to 0, 20 or 80 ppm of acrylonitrile for 6 hours/day, 5 days/week for 2 years. Statistically significant increases in tumor incidence were noted for the following tumor types: brain and spinal cord glial cell tumors (males and females), mammary gland adenocarcinomas (females), small intestine tumors (benign and malignant) (males), tongue squamous cell papillomas and carcinomas (males) and Zymbal gland tumors (males and females). All tumor incidence increases were noted at the highest concentration tested, 80 ppm, except for brain and spinal cord glial cell tumors in females, which were also noted in the 20 ppm group. Tumor incidence data are listed in Table 8.

Table 8. Tumor incidence in male and female Sprague-Dawley rats exposed to acrylonitrile by inhalation (Quast *et al*., 1980b)

Tumor type	Sex	Tumor incidence Acrylonitrile concentration (ppm)		
		0	20	80
Brain and/or spinal cord glial cell tumors[1]	male	0/100	4/99	22/99
	female	0/100	8/100	21/100
mammary gland adenocarcinomas	female	9/100	8/100	20/100
small intestine[1]	male	2/99	2/20	15/98
Zymbal gland tumors[1]	male	2/100	4/100	11/100
	female	0/100	1/100	11/100

1. Benign and/or malignant

Bigner *et al*. (1987) exposed male and female Fischer 344 rats to acrylonitrile in drinking water. Exposure groups were as follows: 147 males and 153 females exposed to 500 ppm acrylonitrile; 50 males and 50 females exposed to 500 ppm acrylonitrile; 50 males and 50 females exposed to 100 ppm acrylonitrile and 51 males and 49 female control animals. The study was not complete at the time of the report (18 months of exposure); however, they reported 49 primary brain tumors in 215 animals examined from the high dose treatment groups.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Acrylonitrile has been demonstrated to cause cancer in humans (O'Berg, 1980; Werner and Carter, 1981; Delzell and Monson, 1982) and rats; routes of administration for rats include gavage (Bio/Dynamics, 1980c), oral exposure (Beliles *et al*., 1980; Bio/Dynamics, 1980a; Bio/Dynamics, 1980b; Quast *et al*., 1980a; Bigner *et al*. 1987) and inhalation (Maltoni *et al*., 1977; Quast *et al*., 1980b). US EPA (1991) chose to use the O'Berg acrylonitrile occupational exposure study as the basis of derivation of a cancer potency factor for acrylonitrile. This study demonstrated the carcinogenicity of acrylonitrile in a cohort which was sufficiently large and which was followed for an adequate time period. Exposure levels were estimated by representatives of the company employing the study cohort, and a dose-response relationship was observed for the increased cancer risk. This increased risk remained after adjusting for smoking. US EPA (1983) noted that the cancer potency values for acrylonitrile derived from human exposure (O'Berg, 1980) was within one order of magnitude of the cancer potencies derived from rat oral exposure (Bio/Dynamics, 1980a; Bio/Dynamics, 1980b; Quast *et al*., 1980a) and inhalation exposure (Quast *et al*., 1980b) studies.

Methodology

A unit risk (UR) for acrylonitrile was calculated by US EPA (1991) from a relative risk model adjusted for smoking and based on a continuous lifetime equivalent of occupational exposure using the relationship

$$UR = PO\ (R-1) / X = 1.5E\text{-}4/ppb * 0.45\ ppb/\mu g/m^3 = 6.8E\text{-}5\ (\mu g/m^3)^{-1}$$

where: PO = 0.036 = background lifetime probability of death from respiratory cancer
R = 5.0/1.6 = 3.1 = relative risk of respiratory cancer adjusted for smoking (O'Berg, 1980)
X = 500 ppb = continuous equivalent lifetime exposure when 9 years = estimated average exposure duration, and 60 years = estimated maximum possible age at the end of the observation period.

CDHS (1988) reestimated the unit risk factor for acrylonitrile, using the standard lifespan typically assumed by CDHS in risk assessments (70 years) and taking into account the uncertainty in the relative risk estimate. The unit risk was corrected using the following relationship:

$$B^* = B(95) * (70/60)^3$$

where B^* is the unit risk and B(95) is the upper 95% bound on B. This bound was estimated directly by substituting R(95), the upper 95% confidence bound on R, which was found to be 6.6; the second factor $[(70/60)^3]$ was used to extrapolate from a 60 year observation period to a 70 year observation period. The resulting unit risk factor derived was 2.9E-4 $(\mu g/m^3)^{-1}$.

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ALLYL CHLORIDE

CAS No: 107-05-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	76.5
Boiling point	44.96°C
Freezing point	-134.5°C
Vapor pressure	295.5 mm Hg at 20°C
Air concentration conversion	1 ppm = 3.13 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.0 E-6 $(\mu g/m^3)^{-1}$

Slope Factor: 2.1 E-2 $(mg/kg\text{-}day)^{-1}$

[Linearized multistage procedure (GLOBAL82) (US EPA, 1986) fitted to NCI (1977) female mouse forestomach tumor data, body weight scaling, adopted by RCHAS/OEHHA (1994), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

A retrospective cohort mortality study of 1,064 male workers potentially exposed to epichlorohydrin and allyl chloride was conducted by Olsen *et al*. (1994). Study subjects had a minimum of 1 month work experience between 1957-1986 in the production or use of epichlorohydrin and allyl chloride and 1 year total employment duration at Dow Chemical's Texas Operations (Freeport, TX). Job exposure categorization was used to quantify individual exposure based on an evaluation of work practices, production processes and available environmental monitoring data. Vital status follow-up occured through 1989; 66 total deaths were recorded. Standardized mortality ratios (SMR) for all malignant neoplasms or lung cancer were not significantly increased when compared to external (U.S.) or internal (Texas Operations) populations. The authors noted that the study results are limited by the cohort's size, duration of follow-up, relatively few number of observed and expected deaths, and the level of potential epichlorohydrin and allyl chloride exposure.

Animal Studies

Several studies exist on the potential carcinogenicity of allyl chloride in animals; these studies have been reviewed by IARC (1985) and U.S. EPA (1986, 1991).

Male and female $B6C3F_1$ mice and Osborne-Mendel rats (50/group) were exposed to allyl chloride (technical grade; 98% pure) by gavage daily 5 days/week for 78 weeks (NCI, 1977). Exposure groups for mice were initially 172 or 199 mg/kg body weight for males and 129 or 258 mg/kg for

females. Exposure groups for rats were initially 70 or 140 mg/kg body weight for males and 55 or 110 mg/kg for females. Due to toxicity, the initial doses were reduced as the study progressed. Final time-weighted average doses for the 78 week dosing period were 172 and 199 mg/kg/day for male mice; 129 and 258 mg/kg/day for female mice; 57 and 77 mg/kg/day for male rats and 55 and 73 mg/kg/day for female rats. Mice and rats were observed for an additional 13 and 30-33 weeks after the end of the dosing period, respectively. Excessive mortality (50% after 14-38 weeks) was noted in the high-dose rats (both sexes) and male mice. The number of surviving animals in all low-dose groups and high-dose female mice were adequate to evaluate late-developing tumor risk.

No significant increases in tumor incidence were noted in rats. Proliferative nonneoplastic lesions of the stomach were noted in mice of both sexes. In male mice, squamous cell carcinomas of the stomach were found in 0/29 controls (17 vehicle and 12 untreated), 2/36 low-dose animals, and 0/10 high-dose animals (only 10 survived past 52 weeks). In female mice, squamous cell papillomas and carcinomas of the forestomach were found in 0/39 controls (19 vehicle and 20 untreated), 3/47 low-dose animals (2 carcinomas) and 3/45 high-dose animals (no carcinomas). Tumor incidence was not significantly increased compared to controls for either dose group of either sex. However, the combined tumor incidence in females and the carcinoma incidence in low-dose males was significantly increased at both doses compared to historical vehicle controls (1/180 female mice with squamous cell papilloma or carcinoma of the forestomach; 1/180 male mice with squamous cell carcinoma of the forestomach). The authors considered the findings to be strongly suggestive of carcinogenicity in mice because of the rarity of the tumor type involved and because the proliferative lesions demonstrated could be preneoplastic.

Female Ha:ICR Swiss mice (30/group) were exposed to allyl chloride by topical application (31 or 94 mg allyl chloride in 0.2 ml acetone) 3 times/week for 63-85 weeks (Van Duuren *et al*., 1979). Skin tumors were not induced. Lung and stomach papillomas were induced in both the low dose group (3 stomach, 14 lung papillomas) and the high dose group (3 stomach, 12 lung papillomas, 1 glandular stomach adenocarcinoma). Tumor incidences were not significantly increased compared to vehicle or untreated controls (control incidence not reported).

Female Ha:ICR Swiss mice (30/group) received a single dermal application of 94 mg technical grade allyl chloride in 0.2 ml acetone followed 2 weeks later by dermal applications of 5 µg 12-*O*-tetradecanoylphorbol 13-acetate (TPA) 3 times/week for life (median survival 61-82 weeks) (Van Duuren *et al*., 1979). Skin papilloma incidence was significantly increased (7/30 treated animals compared to 6/90 TPA control animals, $p < 0.025$) and time to tumor was decreased (first tumor in treated animals at day 197 compared to day 449 in TPA controls) in allyl chloride -treated animals.

Male and female A/St mice (10/group) received intraperitoneal injections of allyl chloride in tricaprylin 3 times/week for 8 weeks; total doses were 1.2, 2.9 and 5.9 g/kg body weight (Theiss *et al*., 1979). Animals were killed 24 weeks after exposure initiation. The only pathological endpoint examined was the induction of lung tumors as determined by gross examination. The average number of adenomas/mouse (20 animals/group, both sexes combined) was 0.19 ± 0.1, 0.60 ± 0.2, 0.50 ± 0.27 and 0.60 ± 0.15 in the control, low, medium and high-dose groups,

respectively. The incidence of lung adenomas in the high-dose group was significantly increased ($p < 0.05$ by Student's T-test or chi-square test).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NCI (1978) carcinogenicity bioassay demonstrated a statistically significant increased incidence of squamous cell papillomas and carcinomas of the forestomach in low-dose male mice (2/46, $p < 0.029$) and low-dose (3/47; $p < 0.003$) and high-dose (3/45; $p < 0.003$) female mice when compared to tumor incidences in male (1/180) and female (1/180) historical controls. The female mouse tumor incidence data from this study was chosen as the basis of a cancer potency factor because it demonstrated induction of a rare tumor type by allyl chloride in the most sensitive sex of a sensitive species.

Methodology

Transformed doses were calculated as follows:

transformed dose = experimental dose × (5 days/7 days) × (78 weeks/92 weeks)

Animals were dosed 5 days/week, and the duration of exposure and of the experiment were 78 and 92 weeks, respectively. Experimental doses were 129 and 258 mg/kg/day; transformed doses were 78 and 156 mg/kg/day. A linearized multistage procedure (GLOBAL82) was then applied to the tumor incidence data; the resulting unadjusted cancer potency factor (q_1^*) was 1.01 E-3 $(mg/kg/day)^{-1}$. A q_1^* for humans was calculated from the unadjusted q_1^* as follows:

human q_1^* = unadjusted $q_1^* \times (70\ kg/0.025\ kg)^{1/3} \times (104\ weeks/92\ weeks)^3$
= 2.1 E-2 $(mg/kg/day)^{-1}$

The reference human body weight and the average female mouse weight were 70 kg and 0.025 kg, respectively, and the experiment length and the mouse lifespan were 92 weeks and 104 weeks, respectively. A unit risk factor of 6.0 E-6 $(\mu g/m^3)^{-1}$ was derived from the human q_1^* by OEHHA/ATES using an inspiration rate of 20 m^3/day.

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2-AMINOANTHRAQUINONE

CAS No: 117-79-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1994) except where noted)

Molecular weight	223.24
Boiling point	sublimes (IARC, 1982)
Melting point	302 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 9.131 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 9.4 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 3.3 E-2 $(mg/kg\text{-}day)^{-1}$
[Male rat liver tumor data (NCI, 1978), contained in Gold *et al*. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 2-aminoanthraquinone (2-AA) on humans are known to exist.

Animal Studies

Results from the National Cancer Institute (NCI) (1978) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats are tabulated in Gold *et al*. (1984). 2-Aminoanthraquinone (technical grade, unspecified impurities) was administered in feed to groups of 50 male and 50 female animals of each species. Matched control groups were included for each mouse dose group (50 animals/sex/species). Control groups of 50 male and 25 female rats were also included; these animals were observed for 107-109 weeks. Diet fed to mice contained 5000 or 10000 mg/kg 2-AA; diet fed to female rats contained 2000 mg/kg 2-AA. Diet fed to male rats contained 10000 or 20000 mg/kg 2-AA for the first 10 weeks; this was reduced to 2500 or 5000 mg/kg for the remaining 68 weeks. For rats, NCI reported the time-weighted average dietary concentrations to be 0.69% and 0.35% for high and low dose males, and 0.2% for treated females over a 78-week period. An additional observation period of 28-32 weeks was included after treatment ended. High and low dose mice of both sexes were administered time-weighted average dietary concentrations of 1.0% (over 80 weeks) and 0.5% (over 78 weeks) respectively, and were observed for an additional 15-16 weeks after treatment ended.

At study termination, 82, 78, 94 and 86% of male mice and 78, 76, 88 and 76% of female mice were still alive in the low-dose control, high-dose control, low-dose and high-dose groups, respectively. In male rats, 54% of the controls, 64% of low-dose and 70% of high-dose animals

were alive at the end of the study. Insufficient numbers of female rats survived to the latter portion of the experimental period to permit analysis of late-developing tumors.

High-dose male and female mice demonstrated a significantly increased incidence of hepatocellular carcinomas. Tumor incidence in male mice was 12/46 in low-dose controls, 6/48 in high-dose controls, 20/47 in low-dose animals, and 36/49 ($p < 0.001$) in high-dose animals; in female mice, the frequencies were 4/46, 1/50, 5/47 and 12/47 ($p < 0.001$) (NCI, 1978; Murthy *et* al., 1979). A dose-dependent increase in hepatic neoplastic nodules and hepatocellular carcinomas ($p < 0.001$) was noted in 18/41 low-dose and 18/45 high dose males; tumors were observed in 0/36 control male rats.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NCI carcinogenicity bioassay of 2-AA indicated that 2-AA induced tumor formation in both rats and mice. The cancer potency value derived is based on the dose-response data for hepatic tumors in the more sensitive sex and species, the male rat (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. The average dose administered to the male rat high-dose group as calculated by Gold *et al*. (1984) was 102 mg/kg/day. Analysis of the data set using the computer program TOX_RISK (Crump *et al*., 1991) indicated that inclusion of the high dose group resulted in a p-value of = 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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ANILINE

CAS No: 62-53-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	93.12
Boiling point	184-186°C
Melting point	-6.3°C
Vapor pressure	0.67 mm Hg at 25°C
Air concentration conversion	1 ppm = 3.82 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 5.7 E-3 $(mg/kg\text{-}day)^{-1}$
[Derived from a cancer potency factor calculated by US EPA/IRIS (1990, 1994) from male rat primary splenic sarcoma incidence data (CIIT, 1982) using a linearized multistage procedure, extra risk; adopted by CDHS/RCHAS (1990)]

III. CARCINOGENIC EFFECTS

Human Studies

US EPA (1994) reviewed a study that examined the occurrence of bladder tumors in British workers in the chemical dye industry (Case *et al.*, 1954). A group of 4622 men employed for more than 6 months in the United Kingdom chemical industry during the period 1910-1952 were studied. In a subgroup of 1233 men exposed solely to aniline, one death from bladder cancer was observed compared to 0.83 expected from English/Welsh male mortality data. Among the entire group (who had generally been exposed to a number of aromatic amines including napthylamine, benzidine, auramine and aniline; no detailed exposure information was available), 127 deaths from bladder cancer were observed compared to 4.1 expected. The authors concluded that the data provided insufficient evidence to suggest that aniline itself causes bladder tumors.

Animal Studies

Forty-three male and female Osborne-Mendel rats were fed diets containing 330 mg/kg aniline hydrochloride for up to 1032 days (White *et al*., 1948). Hepatomas and splenic sarcomas were noted in 4 and 3 animals, respectively. No control group was included in the study; however, the authors claimed that liver and spleen tumors were rare in the rat strain used in the study.

IARC (1982) reviewed a study by Druckrey (1950) in which rats (random bred, sex unspecified) were exposed to aniline hydrochloride in drinking water (22 mg/rat/day) over their lifetime. Mortality was quite high; 50% mortality occurred at day 450 and 100% mortality at day 750. No tumors were observed in the treated animals; however, only the bladder, liver, spleen and kidney were evaluated for tumors.

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice were fed diets containing aniline hydrochloride for 103 weeks (NCI, 1978). Rats were fed diets containing 0, 3000 or 6000 mg/kg diet aniline hydrochloride; mice were fed diets containing 0, 6000 or 12000 mg/kg diet aniline hydrochloride. Group sizes were 50/sex/group, except for high dose female mice (n = 49), and control rats (25/sex). Surviving rats and mice were sacrificed at 107-108 and 107 weeks, respectively. No significantly increased treatment-related tumor incidences were noted in treated mice. Male rats demonstrated significantly elevated incidences of hemangiosarcomas in the spleen, as well as fibrosarcomas and sarcomas (not otherwise specified) in multiple organs of the body cavity and spleen. There were also significant dose-related trends in the incidence of hemangiosarcomas, sarcomas or fibrosarcomas and malignant pheochromocytomas. For female rats, a dose-related trend was observed in the incidence of fibrosarcomas and sarcomas in the spleen and in multiple organs of the body cavity. No fibrosarcomas, or sarcomas of the spleen or multiple organs of the body cavity were observed in pooled (249 female and 250 male) control animals. Tumor incidence data is listed in Table 1.

Table 1. Aniline hydrochloride-induced tumor incidence data in male and female Fischer 344 rats (NCI, 1978)

Tumor type	Sex	Tumor incidence aniline hydrochloride dietary concentration (mg/kg diet)		
		0	3000	6000
spleen hemangiosarcoma	male	0/25	19/50	20/46
spleen fibrosarcoma/sarcoma NOS	male	0/25	7/50	9/46
multiple organ fibrosarcoma/sarcoma NOS	male	0/25	2/50	9/48
	female	0/24	1/50	7/50
adrenal pheochromocytomas	male	2/24	6/50	12/44

NOS = not otherwise specified

Hagiwara *et al.* (1980) administered aniline in the diet at a concentration of 300 mg/kg diet to 28 male Wistar rats over a period of 80 weeks. An untreated control group of 28 rats was also included. No significant increase in tumor incidences were observed as a result of aniline exposure. However, the treatment group sizes used were relatively small, and the exposure was relatively low and less than lifetime.

Male and female CD-F rats (130/sex/exposure group) were exposed to aniline hydrochloride in the diet for 2 years at exposure levels of 0, 10, 30 and 100 mg/kg body weight/day (CIIT, 1982). An increased incidence of primary splenic sarcomas was noted in the male 100 mg/kg exposure group (high dose group); stromal hyperplasia and fibrosis of the splenic red pulp, a potential sarcoma precursor lesion, was also observed in high dose males, and to a lesser degree, in high dose females. No fibrosarcomas, stromal sarcomas, capsular sarcomas or hemangiosarcomas were noted in female rats. Tumor incidence data is listed in Table 2.

Table 2: Incidence of splenic tumors in male CD-F rats fed diets containing aniline hydrochloride (CIIT, 1982)

Dietary aniline hydrochloride concentration (approximate) (ppm)	Aniline hydrochloride exposure level (mg/kg body weight/day)	Human equivalent dose[1] $(mg/kg/day)^{-1}$	Tumor incidence[2]
0	0	0	0/64
200	10	1.23	0/90
600	30	3.69	1/90
2000	100	12.29	31/90

1. Calculation of the doses included a correction for the difference in molecular weight of aniline and aniline hydrochloride (compound administered) (US EPA, 1992).
2. Tumor incidence includes fibrosarcomas, stromal sarcomas, capsular sarcomas, and hemangiosarcomas as reported by US EPA (1992).

Syrian golden hamsters (15 male and 15 female) received subcutaneous injections of aniline (521 mg/kg body weight; total dose 9219 mg/kg) for 52 weeks (Hecht *et al*., 1983). Although mean survival was reduced in the aniline-treated groups, no increase in tumor incidence was observed. However, the experimental exposure was less than lifetime, and the number of exposed animals was small.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that the value derived from that data set is not appropriate (CDHS, 1985). Male rat spleen tumor data (CIIT, 1982) was used to generate a cancer potency factor for aniline. Male rats in the high-dose group showed a marked increase in the incidence of splenic tumors (see Table 2). US EPA (1994) also noted the presence of stromal hyperplasia and fibrosis of the splenic red pulp in high-dose males and, to a lesser degree, in females; this may represent a precursor lesion of sarcoma.

Methodology

A linearized multistage procedure (US EPA,1980) was used to calculate a slope factor of 5.7 E-3 $(mg/kg\text{-}day)^{-1}$ from the CIIT (1982) male splenic tumor incidence data. Calculation of the transformed doses for aniline included a correction for the difference in molecular weights of aniline and aniline hydrochloride, the form in which the compound was administered in the NCI and CIIT bioassays. Calculation of the unit risk by OEHHA/ATES from the US EPA slope factor assumed a body weight of 70 kg and an inspiration rate of 20 m^3/day.

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ARSENIC (INORGANIC)

CAS No: 7440-38-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	74.92
Boiling point	613 °C (sublimes)
Melting point	817 °C @ 28 atm
Vapor pressure	1 mm Hg at 372 °C
Air concentration conversion	1 ppm = 2.21 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.3 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 1.2 E+1 $(mg/kg\text{-}day)^{-1}$
[Human occupational exposure lung tumor incidence (Enterline *et al.*, 1987a);. relative risk model, adjusted for interaction with tobacco smoking (CDHS, 1990).]

Oral slope factor: 1.5 E+0 $(mg/kg\text{-}day)^{-1}$
[Human skin cancer incidence (Tseng *et al.*, 1968, 1977), time- and dose-related formulation of the multistage procedure (U.S. EPA, 1988).]

III. CARCINOGENIC EFFECTS

Human Studies

Inhalation

Cancer mortality has been studied among workers employed in three major smelters in the U.S., in (1) Tacoma, Washington, (2) Anaconda, Montana, and (3) Garfield, Utah. Smelter workers in Sweden (Ronnskarverken) and in Japan (Sagnoseki-Machi) and cohorts of both miners and smelter workers in China have also been studied.

Enterline and Marsh (1982) and Enterline *et al*. (1987a) examined the longest follow-up period for the Tacoma, Washington cohort. The 1982 report used cumulative doses based on urinary arsenic measurements. Standardized mortality ratios (SMRs) for respiratory cancer ranged from 170 for those receiving the lowest intensity and shortest duration of exposure, to 578 for those with the highest intensity and with 20-29 years duration of exposure. A strong dose-response relationship was evident only when the analysis was limited to the 582 retired workers in the cohort. In the 1987 reanalysis, Enterline and colleagues incorporated newly available historical air sampling data (Enterline *et al*., 1987a); in this study, the dose-response relationship appears more clearly.
The Anaconda, Montana cohort was also the subject of numerous publications. Lee-Feldstein (1983, 1986) divided the 8,045 men of the full study group into nine subcohorts based on arsenic exposure and year of first employment. When considering only those men who had been in their maximum exposure category for at least 12 months, each of the nine subcohorts, except for one

subgroup which had a very small sample size, showed significantly elevated respiratory cancer rates relative to the combined male population of Idaho, Montana and Wyoming (Lee-Feldstein, 1983). Lee-Feldstein (1983) also investigated the association of sulfur dioxide (SO_2) with respiratory cancer in this cohort. Findings from this study could not conclude that arsenic trioxide was the primary environmental agent causing the excessive respiratory cancer seen in the study group.

In another study, Lee-Feldstein (1986) incorporated quantitative exposure estimates based on industrial hygiene data collected between 1943 and 1958. In all but the latest-employed cohort, a statistically significant linear dose-response relationship was observed between arsenic exposure and the directly standardized death rate (DSDR) for respiratory cancer. Lee-Feldstein (1986) reiterated that the latest-employed cohort may not have been followed long enough to display a dose-related mortality pattern, and the men in this cohort may have experienced prior exposures which confound the relationship between arsenic exposure and respiratory cancer mortality. Also, men who were younger at the start of employment were at greater risk for lung cancer than those who began employment later in life. Further analysis of the same cohort by Welch *et al*. (1982) and Higgins *et al*. (1985) confirmed the linear dose-response relationship between exposure and respiratory cancer.

The Garfield, Utah smelter was studied by Rencher *et al*. (1977), who found a three- to five-fold increase in the proportion of deaths due to lung cancer among smelter workers when compared to workers in the mine or concentrator. Similar results were reported by Tokudome and Kuratsune (1976) who studied 839 copper smelter workers in Japan. A dose-response effect on respiratory cancer was observed using either duration of employment or intensity of exposure. For the same duration of employment, risks were greater among those employed in earlier periods.

Workers at the Ronnskarverken smelter in Sweden experienced lung cancer mortality at about five times the rate of residents of the county (Wall, 1980). Pershagen *et al*. (1981) conducted a nested case-control study within this cohort, focusing on the interrelationship of smoking, arsenic and lung cancer. For smokers and nonsmokers, the age-standardized rate ratios (SRRs) were 3.0 and 2.9. Among roaster workers, the most heavily exposed in this plant, the SRRs were 4.4 and 4.5. Exposures were not quantified in this analysis.

Other studies of cancer incidence and mortality among workers at the Ronnskar smelter in Sweden confirmed the excess lung cancer risk (Sandstrom *et al*., 1988; Jarup *et al*., 1989a,b). An analysis of age-adjusted rates by calendar year showed a decline in lung cancer starting in the mid-1970s, possibly due to lower exposures, earlier notification of health problems, and/or changing smoking habits (Sandstrom *et al*., 1988). However, among the most recently hired cohort, lung cancer incidence was greater than expected.

Taylor *et al*. (1989) conducted a case-control study among tin miners in China to examine the relationship between arsenic exposure and lung cancer. After adjusting for tobacco use and radon exposure, the risk of lung cancer for subjects in the highest quartile of arsenic exposure was 22.6-fold higher than for those in the lowest quartile. Duration but not intensity of exposure appeared to be a predictor of lung cancer risk.

Another report from China covers a cohort consisting of workers employed at two copper smelters, one arsenic smelter and a mine (Wu, 1988). Wu reported that nearly 19,000 person-years were followed, resulting in 40 lung cancer deaths.

Enterline *et al*. (1987b) analyzed data from eight smelters with fairly low levels (relative to the Anaconda, Tacoma, and Ronnskar smelters) of arsenic. When data from the six smelters were combined and examined, the results suggested an increasing trend in risk with increasing exposure ($p = 0.06$). A significant effect was observed for cumulative exposure to arsenic and for smoking.

Reports on cancer and insecticide manufacturing exposures to arsenic were by Ott *et al*. (1974), Baetjer *et al*. (1975b; as cited in Mabuchi *et al*., 1979), Mabuchi *et al*. (1979), and Sobel *et al*. (1988). A study of orchardists who potentially sprayed arsenic-containing pesticides is reviewed by Wicklund *et al*. (1988). The report by Mabuchi *et al*. (a more extensive follow-up of the same cohort Baetjer analyzed) found a sharp increase in the lung cancer SMR with increasing duration of employment among those predominantly exposed to arsenic, although no increase was observed for those with exposure to arsenic only. However, more than 99 percent of this latter group were employed for five years or less.

Ott *et al*. (1974) observed a marked increase in respiratory cancer mortality with increasing cumulative dose in workers previously employed in an insecticide manufacturing plant. Sobel *et al*. (1988) updated the study by Ott *et al.* by 9 additional years of follow-up and by tracing more than 99% of those who had been lost to follow-up in the study by Ott *et al*. The 9 follow-up years yielded a non-statistically significant respiratory cancer SMR of 116.

A case-control study of deaths among orchardists (Wicklund *et al*., 1988) found no association between exposures to arsenic-containing pesticides and respiratory cancer, after controlling for smoking.

In summary, for smelter workers, the association between respiratory cancer mortality and arsenic exposure is a consistent, replicable finding of substantial magnitude with a clear dose-response relationship, and high statistical significance. The mortality data on workers employed in the manufacturing of insecticides provide further evidence that arsenic acts as a respiratory tract carcinogen.

Oral

Chronic exposure to high levels of arsenic in drinking water has been identified as increasing skin cancer incidence in humans (US EPA, 1988, 1995).

In a region on the southwest coast of Taiwan, artesian well water with high arsenic concentrations ranging from 0.01-1.82 ppm had been in use for more than 45 years (Tseng *et al*., 1968, 1977). 40,421 inhabitants of 37 villages of the regions were examined for skin lesions, peripheral vascular disorders and cancers. The study identified 7,418 cases of hyperpigmentation, 2,868 of keratosis (Type A/benign), 428 of skin cancer (squamous cell carcinoma, basal cell carcinoma, *in situ* squamous cell carcinoma, and Type B keratoses/intraepidermal carcinomas) and 360 cases of

Blackfoot disease. The incidence rates for keratosis and skin cancer were 183.5 and 10.6/1000, respectively. A control population of 7,500 people did not exhibit any of the above disorders.

The above exposed population was divided into "low", "mid" and "high" exposure groups based upon the well-water arsenic concentration in each village (<0.3, 0.3-0.6, and >0.6 ppm, respectively). A dose-response relationship was identified for the prevalence of skin cancer and Blackfoot disease (no dose-response data was presented for hyperpigmentation and keratosis). The prevalence of both disease was also found to increase with age. Males were found to have higher prevalence rates than females (male to female ratios for skin cancer and Blackfoot disease were 2.9 and 1.3, respectively).

Additional studies of chronic human arsenic exposure resulting in increased skin cancer or internal organ cancer incidence have been identified and reviewed (Fierz, 1965; Borgono and Greiber, 1972; Cebrian *et al*., 1983; Yue-Zhen *et al*., 1985; Chen *et al*., 1985, 1986; reviewed by US EPA, 1988).

Animal Studies

There were two animal inhalation studies on the carcinogenicity of arsenic available at the time the document *Report to the Air Resources Board on Inorganic Arsenic. Part B. Health Effects of Inorganic Arsenic Compounds* was written (CDHS, 1990). Berteau *et al*. (1977, 1978) exposed mice to a respirable aerosol of arsenic(III) (containing approximately 27 mg arsenic(III)/m^3) for 40 minutes/day for 26 days and 20 minutes/day thereafter. Inhaled doses were approximately 1.3 mg arsenic/kg/day and 0.69 mg arsenic/kg/day. No evidence of neoplasia was observed grossly in exposed animals.

In an inhalation study of arsenic trioxide, Glaser *et al*. (1986) exposed 20 rats for 18 months, at approximately 60 µg arsenic/kg/day and 40 rats at approximately 20 µg arsenic/kg/day. No tumors were observed in exposed animals. The report lacked important methodological details, including sampling to verify exposure levels. Also, the study tested fewer animals than required by standard cancer bioassay protocols.

In an arsenic (III) trioxide-treated group of 47 male hamsters, Pershagen *et al*. (1984) found three carcinomas: two of bronchi or lungs (an adenocarcinoma, and an anaplastic carcinoma) and one of larynx or trachea (a squamous cell carcinoma). These carcinomas were not statistically significant when considered in relation to the concurrently treated controls but were statistically significant when considering additional controls from the same colony ($p = 0.01$, one-tailed test). In female hamsters, benign lung tumors (adenomas) were induced by intratracheal instillation of a suspension of solid arsenic trioxide in a phosphate buffer (Ishinishi *et al*., 1983; Ishinishi and Yamamoto, 1983), but Ohyama *et al*. (1988) did not induce lung tumors in male hamsters similarly treated with arsenic trioxide or gallium arsenide.

Arsenic (V) has also induced tumors in animals. Calcium arsenate injected intratracheally induced lung adenomas in male hamsters (Pershagen and Bjorklund, 1985) and leukemia and lymphoma were produced by sodium arsenate by subcutaneous injection in mice (Osswald and Goerttler, 1971).

Among oral studies, only one study reported positive findings. Tumors, including adenocarcinomas of the skin, lung, and lymph nodes, were noted in mice given Fowler's solution (potassium arsenite), but the report lacks experimental details necessary for critical assessment (Knoth, 1966; as reviewed in U.S. EPA, 1984).

Other oral studies reported that arsenite (3 μg arsenic/l in drinking water) reduced the total tumor incidence in male and female white Charles River CD mice (Kanisawa and Schroeder, 1967), and enhanced the growth rate of "spontaneous" (common) mammary tumors in female inbred C3H mice (Schrauzer and Ishmael, 1974; Schrauzer *et al*., 1978).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Inhalation

The International Agency for Research on Cancer (IARC) evaluated arsenic in 1980 and classified "arsenic and arsenic compounds" in Group 1, which includes the "chemicals and groups of chemicals (which) are causally associated with cancer in humans." Ingestion of arsenic is associated with cancer at sites different from those associated with arsenic inhalation: ingestion is associated with skin cancer, while inhalation results in lung neoplasms.

In contrast, arsenic has not conclusively produced carcinogenesis in animals. Arsenic produces tumors in animals, but these tumors are rarely malignant. The few reports of carcinogenic effects of arsenic compounds in animals are seriously flawed. The hypothesis that arsenic may act as a tumor promoter has been tested but not proven in animals.

CDHS (1990) used human data for its cancer risk assessment of arsenic because (1) these data showed a strong, consistent association with increased respiratory cancer in epidemiologic studies, (2) quantitative exposure measurements were made in several of these studies, and (3) clear dose-response relationships were observed. No risk assessment has been conducted using animal data because the cancer bioassays using relevant routes of exposure have been negative and because no adequate inhalation bioassay has been published.

The quantitative cancer risk assessment for arsenic considered data from the occupational mortality studies of smelter workers in Anaconda, Montana by Welch *et al*. (1982), Higgins *et al*. (1985) and Lee-Feldstein (1986), and in Tacoma, Washington by Enterline *et al*. (1987a).

Oral

US EPA (1995) conducted a review of the available literature and identified the studies by Tseng *et al*. (1968, 1977) as the key references for quantifying ingested arsenic cancer potency. US EPA stated that these studies demonstrate a causal association between arsenic ingestion and an elevated risk of skin cancer. These data were considered reliable for the following reasons: 1) the study and control populations (40,421 and 7,500, respectively) were large enough to provide reliable estimates of the skin cancer incidence rates; 2) a statistically significant elevation in skin cancer incidence in the exposed population compared to the control population was observed many years after first exposure; 3) a pronounced skin cancer dose-response by exposure level was demonstrated; 4) the exposed and control populations were similar in occupational and socioeconomic status, with ingestion of arsenic-contaminated drinking water the only apparent difference between the two groups, and 5) over 70% of the observed skin cancer cases were pathologically confirmed.

Methodology

Inhalation

Data from the Anaconda and Tacoma smelters show nonlinear relationships between cumulative dose and the relative risk (or SMR) for death from lung cancer. These dose-response curves are concave downward (their slopes remain positive but decrease as exposure increases). Notwithstanding this observation, the staff of DHS used linear models for this risk assessment. In these models, the dose of arsenic was measured as cumulative $\mu g/m^3$-years; the response was measured as the relative increase in risk over the background (risk ratio). In addition, the models assume that the mechanism of carcinogenesis is a nonthreshold process.

The data from Enterline *et al*. (1987a), Higgins *et al*. (1985), and Lee-Feldstein (1986) were fitted to the model. The regression model used to achieve a linear extrapolation is described by the equation:

$$E[obs_i] = [\alpha + \beta(d_i)] \times Exp_i$$

where $E[\cdot]$ represents the expectation of a random variable, d_i represents the average cumulative dose of arsenic (in $\mu g/m^3$-years) for exposure group i, obs_i represents the observed number of deaths in exposure group i, Exp_i represents the expected number of deaths in group i based on the standard population, α represents the risk ratio predicted for a cumulative dose (d) of zero, and β is the slope parameter (in $[\mu g/m^3\text{-years}]^{-1}$).

To calculate unit risk, the staff of DHS selected the MLE (maximum likelihood estimate) slope and upper 95% confidence limit (UCL) based on use of the four lowest exposure groups from the Enterline *et al*. (1987a) analysis.
A risk assessment was also conducted using an adjustment for the strong interaction between arsenic and smoking observed in several occupational cohorts. The prevalence of smoking was independent of the level of arsenic exposure in the Anaconda cohort (Welch *et al*., 1982), but may have been higher than in the general population. Also, there appeared to be no reason for smokers

to be distributed differently among the exposure levels in the Tacoma cohort, hence smoking was assumed to be independent of arsenic exposure in this cohort as well.

Each dose-specific crude SMR was adjusted taking the low-dose SMR in each study as the baseline. Next, a nonsmokers' SMR and a smokers' SMR were derived. From the nonsmokers' SMR, observed and expected deaths among nonsmokers were inferred. Finally, a regression model was fitted to the inferred nonsmokers' data to find the slope of the line relating cumulative arsenic dose to excess relative risk. This procedure was applied to the data of Enterline *et al.* (1987a) under the assumption that the interaction between smoking and arsenic varies as a function of dose, and that the joint effects at low doses are multiplicative.

The MLE for β was 2.30×10^{-4} using the data on nonsmokers from the study by Enterline *et al.* (1987a). An 95% UCL was estimated and used in evaluating unit risks.

Risks were evaluated separately by sex and for four smoking categories: never, former, light (< 1 pack/day) and heavy smokers. Unit risks for these categories range from 400 to 8,400 per million persons, with upper bounds ranging from 630 to 13,000 per million.

The staff of DHS recommended that the range of risk for ambient exposures to arsenic be based on the 95% UCL predicted from fitting a linear model to the human data adjusted for interaction with smoking. The staff of DHS further recommended that the overall unit risk, 3.3×10^{-3} per $\mu g/m^3$, be considered the best estimate of the upper bound of risk.

Oral

A generalized multistage procedure with both linear and quadratic dose assumptions was used to predict the prevalence of skin cancer as a function of arsenic concentration in drinking water (d) and age (t), assuming exposure to a constant dose rate since birth. F(t,d) represents the probability of developing skin cancer by age t after lifetime exposure to arsenic concentration d. The procedure used is expressed as follows: $F(t,d) = 1 - \exp[-g(d)\, H(t)]$, where g(d) is a polynomial in dose with non-negative coefficients, and H(t) is $(t-w)^k$, where k is any positive real number, and $t > w$ for induction time w. The cancer potency calculation was based on skin cancer incidence data for Taiwanese males (Tseng *et al*., 1968) because their skin cancer prevalence rates were higher than the females studied. The calculation was also based on several assumptions listed below.

1. The mortality rate was equal for both diseased (skin cancer) and nondiseased persons.

2. The population composition (with respect to skin cancer risk factors) remained constant over time, implying that there was no cohort effect.
3. Skin cancers were not surgically removed from diseased persons.

The population at risk was classified into 4 age groups (0-19, 20-39, 40-59 and ≥ 60 years of age) and three dose groups (0 - 0.3, 0.3 - 0.6 and > 0.6 ppm drinking water arsenic concentration) for males and females separately from the reported prevalence rates (Tseng *et al*., 1968, 1977) as percentages. The assumption was made that the Taiwanese persons had a constant arsenic exposure from birth, and that males and females consumed 3.5 L and 2 L drinking water/day,

respectively. The multistage procedure was used to predict dose-specific and age-specific skin cancer prevalence rates associated with ingestion of inorganic arsenic. Both linear and quadratic model fitting of the data were conducted. The maximum likelihood estimate (MLE) of skin cancer risk for a 70 kg person drinking 2 L of water/day, adjusted for U.S. population survivorship by life-table analysis, ranged from 1 E-3 to 2 E-3 for an arsenic intake of 1 µg/kg/day. Expressed as a single value, the cancer unit risk for drinking water is 5 E-5 $(\mu g/L)^{-1}$; the corresponding cancer potency value is 1.5 E-0 $(mg/kg/day)^{-1}$.

V. REFERENCES

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ASBESTOS

CAS No: 1332-21-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1998) except as noted)

Molecular weight	not applicable
Boiling point	decomposes
Melting point	decomposes at 600ºC (NIOSH, 1994)
Vapor pressure	not applicable
Air concentration conversion	not applicable

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.3 E-2 $(\mu g/m^3)^{-1}$ [1.9 E-4 (100 PCM fibers/m^3)$^{-1}$; see Appendix D]
Slope Factor: 2.2 E+2 $(mg/kg\text{-}day)^{-1}$
[Human occupational asbestos lung tumor and mesothelioma incidence data, excess relative risk model (CDHS, 1986).]

III. CARCINOGENIC EFFECTS

Human Studies

Asbestos has been consistently demonstrated to be carcinogenic in humans and is recognized as a human carcinogen by the International Agency for Research on Cancer (IARC, 1977; NRC, 1984; Ontario Royal Commission, 1984). In occupational cohort mortality studies, exposure to the three principal commercial forms of asbestos – chrysotile, amosite, and crocidolite – has been repeatedly linked with increased risks for lung cancer, mesothelioma and, to a lesser extent, other neoplasm, particularly gastrointestinal and laryngeal cancer (IARC, 1977; NRC, 1984). Occupational exposure to anthophyllite has been associated with an increased risk for lung cancer. Cigarette smoking acts synergistically with occupational exposure to asbestos in increasing the risk of lung cancer, but not mesothelioma (Hammond *et al.*, 1979; NRC, 1974).

Tremolite and actinolite are often contaminants of other ores and have not been extensively studied with respect to their biological effects in humans.

The epidemiologic studies on asbestos are extensive. These have been reviewed by the Consumer Product Safety Commission (1983), the National Academy of Sciences (NRC, 1984), Nicholson (1985), and the Ontario Royal Commission (1984). The relevant studies used in deriving the cancer risk for asbestos are summarized in the tables below.

Table 1: Summary of epidemiologic studies used in quantitative risk assessment for lung cancer.

Study	Cohort Occupation	Fiber type	Sex	Cohort Number	F/U	Lung Cancer Mortality		
						Exp	Obs	SMR
Finkelstein, (1983)	asbestos cement manufacturing	chrysotile, crocidolite	M	241	1963-80	3.3	20	606
Selikoff *et al*., (1979)	insulation	chrysotile, amosite	M	17,800	1967-76	93.7	390	416
Seidman *et al*., (1979)	insulation manufacturing	amosite	M	820	1961-76	21.9	83	380
Dement *et al*. (1982; 1983a-b)	textile products manufacturing	chrysotile	M	1,261	1940-75	9.8	33	336
Henderson and Enterline (1979)	asbestos manufacturing	chrysotile, amosite, crocidolite	M	1,075	1941-73	23.3	63	270
Newhouse and Berry (1979)	asbestos products manufacturing	chrysotile, amosite, crocidolite	M	4,600	1936-75	43.2	103	238
Newhouse and Berry (1979)	asbestos products manufacturing	chrysotile, amosite, crocidolite	F	922	1936-75	3.2	27	843
Nicholson *et al*. (1979)	mining	chrysotile	M	544	1961-77	11.1	25	225
Peto (1977; 1980)	textile products manufacturing	chrysotile	M	822	1933-74	22.9	49	214
McDonald *et al*. (1984)	friction products	chrysotile	M	3,177	1938-77	49.1	73	1149
Weill *et al*. (1979)	asbestos cement manufacturing	chrysotile, crocidolite	M	5,645	1940-74	49.2	51	104
Berry and Newhouse (1983)	friction products	chrysotile, crocidolite	M	7,474	1942-80	139.5	143	103
Berry and Newhouse (1983)	friction products	chrysotile, crocidolite	F	3,708	1942-80	11.3	6	50
Rubino *et al*. (1980)	mining	chrysotile	M	952	1946-75	8.7	9	103
McDonald *et al*. (1980)	mining	chrysotile	M	9,767	1926-75	184	230	125

F/U = Follow-up, Exp = Expected, Obs = Observed, SMR = Standard Mortality Ratio

Table 2. Summary of epidemiologic studies used in quantitative risk assessment for mesothelioma

Study	Cohort Occupation	Fiber type	Cohort Number	Sex	F/U	No. Mesotheliomas	
						Pleural	Peritoneal
Selikoff *et al*. (1979)	Insulation	Chrysotile, Amosite	17,800	M	1967-76	63	112
Peto (1980)	Textile manufacturing.	Chrysotile	822	M	1933-74	9	0
Seidman *et al*. (1979)	Insulation manufacturing.	Amosite	820	M	1961-76	7	7
Finkelstein (1983)	Asbestos Cement manufacturing.	Chrysotile, Crocidolite	241	M	1963-80	6	5

F/U = Follow-up

Animal Studies

Many studies using laboratory animals have been conducted to investigate the carcinogenic potential of various forms of asbestos administered by inhalation, by ingestion (in food or drinking water), and via intraperitoneal and intrapleural injection or deposition. The animal studies have been reviewed by Condie (1983), NRC (1984), and Nicholson (1985).

Gross *et al*. (1967) exposed male rats to airborne chrysotile to a mean concentration of 86 mg/m^3, 30 hours/week for their lifetime and found that a large number of treated animals developed malignant lung tumors (24/72; adenocarcinomas, squamous cell carcinomas and fibrosarcomas, compared to 0/39 for controls) and one developed mesothelioma. Reeves *et al*. (1971) exposed rats, rabbits, mice and hamsters to amosite, crocidolite or chrysotile at a concentration of approximately 48 mg/m^3, 16 hours/week for up to two years. No lung tumors were reported in control or treated hamsters, mice or rabbits. Lung tumors were found in 2/31 rats exposed to crocidolite; no lung tumors were reported for the controls or other fiber exposure groups. In a similar study, Reeves *et al*. (1974) found that gerbils, guinea pigs, hamsters and rabbits exposed to amosite, crocidolite or chrysotile at a concentration of approximately 49 mg/m^3, 16 hours/week for up to two years did not develop lung tumors. Lung tumor incidences in rats exposed to chrysotile, amosite or crocidolite were 3/43, 4/46 and 3/36, respectively; no lung tumors were noted in the 12 controls. Lung tumors were noted in the chrysotile-exposed mice (2/18), but this incidence was not significantly increased compared to controls (1/6).

Wagner *et al*. (1974) compared the carcinogenic effect of five different Union Internationale contre le Cancer (UICC) asbestos samples, amosite, anthophyllite, crocidolite, chrysotile (Canadian), and chrysotile (Rhodesian). Exposure varied from 9.7 to 14.7 mg/m^3 from one day to 24 months, although all animals were followed for their lifetimes. Malignant lung tumors (adenocarcinoma and squamous cell carcinoma) were found in rats from all five asbestos exposure groups (11/146, 16/145, 16/141, 17/137, and 30/144, for the respective fiber types). All but the group exposed to Rhodesian chrysotile had at least one animal demonstrating a mesothelioma. Davis *et al*. (1978) exposed rats to chrysotile (2 or 10 mg/m^3), crocidolite (5 or 10 mg/m^3), or amosite (10 mg/m^3).

Twenty percent (8/40) of the animals exposed to 10 mg/m^3 chrysotile developed malignant lung tumors. One out of 40 animals exposed to the low concentration of chrysotile (2 mg/m^3) developed a peritoneal mesothelioma. Neither amosite nor crocidolite induced malignant lung tumors in the rats.

Several long-term ingestion studies have been conducted on asbestos. Cunningham *et al*. (1977) and Gross *et al*. (1974) fed diets containing chrysotile to rats. Neither study indicated that ingested chrysotile induced an increased incidence of intestinal tumors. Smith *et al*. (1980) reported that amosite given to male and female hamsters via their drinking water did not significantly increase the incidence of cancer. In a lifetime rat feeding study using a diet containing 10% chrysotile, there was some evidence of penetration of asbestos into the colonic mucosa and possible cytotoxicity to the colonic tissues (Donham *et al*., 1980). McConnell *et al*. (1983a, b) reported on a number of studies conducted by the National Toxicology Program (NTP) in which hamsters and rats were fed diets containing different types of asbestos. These studies were generally negative; however, NTP (1985) stated that there was some evidence of carcinogenicity in male rats exposed to intermediate-range (size) chrysotile asbestos as indicated by an increased incidence of adenomatous polyps in the large intestine.

A number of studies have shown that intrapleural administration of asbestos results in the development of mesothelioma (Donna, 1970; Reeves *et al*., 1971; Pylev and Shabad, 1973; Shabad *et al*., 1974; Smith and Hubert, 1974). Chrysotile, amosite, anthophyllite, and crocidolite have all induced mesothelioma when administered intrapleurally to rats, rabbits, and/or hamsters.
Wagner *et al*. (1973) demonstrated a dose-response relationship between the amount of asbestos (superfine chrysotile or crocidolite) administered intraperitoneally and incidence of mesothelioma in treated rats. Stanton and Wrench (1972) showed that commercial asbestos fibers as well as glass and other mineral fibers implanted onto the pleural surface of rats were able to induce formation of mesotheliomas.

Maltoni and Annoseia (1974) found that intraperitoneal injection of crocidolite into Sprague-Dawley rats resulted in over 60% developing mesothelial tumors. Pott and Friedrichs (1972) and Pott *et al*. (1976) reported that several commercial varieties of asbestos, as well as other fibrous materials, induced peritoneal mesotheliomas in mice and rats injected intraperitoneally.

In summary, the animal studies clearly indicated that asbestos is carcinogenic in a variety of species when administered by inhalation or directly into the peritoneum or pleural space. Results of bioassays where asbestos was ingested are inconclusive.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The IARC and US EPA carcinogen classifications for asbestos are 1 and A, respectively – that is, a known human carcinogen. Ample data exists indicating that asbestos induces lung tumors and mesotheliomas in both humans and animals. In cases where both human and animal cancer data exist for a substance and both are suitable for quantitative risk assessment, use of the human data

is preferred by OEHHA. The cancer quantitative risk assessment of asbestos was therefore based on human occupational lung cancer and mesothelioma incidence data, since both posed potential population risks at ambient concentrations of asbestos.

Methodology

The CDHS (1986) risk assessment relies extensively on work done by the Consumer Product Safety Commission (1983), the National Academy of Sciences (NRC, 1984), Nicholson (1985), and the Ontario Royal Commission (1984). As with these risk assessments, the DHS risk assessment on asbestos was based exclusively on the results of occupational epidemiologic studies.

Animal bioassay data were excluded from this analysis as there are numerous epidemiologic studies of populations occupationally exposed to asbestos, which contain or have been supplemented with exposure data adequate for purposes of quantitative risk assessment.

DHS adapted linear models developed and/or used in the work cited above to estimate risks of mesothelioma and lung cancer to the general population. The models extrapolate risks observed in numerous occupationally exposed cohorts to lower levels of asbestos found in the general environment. In this case the range of extrapolation was four to five orders of magnitude. Results are presented below.

Table 3: Estimated lifetime risks of lung cancer and mesothelioma due to continuous exposure to 0.0001 fibers/cm^3 of asbestos (expressed as cases per million population)

Exposure Group	Lung Cancer	Mesothelioma
Male Smokers	11 (110)	24 (120)
Female Smokers	5 (50)	32 (160)
Male Nonsmokers	2 (15)	32 (160)
Female Nonsmokers	1 (6)	38 (190)

Numbers in parentheses represent approximate upper 95% confidence limits.

The use of excess lung cancer lifetime risk values between 11 and 110 per million for 0.0001 fibers/cm^3***** of asbestos exposure were recommended. (*****Fiber/cm^3 = asbestos fibers ≥ 5μm in length, ≥ 0.3 μm in width, with a length/width ratios of ≥ 3:1. Such fiber counts can be converted to total fibers measurable by transmission electron microscopy (TEM) by multiplying by 100 to 1,000. Therefore, 0.0001 (PCM) fibers/cm^3 = 0.01 to 0.1 TEM fibers/cm^3 = 10,000 to 100,000 TEM fibers/m^3.) For mesothelioma, recommended lifetime risk values are between 18 and 190 per million for each 0.0001 fibers/cm^3***** of asbestos exposure. These recommendations are based on best estimates and approximate upper confidence limits for the groups theoretically at highest risk for lung cancer and mesothelioma: male smokers and female nonsmokers, respectively. The above values represent theoretical lifetime risk of cancer assuming continuous average daily exposure to 0.0001 fibers/cm^3***** throughout life.

These fibers can be measured by phase contrast microscopy (PCM) and for historical reasons represent the basis for all recent asbestos risk assessments. The unit risk factor selected for asbestos is 1.9 E-4 (100 PCM fibers/m^3)$^{-1}$ and in units of μg/m^3, 6.3 E-2(μg/m^3)$^{-1}$. This was based on mesothelioma in female nonsmokers. The original TAC unit risk value has been converted

using a factor of 0.003 µg asbestos = 100 asbestos fibers which has been derived from information published by U.S. EPA (1985) (see Appendix D). The number of asbestos fibers associated with a given mass of asbestos can vary appreciably. Also, U.S. EPA (1985) has stated that this conversion factor is the geometric mean of measured relationships between optical fiber counts and mass airborne chrysotile in several published studies. The range of the conversion factor between the different studies is large (0.0005 - 0.015 µg asbestos/100 asbestos fibers) and carries with it an appreciable uncertainty. Use of the unit risk factor listed in the asbestos TAC document [1.9 E-4(100PCM fibers/m^3)$^{-1}$], wherever possible, will result in a more precise risk estimation.

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BENZENE

CAS No: 71-43-2

I. PHYSICAL AND CHEMICAL PROPERTIES (from HSDB, 1998)

Molecular weight	78.1
Boiling point	80.1° C
Melting point	5.5° C
Vapor pressure	100 mm Hg @ 26.1° C
Air concentration conversion	1 ppm = 3.2 mg/m^3 @ 25° C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor	2.9 E-5 $(\mu g/m^3)^{-1}$
Slope Factor	1.0 E-1 $(mg/kg\text{-}day)^{-1}$

[Human occupational exposure leukemia incidence (Rinsky *et al.*, 1981); excess risk calculated using a Weighted Cumulative Exposure/relative risk procedure (CDHS, 1984).]

III. CARCINOGENIC EFFECTS

Human Studies

Case studies of workers exposed to benzene were responsible for generating the hypothesis that benzene causes leukemia in humans. Epidemiological studies performed to test the hypothesis supported the causal nature of the benzene-leukemia association. A summary of some of the more salient features from 23 major epidemiologic studies are shown in Table 1.

Table 1: Epidemiologic studies of carcinogenicity in humans.

Study	Population Studied	Duration	Results[1]
Tabershaw Cooper Assoc. (1974)	petroleum industry workers		Increase in rate of lymphomas (NS)
Thorpe (1974)	petroleum industry workers	1962-1972	Leukemia SMR=121 (NS) (SMR in worker controls = 60)
Aksoy *et al*. (1974, 1976)	Shoemakers exposed to 210-650 ppm benzene	1967-1975	Annualized crude rate of acute leukemia 2-fold greater than expected
McMichael *et al*. (1976)	rubber industry workers		Excess in mortality from: chronic lymphatic leukemia, myelogenous leukemia, lymphosarcoma
Vigliani (1976)	patients with benzene hemopathy; exposures estimated at 200-500 ppm	1942-1975 1959-1974	Leukemia incidence: 11/66 13/135 Estimated relative risk (RR)=20

Table 1 (continued): Epidemiologic studies of carcinogenicity in humans.

Study	Population Studied	Duration	Results[1]
Infante *et al*. (1977)	748 rubber industry workers followed to 7/75		1940-1949: 7 cases of myeloid/monocytic leukemia SMR=506 (U.S. white males) SMR=474 (worker controls)
Ott *et al*. (1978)	benzene workers (Dow); 594 workers followed to 1973	1938-1970	2 deaths from anemia (one pernicious, one aplastic); 3 deaths from leukemia. Mortality results NS but leukemia rates exceed expectation ($p < 0.05$)
Fishbeck *et al*. (1978)	10 chemical workers exposed to benzene	1953-1963	Changes in blood but '… no persisting significant adverse health effects.'
Brandt *et al*. (1978)	case-control study of 50 acute non-lymphocytic leukemia	1969-1977	History of exposure to petroleum products among cases.
Vianna and Polan (1979)	workers in NY State exposed to benzene		RR=2.1 lymphosarcoma RR=1.6 reticulum cell sarcoma RR=1.6 Hodgkin's Disease For workers > 45 years old, the observed number of cases was SS greater than the expected number.
Greene *et al*. (1979)	U.S. Gov't Printing Office workers		Higher proportion of deaths from multiple myeloma, leukemia, and Hodgkin's disease related to exposure to benzene (SS).
Linos *et al*. (1980)	case-control study of 138 leukemics		4 cases found, 3 were chronic lymphocytic leukemia. RR = 3.3 (NS)
Schottenfeld *et al*. (1981)	worker cancer registry compiled by API		Incidence of lymphocytic leukemia & multiple myeloma increased (SS).
Rushton and Alderson (1981)	petroleum refinery workers		Risk of leukemia increased 2-fold in high and medium benzene exposed vs. low exposed ($p = 0.05$).
Rinsky *et al*. (1981)	continuation of follow-up of Infante study		SMR=560 leukemia SMR=2100 leukemia in workers with 5 or more years exposure.
Thomas *et al*. (1982)	refinery workers		SMRs for multiple myeloma and other lymphomas elevated (SS)
Hanis *et al*. (1982)	refinery and chemical workers		SMR for cancer of the lymphopoietic tissues elevated but NS.
Decoufle *et al*. (1983)	chemical plant workers; 259 men followed through 1977	1960-1974	SMR=377 (SS) L & H SMR=682 (SS) leukemia
Tsai *et al*. (1983)	454 refinery workers		No deaths observed from L & H cancer; 0.42 expected (NS).
Arp *et al*. (1983)	rubber industry workers		For lymphocytic leukemia: RR=4.5 (NS) benzene exposure RR=4.5 (NS) other solvent exposure
Environmental Health Associates (Wong *et al*., 1983)	chemical workers	1946-1975	SMRs elevated (NS) for L & H cancer, leukemia, non-Hodgkin's lymphoma; RR=3.2 (SS) L & H cancer (vs. worker control). Dose-response trend found, SMRs for lung cancer and several other cancers elevated (NS)

[1] NS = not statistically significant; SS = statistically significant ($p < 0.05$)
SMR = standardized mortality ratio; L & H = lymphocytic and hematopoietic cancer

Animal Studies

Available experimental data prior to 1976 has been summarized by Maltoni *et al.* (1983). These earlier studies did not provide evidence for carcinogenicity in animals. Since then two significant series of bioassay studies have been reported, those of Maltoni *et al.* (1983) and the National Toxicology Program (NTP, 1983).

In a series of oral studies, reported by Maltoni *et al.* (1983), rats were administered benzene via gavage tube. Male and female Sprague-Dawley rats were administered benzene at 0, 50 or 250 mg/kg benzene in olive oil, 4 to 5 times per week, for 52 weeks. Dose-related increases were observed for Zymbal gland carcinoma in the female rats only. In Sprague-Dawley rats administered 0 and 500 mg/kg benzene in olive oil, 4 to 5 times per week for 104 weeks significant increases relative to controls were reported for Zymbal gland carcinoma (males and females), and oral cavity carcinoma (males and females).

Maltoni *et al.* (1983) also chronically exposed pregnant Sprague-Dawley rats (breeders) and their offspring to high concentrations of benzene using a complex dosing regimen. Exposure concentrations ranged from 200 to 300 ppm. Among the breeders, a slight increase (not significant) in the incidences of Zymbal gland carcinoma and mammary tumors were reported. Among offspring, significant increased incidences in Zymbal gland tumors and non-significant increases in cancers of oral and nasal cavity, mammary gland and liver were reported. Selected study data are listed in Table 2.

Table 2: Maltoni *et al.* (1983) benzene rat bioassay summary

Organ (Site)	Tumor Type	Route of Exposure	Sex	Dose (mg/kg-day)	Cochran-Armitage Linear Trend Test	Fisher Exact Test	Difference in Cancer Attack Rate per 100 (Dose-Control)
Zymbal gland	carcinomas	gavage[1]	F		$p < 0.001$		
				13.9	----	$p = 0.25$	6.7
				66.7	----	$p = 0.003$	25.0
Hemolympho -reticular	'leukemias'	gavage[1]	M		$p = 0.005$		
				13.9	----	$p = 1.0$	0.0
				66.7	----	$p = 0.078$	12.1
Mammary	carcinomas	gavage[1]	F		$p = 0.091$		
				13.9	----	$p = 0.5$	3.3
				66.7	----	$p = 0.178$	11.9
Zymbal gland	carcinomas	gavage[2]	F	321.4	N/A (single dose level)	$p = 0.007$	15.0
	carcinomas	gavage[2]	M, F	321.4		$p < 0.001$	14.0
Oral Cavity	carcinomas	gavage[2]	M	321.4	N/A (single dose level)	$p = 0.003$	17.5
	carcinomas	gavage[2]	M, F	321.4		$p < 0.001$	13.7
Zymbal gland	carcinomas	inhalation[3]	F	17	N/A (single dose level)	$p = 0.27$	3.9

Table 2 (continued): Maltoni *et al.* (1983) benzene rat bioassay summary.

Organ (Site)	Tumor Type	Route of Exposure	Sex	Dose (mg/kg-day)	Cochran-Armitage Linear Trend Test	Fisher Exact Test	Difference in Cancer Attack Rate per 100 (Dose-Control)
Zymbal gland	carcinomas	inhalation[4]	M, F	16.4	N/A (single dose level)	$p = 0.002$	5.1
Liver	hepatomas	inhalation[5]	F	1.42	N/A (single dose level)	$p = 0.022$	5.1

Source: CDHS (1984) TAC document. Results of Maltoni *et al.* (1983) studies.

[1]Experiment 1: (#BT901), animals dosed for 52 weeks.
[2]Experiment 2: (#BT902), 92-week interim results, dosing to be carried out for 104 weeks, 118-week interim results.
[3]Experiment 3: (#BT4004), inhalation exposure of 13-week old breeder rats for 104 weeks, 118-week interim results.
[4]Experiment 4: (#BT4004), inhalation exposure of 12-day old embryos for 104 weeks. Dose *in utero* not considered, 118-week interim results.
[5]Experiment 5: (#BT4006), inhalation exposure of 12-day old embryos for 15-weeks. Dose *in utero* not considered, 118 week interim results.

The National Toxicology Program (NTP, 1983) conducted a 2-year bioassay on the carcinogenic effects of oral (gavage) exposure to benzene in F344 rats and B6C3F$_1$ mice. Female rats and mice were administered benzene in corn oil at doses of 0, 25, 50, and 100 mg/kg, 5 days/week, for 103 weeks. Male rats and mice were administered benzene at doses of 0, 50, 100, and 200 mg/kg, 5 days/week for 103 weeks. In F344 rats, statistically significant dose-related increases in the incidences of neoplasms were reported for the oral cavity (males and females), Zymbal gland (males and females), uterus (females) and skin (males). In B6C3F$_1$ mice, statistically significant dose-related increases in the incidences of tumors were reported for the Zymbal gland (males and females), ovary (females), mammary gland (females), Harderian gland (males and females), lung (males and females), preputial gland (males) and for lymphoma/leukemia combined (males and females). Selected study data are listed in Table 3.

Table 3: Summary of NTP bioassay results for significant neoplasms[1,2].

Organ (site)	Tumor Type	Species	Sex	Cochran-Armitage Trend Test	Fisher Exact Test	Difference in Cancer Attack Rate per 100 (High Dose - Control)
Zymbal gland	squamous cell carcinoma	rat	M	$p < 0.001$	$p < 0.001$	30
		rat	F	$p < 0.001$	$p < 0.001$	28
		mouse	M	$p < 0.001$	$p < 0.001$	43
		mouse	F	$p = 0.022$	$p = 0.121$	6
Skin	squamous cell carcinoma	rat	M	$p = 0.007$	$p = 0.003$	16
		mouse	M	$p = 0.028$	$p = 0.121$	6
Lip	squamous cell carcinoma	rat	M	$p = 0.012$	$p = 0.003$	16
Tongue	squamous cell carcinoma	rat	M	$p = 0.078$	$p = 0.059$	8
		rat	F	$p = 0.078$	$p = 0.059$	8
Oral cavity	squamous cell carcinoma	rat	M	$p = 0.006$	$p = 0.006$	14
		rat	F	$p = 0.011$	$p = 0.028$	10
Hematopoietic system	malignant lymphomas or leukemia	mouse	M	$p = 0.006$	$p = 0.005$	23
Lung	alveolar/bronchiolar carcinoma	mouse	M	$p = 0.028$	$p = 0.020$	19
		mouse	F	$p = 0.021$	$p = 0.013$	12
Preputial gland	all carcinomas	mouse	M	$p < 0.001$	$p < 0.001$	63
Mammary gland	carcinomas	mouse	F	$p < 0.001$	$p < 0.001$	20
	carcinosarcoma	mouse	F	$p = 0.006$	$p = 0.059$	8
Harderian gland	adenoma or carcinoma	mouse	M	$p = 0.001$	$p < 0.001$	27
	carcinoma	mouse	F	$p = 0.004$	$p = 0.059$	8
Ovary	granulosa cell tumor or carcinoma	mouse	F	$p = 0.003$	$p = 0.017$	15

[1]Source: CDHS (1984) TAC document. Results of NTP gavage study (NTP, 1983).
[2]Comparison of highest dose group with control. Mice of both sexes and female rats were administered 71.4 mg/kg-day by gavage, male rats were administered 143 mg/kg-day.

In summary, benzene has been shown to be carcinogenic in animal studies either by inhalation or oral routes of administration. Cancer was observed at multiple sites in these studies.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

CDHS (1984) used both animal and human data for this quantitative risk assessment. The cancer potency estimates based on animal data were obtained from data on Zymbal gland carcinomas in rats exposed via inhalation or gavage by Maltoni *et al.* (1983); and Zymbal gland carcinomas, preputial gland carcinomas, and lymphoma or leukemia in male mice or mammary carcinomas in female mice exposed by gavage by the National Toxicology Program (NTP, 1983). The epidemiological studies analyzed were those of leukemia in workers exposed to benzene via inhalation reported by Infante *et al.* (1984), Rinsky *et al.* (1981), Aksoy *et al.* (1974; 1976), Aksoy (1977), and Ott *et al.* (1978).

Methodology

A summary of the calculated low-dose risk assessments from a number of animal and human studies is shown in Table 4. The epidemiological data were analyzed using a linear nonthreshold model to estimate risk. The animal data were analyzed by fitting a linearized multistage procedure to dose-response data from the animal cancer bioassays. The results of the U.S. EPA's Carcinogen Assessment Group (CAG) epidemiologic-based assessments are also included in the table for comparative purposes (U.S. EPA, 1979).

CDHS (1984) recommended that cancer potency values in the range of 24 to 170 × 10^{-6} per ppb (i.e., 0.024 to 0.17/ppm) be used in estimating risks from low level exposure to benzene. Slightly higher upper bound values were obtained when shortened survival times in the studies analyzed were taken into account. Assuming that humans breathe 20 m^3 per day and weigh 70 kg and that an air concentration of 1 ppm benzene is equivalent to 3.25 mg/m^3, the CDHS range of potency values is equivalent to 0.03 to 0.2 $(mg/kg\text{-}day)^{-1}$.

In 1988, CDHS (under Proposition 65) recommended that the potency value of 0.1 $(mg/kg\text{-}day)^{-1}$ [unit risk = 2.9 × 10^{-5} $(\mu g/m^3)^{-1}$] be used to estimate risk specific intake levels from exposure to benzene. This value falls within the range of estimates derived by CDHS (1984) and the U.S. EPA (1979, 1985), and is the upper 95% confidence bound estimate from the analysis of human data considered most credible by the U.S. EPA.

Subsequent to the development of the benzene TAC cancer unit risk value, OEHHA described new benzene occupational exposure cancer epidemiology data in the 2001 Public Health Goal (PHG) for Benzene in Drinking Water document (OEHHA, 2001)

Yin *et al*. (1987) reported on a large retrospective cohort study of benzene-exposed workers in China. The study examined 28,460 exposed workers from 233 factories and 28,257 control workers from different industries. Thirty leukemia cases were identified (23 acute, 7 chronic) in the exposed workers compared with four cases in the unexposed controls (SMR 574, $p < 0.01$). Exposure estimates from grab-samples taken at the time of the survey ranged from 3 to 313 ppm with the majority of exposures in the range of 16 to 157 ppm.

A number of detailed reports describing further study and analysis of the Chinese Worker Cohort have been published. Yin *et al*. (1994) reported that the cohort had been expanded to include 74,828 benzene-exposed workers (since 1949) and 35,805 controls from 712 factories located in 12 Chinese cities. Dosemeci *et al*. (1994) described the exposure assessment methods. Quantitative estimates of benzene exposure took into account job title and assignment to individual work units, and reflected exposures of individual workers. Li *et al*. (1994) investigated gender differences in hematopoietic and lymphoproliferative disorders and other cancers among the benzene-exposed cohort. No statistically significant differences in cancer mortality were observed for males versus females, although the number of cases for most endpoints was small.

Travis *et al*. (1994) reported on the hematopoietic malignancies and other blood disorders in the benzene-exposure workers in China. Eighty-two hematopoietic neoplasms and related disorders were observed, including 32 cases of acute leukemia, seven cases of myelodysplastic syndromes,

nine cases of chronic granulocytic leukemia, 20 cases of malignant lymphoma, and nine cases of aplastic anemia. In the control workers, 13 hematological malignancies were observed, including six leukemias. Yin *et al*. (1996) reported the overall cancer findings among the expanded benzene-exposed and control worker cohorts. An increased incidence in the benzene-exposed group compared to controls was observed for leukemia (RR 2.6, 95 percent CI = 1.3 to 5.0), malignant lymphoma (RR 3.5, 95 percent CI = 1.2 to 14.9), and lung cancer deaths (RR 1.4, 95 percent CI = 1.0 to 2.0). Among leukemia cases, incidence of acute myelogenous leukemia was increased in the benzene-exposed group (RR 3.1, 95 percent CI = 1.2 to 10.7). Significant increases were also reported for aplastic anemia and myelodysplastic syndromes.

The best upper-bound estimates of leukemia risk resulting from continuous lifetime air exposures of the general population to benzene in the benzene PHG document (OEHHA, 2001) were similar for the U.S. rubber workers (0.044 ppm^{-1}), the Chinese workers (0.056 ppm^{-1}), and for the mean of the two studies combined (0.050 ppm^{-1}). The three lifetime risk estimates all convert to a population-based cancer potency of 0.1 $(mg/kg\text{-}d)^{-1}$ for oral exposures after rounding, which can be scaled to 0.05 $(mg/kg\text{-}d)^{-1}$ for inhalation exposures. These values are similar to the TAC benzene cancer potency value of 0.1 $(mg/kg\text{-}d)^{-1}$.

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Table 4: Summary of benzene low-dose risk assessments.

Study	Route of Exposure	Lifetime[a] TWA Dosage	Tumor Type	Species	Sex	Type of Analysis	Multi-Stage Model for Human Equivalent Cancer Risk/ppb Benzene
NTP (1983)	Gavage	17.9 mg/kg-day[b]	Zymbal gland carcinomas	Mouse	M	Crude Attack Rate	MLE: 7.4×10^{-6} 95% UCL: 34×10^{-6}
						Lifetable Adj. Rate	MLE: 6.9×10^{-6} 95% UCL: 47×10^{-6}
NTP (1983)	Gavage	17.9 mg/kg-day[b]	Preputial gland carcinomas	Mouse	M	Crude Attack Rate	MLE: 78×10^{-6} 95% UCL: 170×10^{-6}
						Lifetable Adj. Rate	MLE: 140×10^{-6} 95% UCL: 340×10^{-6}
NTP (1983)	Gavage	17.9 mg/kg-day[b]	Lymphoma or Leukemia	Mouse	M	Crude Attack Rate	MLE: 49×10^{-6} 95% UCL: 81×10^{-6}
						Lifetable Adj. Rate	MLE: 170×10^{-6} 95% UCL: 230×10^{-6}
NTP (1983)	Gavage	17.9 mg/kg-day[b]	Mammary carcinomas	Mouse	F	Crude Attack Rate	MLE: 32×10^{-6} 95% UCL: 57×10^{-6}
						Lifetable Adj. Rate	MLE: 61×10^{-6} 95% UCL: 92×10^{-6}
Maltoni *et al*. (1983)	Gavage	13.9 mg/kg-day[c]	Zymbal gland carcinomas	Rat	F	Crude Attack Rate	MLE: 26×10^{-6} 95% UCL: 42×10^{-6}
Maltoni *et al*. (1983)	Inhalation[d]	16.45 mg/kg-day[e]	Zymbal gland carcinomas	Rat	M, F	Crude Attack Rate	MLE: 6.4×10^{-6} 95% UCL: 12×10^{-6}
Infante *et al*. (1977)	Inhalation	2.81 ppm[f] (2.99 mg/kg-day)	Leukemia (Myelocytic or Monocytic)	Human	M	Fatal Tumor Life Table	15×10^{-6}
Rinsky *et al*. (1981)	Inhalation	2.81 ppm[f] (2.99 mg/kg-day)	Leukemia (Myelocytic or Monocytic)	Human	M	Fatal Tumor Life Table	48×10^{-6}
Askoy *et al*. (1974, 1976,1977)	Inhalation	4.22 ppm[f] (4.49 mg/kg-day)	Leukemia	Human	M	Fatal Tumor	20×10^{-6}
Ott *et al*. (1978)	Inhalation	0.171 ppm[f] (0.182 mg/kg-day)	Leukemia	Human	M	Fatal Tumor	46×10^{-6}
CAG (US EPA, 1979)	Inhalation		Leukemia	Human	M	Fatal Tumor	24×10^{-6}

Assumptions: 60 kg person, human inhalation at 20 m^3/day. MLE = Maximum likelihood estimate. 95% UCL = 95% upper confidence limit on risk for provided dose.

[a] Dosages provided without scaling factors.

[b] Lowest dose used in three dose risk assessment, Cochran-Armitage linear trend test for these tumors: preputial gland, $p < 0.001$; Zymbal gland, $p < 0.001$; lymphoma or leukemia, $p = 0.035$; mammary carcinoma, $p < 0.001$.

[c] Lowest dose used in two point risk assessment, Cochran-Armitage linear trend test for these tumors, $p < 0.001$.

Table 4 (continued): Summary of benzene low-dose risk assessments.

[d] Pregnant Sprague-Dawley rats from the twelfth day of pregnancy at a concentration of 200 ppm, 4 hours/day, 5 days/week to delivery, then offspring assumed to be exposed to 200-300 ppm 4-7 hours/day, 5 days/week for 104 weeks. Exposure *in utero* not calculated for total lifetime dosage.
[e] Provided for comparative purposes.
[f] Estimated lifetime dosage by the U.S. EPA-CAG (US EPA, 1979)

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BENZIDINE

CAS No: 92-87-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	184.2
Boiling point	402°C
Melting point	115-120°C
Vapor pressure	0.0005 mm Hg
Air concentration conversion	1 ppm = 7.53 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.4 E-1 $(\mu g/m^3)^{-1}$
Slope Factor: 5.0 E+2 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Case *et al.* (1954) examined mortality among British chemical workers exposed to benzidine. Among the population examined (total number not specified), ten deaths were certified as due to bladder cancer. The death rate from bladder cancer in the male Welsh and English population predicts 0.72 deaths from this cause, giving a standard mortality ratio of 13.9 (10/0.72, $p < 0.001$). Non-fatal bladder cancers were also noted among the exposed population.

Mancuso and El-Atar (1967) examined the incidence of urinary tract cancer among 639 male employees of an Ohio plant where benzidine and β-naphthylamine were made, with potential exposure occurring between 1938 and 1939. Six cases of bladder cancer occurred among white workers, giving a population incidence of 204 per 10^5. The expected incidence of bladder cancer among Ohio white males is 4.4 per 10^5. The authors do not present the significance of the change in incidence because of exposure of workers to other compounds.

Zavon *et al.* (1973) conducted a prospective study of workers exposed to benzidine during its manufacture. The authors report on the health surveillance of all 25 employees of a chemical plant who were exposed to benzidine from 3 to 28 years (1930-1958). During the 13 year follow-up period (1957-1970), 11 cases of transitional cell bladder cancer and 2 cases of benign bladder tumors developed. Among the workers with bladder cancers,

two also developed kidney carcinomas and one a benign tumor of the kidney. No background tumor incidences were reported. The average exposure duration for workers with tumors was 13.6 years, whereas the average exposure duration for those without tumors was 8.9 years. Levels of urinary benzidine were measured at the beginning of the follow-up period of the study, with samples taken at the beginning and end of the work day and at the before the work week began. Mean levels were reported to be ~0.01 mg/l before shift, ~0.04 mg/l after shift, and ~0.004 mg/l Monday morning. Quantitative estimates of exposure have been based on these levels. Exposure conditions at the time of the sampling were reported to be representative of conditions in the previous years of plant operation. Air sampling at different locations in the chemical plant showed benzidine concentrations ranged from <0.007 to 17.6 mg/m^3. Potential confounding variables in the study include smoking and exposure to other carcinogens in the work environment such as β-naphthylamine, o-toluidine, and dichlorobenzidine.

Tsuchiya *et al.*(1975) report on the incidence of bladder cancer among 1303 Japanese workers employed in benzidine production or use. Among workers involved in the manufacture of benzidine 61/542 developed bladder cancer. Among workers involved in benzidine use, 11/761 developed bladder cancer. Exposure levels to benzidine and population background incidence of bladder cancer in the Japanese population were not provided in the study. A statistically significant difference in bladder cancer incidence was observed between workers involved in benzidine production versus those involved in benzidine use ($p < 10^{-10}$, Fisher's exact test).

Meigs *et al.* (1986) conducted a 30-year follow-up study of 597 male workers at a benzidine manufacturing plant in Connecticut. Workers were categorized based upon time of employment, but benzidine levels were not quantitated. Among workers in the high exposure category (> 2 years of employment) 6/105 developed bladder cancer. Among workers in the medium (6 mo.-2 yrs.) and low (1 day-6 mo.) exposure categories, 1/147 and 0/345 developed bladder cancer, respectively. Connecticut cancer statistics predict 1.77 cases of bladder cancer in an unexposed population of 597 people. A significant difference in incidence between high exposure workers and unexposed populations was found ($p < 0.003$).

Animal Studies

Saffioti *et al.*(1967) exposed Syrian Golden hamsters (30/sex/group) for life to 0 or 1000 ppm benzidine or benzidine dihydrochloride in feed, and examined them for evidence of liver tumors. Among animals treated with benzidine, 19/22 males and 6/26 females developed cholangiomatous liver tumors (none in controls). Among animals treated with benzidine dihydrochloride, 10/20 males and 12/27 females developed cholangiomatous liver tumors (none in controls). Liver tumor incidence was found to be significantly elevated in exposed animals in each group ($p < 0.001$, Fisher's exact test).

Griswold *et al* .(1968) treated female Sprague-Dawley rats with benzidine by oral gavage. Animals received 1.2 or 2.5 mg/dose (10 animals/group) or 3.5 or 5 mg/dose (20 animals/group) every 3 days, with a total of 10 administrations. After 9 months, surviving

animals were examined for tumors. Increased incidence of mammary carcinoma was found in benzidine treated groups, with 5/10, 7/9, and 4/5 showing tumors in the 1.2, 2.5, and 5 mg dose groups, respectively, versus 3/127 in control animals. There were no survivors among the animals receiving 3.5 mg benzidine. Miakawa and Yoshida (1975) fed female dd strain mice (50/group) diet containing either 0 or 0.2% benzidine for 280 days. Hepatocellular carcinomas were identified in 11 of 32 mice surviving 140 days or more, whereas no hepatocellular carcinomas were reported among control mice. The significance level of the difference in incidence was $p < 0.001$ by Fisher's exact test.

Littlefield *et al.*(1984) exposed male and female F_1 generation mice (BALB/c males × C57BL females) to benzidine in drinking water for life (~33 months). Mice from a cross of F_1 generation males and females were also exposed as above . Exposure levels and incidence of hepatocellular carcinomas are presented in Table 1. Significant differences in the incidence of hepatocellular carcinoma were observed in all exposed groups ($p < 0.05$, Fisher's exact test). Frith *et al.* (1980) also exposed F_1 and F_2 generation mice (BALB/c males × C57BL/6 females) to 30-400 ppm benzidine dihydrochloride in drinking water for 40, 60, or 80 weeks at which time animals were sacrificed. As in the Littlefield *et al*. (1984) study, animals showed a dose-dependent increase in hepatocellular carcinoma incidence. This effect was also shown to be dependent upon duration of exposure.

Table 1. Incidence of hepatocellular carcinoma in F_1 and F_2 generation mice (BALB/c × C57BL) exposed to benzidine in drinking water (Littlefield *et al*., 1984).

hepatocellular carinoma incidence					
males			Females		
exposure level (ppm)	F_1	F_2	exposure level (ppm)	F_1	F_2
0	14/125	17/123	0	3/124	10/125
30	24/119	20/118	20	51/120	54/119
40	30/96	20/95	30	52/95	43/95
60	32/71	23/72	40	45/72	31/71
80	35/71	24/71	60	55/71	37/72
120	61/71	37/71	80	60/69	51/69
160	49/71	32/71	120	64/72	56/72

Vesselinovitch *et al.* (1975) treated male $B6C3F_1$ mice with feed containing 150 ppm benzidine dihydrochloride from weeks 6 to 45 of life. Groups of 50 mice thus treated were sacrificed at 45, 60, 75, or 90 weeks and examined for liver tumors. Hepatoma incidence was reported to be 8/50, 20/50, 31/50, and 35/50, respectively, at successive sacrifice times, while only one hepatoma was found among 98 control animals sacrificed at 90 weeks ($p < 0.001$; Fisher's exact test). Among the animals with hepatomas, the incidence of hepatocellular carcinoma was 2/50, 5/50, 14/50, and 24/50, respectively, at the successive sacrifice times.

Two other feeding studies have been conducted. Boyland *et al.* (1954) found cases of hepatocellular carcinoma in rats fed diet containing 0.017% benzidine or benzidine plus

tryptophan for life. Inadequate study size, data on controls and poor survival, however, limit the usefulness of this study. Marhold *et al.* (1968) found no tumors in lifetime benzidine feeding study, but poor survival also limits the study's value.

Zabezhinski (1970) exposed 48 albino rats (male and female numbers not specified) to 10-20 mg/m^3 benzidine aerosol for 4 hours/day, 5 days/week for 20 months. Among animals surviving at 13 months, 5/28 developed leukemia (0/21 untreated; p =0.052)
Tumors have also been observed in animals injected subcutaneously with benzidine. They include hepatocellular carcinomas, Zymbal gland tumors and injection-site tumors (Spitz *et al*., 1950; Bonser *et al*, 1956; Pliss, 1964; Prokofjeva, 1971). Intraperitoneal injection of benzidine resulted in the induction of mammary tumors in a single study (Morton *et al*, 1981).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The data presented by Zavon *et al.* (1973) are the only human cancer data appropriate for the development of a cancer potency value for benzidine. The US EPA (1986, 1987, 1988), Allen *et al.* (1987), and CDHS (1988) have each provided estimates of cancer potency based on human data. However, different assumptions made in the calculation of exposure levels has resulted in different estimates of the cancer potency. Potencies derived in these studies assume that cancer risk is proportional to cumulative exposure. Previously, IARC (1982) had suggested that benzidine cancer risk be based on the assumption that the empirical distribution of cumulative incidence rate is a function of the duration of continual exposure. Derivations of cancer potencies from the human data using these different methodologies and exposure assessments are described in the *Methodology* section below.

Cancer potency values have also been derived from animal studies, in particular those of Griswold *et al*. (1968), Miakawa and Yoshida (1975), Saffioti *et al* (1967), and Littlefield *et al*. (1984). Resulting potency estimates were well below those derived from the human data, suggesting humans may be more sensitive to the carcinogenic effects of benzidine, and therefore animal data are not appropriate for use in the establishing a cancer potency value. CDHS has based its benzidine cancer potency value on the human data of Zavon *et al*. (1973) using exposure level assessment modifications of Allen *et al.* (1987) and the methodology of US EPA (1986, 1987, 1988).

Methodology

US EPA (1986, 1987, 1988) made exposure estimates from the Zavon *et al.* study (1973) based upon reported mean urinary concentrations of 0.04 mg/l. Assuming that average body weight is 70 kg, average urinary output is 1.2 l/day, and 1.45% of absorbed benzidine is excreted in the urine, US EPA calculated the average daily dose to be 0.047 mg/kg-day. Adjusting this value for work time exposure, with 11.46 years the average time exposed,

56.5 years the average age of the cohort, and 240 work days per year, final lifetime exposure levels were calculated to be 0.0063 mg/kg-day.

US EPA (1986,1987, 1988) based estimates of cancer potency on the following relationship where p(t) is the probability of developing a tumor in a study of cohort of average age t at the end of the follow-up period (56.5 years) and an average lifespan t_L (71.3 years), exposed to dose level d (0.0063 mg/kg-day), and assuming that background tumor incidence is negligible:

$$\text{cancer potency} = \frac{-\ln(1 - p(t))}{(d)(\frac{t}{t_L})^3}$$

With this model, US EPA used total tumor incidence (13/25, both benign and malignant) in its calculation, giving a final potency value of 234 $(mg/kg\text{-}day)^{-1}$ (See Table 2). Using the upper 95% confidence bound on the tumor incidence (0.68 vs. 0.52) resulted in a cancer potency value of 363 $(mg/kg\text{-}day)^{-1}$.

Using mean urine benzidine concentrations reported at the beginning (0.01 mg/l) and end (0.04 mg/l) of the work day, Allen *et al.* (1987) adjusted benzidine exposure estimates on the assumption of linear increases in urine concentration during the workday and first-order decay during non-work hours. The resulting average urine concentration during workdays was 0.023 mg/l. Based on assumptions that 1.5% of the inhaled benzidine is present in the urine (100% absorption), urinary output is 1.5 l/day, breathing rate is 10 m^3/8-hour work day, and average exposure time of the cohort is 11.24 years, Allen *et al.* (1987) estimated average cumulative dose to be 2.59 mg-yrs/m^3.

Allen *et al.* (1987) calculated potency using this dose value and the malignant tumor incidence only [p(t) = 11/25 = 0.44] with a background tumor incidence factor (α = 0.002; NIH, 1981) and without using a time adjustment factor. That is:

$$\text{cancer potency} = \frac{-\ln [1 - p(t)] + \alpha}{d}$$

The resulting estimate of cancer potency from work place exposure was 0.22 $(mg{\cdot}yrs/m^3)^{-1}$. with upper and lower 90% confidence bounds of 0.81 and 0.045 $(mg{\cdot}yrs/m^3)^{-1}$. Cancer potency from continuous lifetime exposure was calculated by assuming 240 workdays of a 365 day year and 10 of 20 m^3/day total air breathed during the workday. Potencies thus expressed are 0.67 $(mg\text{-}yr/m^3)^{-1}$ with upper and lower confidence bounds of 2.5 and 0.14 $(mg\text{-}yr/m^3)^{-1}$. Assumptions of 70 kg body weight, 70 yr lifespan, and 20 m^3/day breathing rate (CDHS, 1988) result in a cancer potency of 160 $(mg/kg\text{-}day)^{-1}$ with upper and lower 90% confidence bounds of 600 and 30 $(mg/kg\text{-}day)^{-1}$.

An estimate of cancer potency was also made based on a description of cumulative risk described by IARC (1982) (CDHS, 1988). IARC (1982) describe risk based on the assumption that the risk varies linearly with the duration of exposure. IARC (1982) report

the data from Zavon *et al.* (1973) show a cumulative bladder tumor incidence of 25% among workers exposed to benzidine for 15 years. Under such an assumption, cancer potency (B) from lifetime (t_L = 70 yrs) exposure can be based on the following relationship, where $C(t_1)$ is the experimentally derived cumulative tumor incidence (25%) and $d(t_1)$ is the average daily dose at time t_1 (15 years):

$$B = [C(t_1)/d(t_1)] \times [(t_L/t_1)^k]$$

The factor k describes the relationship of time of exposure to potency, in this case k=1 because of the assumption of linear proportionality. From this relationship, CDHS (1988) derived a cancer potency value. Using the average daily dosing derived by Allen *et al.* (0.023 mg/kg-day) and the cumulative incidence data described by IARC (1982), the calculated cancer potency was 50 $(mg/kg\text{-}day)^{-1}$ with upper and lower 95% confidence bounds of 130 and 16 $(mg/kg\text{-}day)^{-1}$ derived from the confidence bounds of the dose.

CDHS (1988) considers the Allen *et al* .(1987) estimation of daily urine concentration of 0.023 mg/l to be the most useful for establishing exposure levels. Assuming 1.5 ℓ/day urinary output, 70 kg body weight, 240 work days per year, and average duration of exposure 11.46 yrs in a cohort of 56.5 yrs average age, lifetime average exposure is 0.0044 mg/kg-day. Using the US EPA (1986, 1987, 1988) methodology and the upper 95% confidence bound on incidence [p(t) = 0.68], the cancer potency is 5.0 E+2 $(mg/kg\text{-}day)^{-1}$.

A unit risk factor of 0.14 $(\mu g/m^3)^{-1}$ was derived by OEHHA/ATES assuming a breathing rate of 20 m^3/day, 70 kg body weight, and 100% fractional absorption of inhaled benzidine.

Table 2. Benzidine cancer potencies derived from Zavon *et al.* (1973).

Source of methodology	Potency $[(mg/kg\text{-}day)^{-1}]$	Upper 95% confidence bound $[(mg/kg\text{-}day)^{-1}]$
US EPA (1986, 1987, 1988)	234	363
Allen *et al*.(1987)	160	600
IARC (1982)*	50	130
CDHS (1988)		500

*Estimate based on IARC methodology using the dosage estimation of Allen *et al.* (1987).

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BENZO[*a*]PYRENE

CAS No: 50-32-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	252.3
Boiling point	360° C
Melting point	179° C
Vapor pressure	1 mm Hg at 20° C
Air concentration conversion	1 ppm = 10.3 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor:		1.1 E-3 $(ug/m^3)^{-1}$
Slope Factor:	(inhalation)	3.9 E+0 $(mg/kg\text{-}day)^{-1}$
	(oral)	1.2 E+1 $(mg/kg\text{-}day)^{-1}$

[Inhalation: male hamster respiratory tract tumor incidence (Thyssen *et al.*, 1981), unit risk calculated using a linearized multistage procedure (OEHHA, 1993). Oral: male and female gastric tumor (papillomas and squamous cell carcinomas) incidence (Neal and Rigdon, 1967), cancer potency factor calculated using a linearized multistage procedure (OEHHA, 1993).]

III. CARCINOGENIC EFFECTS

Human Studies

The predominant sources of airborne benzo[*a*]pyrene (BaP) are combustion processes. Thus, this compound rarely enters the environment alone but rather is associated with additional PAHs and other components frequently present in both vapor phase and particulate form. Available epidemiological information, therefore, is from persons exposed to mixtures such as tobacco smoke, diesel exhaust, air pollutants, synthetic fuels, or other similar materials. Several IARC publications have been dedicated to the analysis of cancer in processes which involve exposure to polynuclear aromatic compounds (PAHs) (IARC, 1983; 1984a; 1984b; 1985; 1987). The types of cancer reported are often consistent with the exposure pathway: scrotal cancer and lung cancer in chimney sweeps exposed to soot; skin cancer (including scrotal cancer) where shale oils are used; and lung cancer where airborne exposure of PAHs occurs, such as in iron and steel foundries.

Shamsuddin and Gan (1988) examined several human tissues collected at surgery or autopsy using rabbit high-specificity antibody to benzo[*a*]pyrene diol epoxide (BPDE)-DNA adducts and light immunocytochemistry. Antigenicity was detected in the lung, ovary, placenta, uterine cervix, and white blood cells. Their results indicated that the tissue concentration of adducts varies substantially in the human population and that BPDE-DNA adducts can be detected in human tissues by immunochemical techniques.

Five of twelve human lung samples obtained at surgery, from smokers or former smokers, showed positive antigenicity for BPDE-DNA adducts (Garner *et al.*, 1988). Higher DNA-adduct levels were detected in the white blood cells of Finnish iron workers with jobs in high PAH exposure areas than in the white blood cells of workers with jobs in low PAH exposure areas (Perera *et al.*, 1988; Hemminki *et al.*, 1990). Workers were classified as high, medium, or low BaP exposure and there was a highly significant correlation between BaP exposure and DNA-adduct levels (Reddy *et al.*, 1991). A similar observation was noted by Ovrebo *et al.* (1992) in a study of workers exposed around coke ovens. Perera *et al.* (1993) extended the technique and found that PAH adducts were higher in an industrialized area in winter than both in a more rural area in winter and in the same urban area in summer (when less burning of fuel would occur).

In studies looking at PAH-derived adducts bound to serum protein, higher levels of PAH-albumin adducts were found in foundry workers and in roofers than in their respective reference groups (Lee *et al.*, 1991). Smokers had higher levels of BaP-derived adducts bound to serum protein than non-smokers, and workers in high BaP exposure areas (foundry) had two to three times the levels of workers in low exposure areas (Sherson *et al.*, 1990).

Studies with human placental tissues have shown that aryl hydrocarbon hydroxylase (AHH) activity is several times higher in smokers than non-smokers and that this activity increases in a sigmoidal manner with increased numbers of cigarettes smoked (Gurtoo *et al.*, 1983). Genetic factors probably contribute to this variability and, ultimately, to susceptibility of individuals to tumor development (Manchester and Jacoby, 1984).

Animal Studies

BaP is carcinogenic by intratracheal, inhalation, and dermal exposure, by intraperitoneal injection, and when given in the diet.

(a) Inhalation and Intratracheal Exposures

Early experiments by Saffiotti *et al.* (1968) indicated that PAHs are at least weakly carcinogenic to the respiratory tract. A mixture of BaP (3 mg) and Fe_2O_3 (hematite, 0.25 μm) (3 mg) in a saline suspension was administered to Syrian golden hamsters by intratracheal instillation, once per week for 15 weeks. Most surviving animals receiving BaP plus Fe_2O_3 developed tumors of the respiratory tract (mostly bronchogenic carcinoma) whereas control animals receiving Fe_2O_3 only or those receiving no treatment did not develop tumors.

Subsequently, Saffiotti *et al.* (1972) determined the carcinogenic dose-response relationship after intratracheal instillation of a suspension of BaP and Fe_2O_3 in male and female Syrian golden hamsters. Test materials were administered once weekly for 30 weeks at 2.0, 1.0, 0.5, and 0.25 mg BaP/animal and an equivalent weight of Fe_2O_3 (hematite) as particulate carrier. Tumors were not present in animals receiving ferric oxide or in untreated controls. Respiratory tract tumors (including squamous cell carcinomas of

the larynx, of the trachea, and of the bronchi, adenocarcinomas of the bronchi, and adenomas of the bronchi and of the bronchioles and alveoli) developed in all groups of BaP/Fe_2O_3 treated animals. The response was dose related.

In another experiment, Feron *et al.* (1973) gave male Syrian golden hamsters intratracheal doses of 0, 0.0625, 0.125, 0.5, or 1 mg BaP weekly for 52 weeks. A variety of tumors were produced throughout the respiratory tract, including bronchoalveolar adenomas and carcinomas.

Thyssen *et al.* (1980) conducted an inhalation study in which male Syrian golden hamsters were exposed to BaP condensation aerosol (in 0.1% saline; particle size ranging from 0.2 to 1.5 μm) for 10 to 16 weeks at a concentration of 9.8 to 44.8 mg BaP/m^3. Neoplastic changes in the respiratory tract were not seen.

In a subsequent experiment, Thyssen *et al.* (1981) exposed male Syrian golden hamsters to BaP condensed onto sodium chloride particles at BaP concentrations of 2.2, 9.5, and 46.5 mg BaP/m^3. Tumors were not observed in the respiratory tract of the unexposed control group or the group that received 2.2 mg/m^3. The incidence of tumors in this organ system increased in a dose dependent manner for the 9.5 and 46.5 mg/m^3 exposure groups. Papillomas, papillary polyps, and squamous cell carcinomas were seen in the nasal cavity, larynx, trachea, pharynx, esophagus, and forestomach. Lung tumors were absent.

(b) Feeding Studies

Feeding of pelletized chow containing BaP (50 to 250 ppm BaP for 4 to 6 months) to male and female CFW mice caused gastric tumors (papillomas and squamous cell carcinomas), pulmonary adenomas, and leukemia (Rigdon and Neal, 1966; 1969; Neal and Rigdon, 1967). The pulmonary adenomas, gastric tumors, and leukemia occurred independently of each other (Rigdon and Neal, 1969). The overall data strongly suggest a positive carcinogenic effect since there were no gastric tumors in 289 control mice while 178 out of 454 mice fed various levels of BaP had gastric tumors (Neal and Rigdon, 1967).

(c) Dermal Application

BaP has been shown to be carcinogenic by dermal application (ATSDR, 1990). Wynder and associates demonstrated a positive dose-response relationship for BaP-induction of skin tumors in Swiss and in C57BL mice and showed a tumor response at doses as low as 0.001% BaP applied topically in acetone every 2 weeks for up to 2 years (Wynder and Hoffmann, 1959; Wynder *et al.*, 1957; 1960). In addition, incidences of 95% for papillomas and carcinomas of the skin were obtained by chronic administration (3 times weekly for 1 year) of 0.001% BaP to the skin of Swiss mice (Wynder and Hoffman, 1959). Extensive experiments conducted by Conney and associates demonstrated the tumor initiating activity of BaP and several of its epoxide and hydroxy derivatives (summarized by US EPA, 1979 and by Conney, 1982).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

A very large number of experiments have demonstrated that BaP causes tumors at several sites, by several routes of administration, in both sexes, and in several animal species. Many studies, however, are very limited in scope or in data reported and are not suitable for risk assessment (Zeise and Crouch, 1984).

OEHHA guidelines prescribe that risk assessment use the most sensitive sex, site, and species where a significant increase in cancer incidence is observed (CDHS, 1985). Since there is no adequate information regarding the carcinogenicity of BaP to humans from epidemiological studies, data from animal bioassays were extrapolated to estimate human cancer risk. Potency estimates were derived by OEHHA (1993) from gastric tumors (papillomas and squamous cell carcinomas) observed in male and female mice due to feeding of BaP (Neal and Rigdon, 1967), respiratory tract tumors in hamsters from the inhalation bioassay of Thyssen *et al.* (1981), and from data obtained after intratracheal administration of BaP (Saffiotti *et al.*, 1972; Feron *et al.*, 1973). The dose-response data from these studies are presented in Tables 1-4 below.

Table 1: Gastric tumors in mice from feeding benzo[*a*]pyrene[a].

Exposure (ppm)	Calculated daily dose (mg/kg-day) (animal)	Incidence of gastric tumors
0	0	0/289
1	0.078	0/25
10	0.781	0/24
20	1.563	1/23
30	2.344	0/37
40	3.126	1/40
45	3.516	4/40
50	3.908	24/34
100	7.815	19/23
250	19.538	66/73

[a]Source: OEHHA (1993). Adapted from Neal and Rigdon (1967) and US EPA (1984).

Table 2: Respiratory tract tumors in hamsters from benzo[*a*]pyrene inhalation[a]

Exposure (mg/m^3)	Hamster dose (mg/kg-day)		Tumor incidence
	based on U.S EPA (1994)	based on US EPA (1988)	
0	0	0	0/27
2.2	0.089	0.152	0/27
9.5	0.385	0.655	9/26
46.5			13/25[b]

[a]Source: OEHHA (1993). Adapted from Thyssen *et al*. (1981) and US EPA (1984)
[b]These data were not used due to shortened lifespan of the hamsters in the exposure group. The carcinogenic response, however, is apparent.

Table 3: Respiratory tract tumors from intratracheal instillation of benzo[*a*]pyrene in hamsters – 30 week exposure[a].

Weekly Dose (mg)	Average Daily Dose (mg)	Lifetime Adjusted Daily Dose (mg/kg-day)	Human Equivalent Dose (mg/kg-day)	Tumor Incidence (Males)	Tumor Incidence (Females)
0	0	0	0	0/47	0/45
0.25	0.036	0.119	0.013	6/47	4/41
0.5	0.071	0.239	0.027	10/33	9/30
1.0	0.143	0.477	0.054	22/33	20/34
2.0	0.286	0.953	0.107	17/28	17/29[b]

[a]Source: OEHHA (1993). Adapted from Saffiotti *et al.*, 1972.
[b]Data group was not used since exposure started 7 weeks after other groups.

Table 4: Bronchoalveolar tumors from intratracheal instillation of benzo[*a*]pyrene in hamsters – 52 week exposure[a].

Weekly dose (mg)	Average daily dose (mg)	Lifetime adjusted daily dose (mg/kg-day)	Human equivalent dose (mg/kg-day)	Tumor incidence
0	0	0	0	0/29
0.0625	0.009	0.0495	0.0059	1/30
0.125	0.018	0.0989	0.0118	4/30
0.25	0.036	0.198	0.0237	6/30
0.5	0.071	0.395	0.0473	17/30
1.0	0.143	0.791	0.0947	19/30

[a]Source: OEHHA (1993). Adapted from Feron *et al.*, 1973.

Methodology

Cancer risk associated with exposure to ambient levels of BaP was estimated by extrapolating from the experimental data to ambient levels by means of the best fitting linearized multistage procedure GLOBAL86 (Howe *et al.*, 1986). In addition, other models were fit to the data for comparison. In its risk assessment, the US EPA used the data for stomach tumors from oral exposure to BaP in mice and the data for respiratory tract tumors from inhalation exposure in hamsters to estimate cancer potency and unit risks associated with exposure to BaP (US EPA, 1984).

For BaP there is compelling evidence that it is genotoxic and an initiator of tumorigenesis. Therefore, OEHHA staff treated BaP-induced carcinogenesis as a nonthreshold phenomenon and, as such, applied a nonthreshold, linear extrapolation model for cancer potency estimation.

The linearized multistage model was fit to the respiratory tract tumor data resulting from inhalation exposure of hamsters to BaP (OEHHA, 1993; Thyssen *et al.*, 1981). The data from the highest dose group were not used since these animals had an appreciably shortened lifespan (59 weeks versus 96 weeks in other groups) (Thyssen *et al.*, 1981; US EPA, 1984). By considering the conditions of exposure given in the report and using an inhalation rate of 0.063 m^3/day and a "standard" body weight of 0.12 kg for hamsters (US EPA, 1988), a dose of BaP in mg/kg-day was estimated. A q_1^* (animal) equal to 0.43 $(mg/kg\text{-}day)^{-1}$ is obtained. Multiplying by the interspecies surface area correction factor of $(70/0.1)^{1/3}$ yields a human equivalent $q_1^* = 1.1 \times 10^{-3}$ $(\mu g/m^3)^{-1}$ for inhalation.

Because of the limited amount of data currently available for risk assessment of BaP, the inhalation unit risk of 1.1×10^{-3} $(\mu g/m^3)^{-1}$ based on respiratory tract tumors in hamsters is used as a best value for inhalation exposures. For exposures to BaP by other routes, the potency of 11.5 $(mg/kg\text{-}day)^{-1}$ based on gastric tract tumors in mice can be used (Neal and Rigdon, 1967).

Cancer Potency for Other PAHs

IARC (1987; 1989) has classified a number of PAHs, their mixtures and derivatives, as carcinogens (Group 1, Groups 2A and Group 2B) and a large number of PAHs into Group 3, a class of chemicals for which there are no human data but limited or inadequate data in animals (Tables 5 and 6). The US EPA has classified several PAHs in Group B2, possibly carcinogenic to humans and Group D, unclassifiable as to carcinogenicity (Table 7).

In their risk assessment, OEHHA staff concluded that while the studies available for carcinogenic risk assessment of BaP are not ideal for risk assessment, those for practically all other individual PAHs are less complete for risk assessment (OEHHA, 1993). However, there are extensive data establishing the genotoxicity, and in some cases the carcinogenicity, of many PAHs or their genotoxic metabolites. In other cases, some PAHs are not considered carcinogens. Several authors have used mutagenicity and various tests of carcinogenicity to rank several PAHs for their relative carcinogenicity (e.g., Deutsch-

Wenzel *et al.*, 1983; Bingham and Falk, 1969; Habs *et al.*, 1980; Wynder and Hoffman, 1959; Wislocki *et al.*, 1986) and their relative genotoxicity (Brown, 1989). Many of these comparisons were summarized by Clement Associates (1988) and Krewski *et al.* (1989). In these analyses dibenz(*a,h*)anthracene was shown to be more potent than BaP, while other PAHs tested were less or much less potent. These comparisons indicated that considering all PAHs to be equivalent in potency to BaP would overestimate the cancer potency of a PAH mixture, but such an assumption would be health protective and is likely to be helpful in a screening estimate of PAH risks (OEHHA, 1993).

If one assumes that PAHs are as carcinogenic as they are genotoxic, then their hazard relative to BaP would be dependent on their concentration in the environment. In light of the limited information available on other PAHs, BaP remains an important representative or surrogate for this important group of chemically diverse air pollutants.

Selection of Risk Values for Other PAHs

BaP was chosen as the primary representative of the class because of the large amount of toxicological data available on BaP (versus the relatively incomplete database for other PAHs), the availability of monitoring techniques for BaP, and the significant exposure expected (and found). Nisbet and LaGoy (1992) presented a Toxic Equivalency Factor (TEF) scheme for 17 PAHs. The paper was an extension of earlier work by other investigators (Clement Associates, 1987; 1988; Krewski *et al.*, 1989). Along similar lines, OEHHA has developed a Potency Equivalency Factor (PEF) procedure to assess the relative potencies of PAHs and PAH derivatives as a group. This would address the impact of carcinogenic PAHs in ambient air since they are usually present together.

Due to the variety of data available on the carcinogenicity and mutagenicity of PAHs, an order of preference for the use of available data in assessing relative potency was developed. If a health effects evaluation and quantitative risk assessment leading to a cancer potency value had been conducted on a specific PAH, then those values were given the highest preference.

Table 5: IARC groupings of PAHs, mixtures with PAHs, and derivatives.

Group 1	Group 2A	Group 2B
Coal-tar pitches Coal-tar Coke production Mineral oils Shale-oils Soots Tobacco smoke	Benz[*a*]anthracene Benz[*a*]pyrene Creosotes Dibenzo[*a,h*]anthracene	Benzo[*b*]fluoranthene Benzo[*j*]fluoranthene Benzo[*k*]fluoranthene Carbon black extracts Dibenz[*a,h*]acridine Dibenz[*a,j*]acridine 7H-Dibenzo[*c,g*]carbazole Dibenzo[*a,e*]pyrene Dibenzo[*a,h*]pyrene Dibenzo[*a,i*]pyrene Dibenzo[*a,l*]pyrene Indeno[1,2,3-*cd*]pyrene 5-Methylchrysene 5-Nitroacenaphthene 1-Nitropyrene 4-Nitropyrene 1,6-Dinitropyrene 1,8-Dinitropyrene 6-Nitrochrysene 2-Nitrofluorene

Source: OEHHA (1993)
Abstracted from IARC Supplement 7 (1987) and IARC Volume 46 (1989).
Group1: carcinogenic to humans.
Group 2A: probably carcinogenic to humans.
Group 2B: possibly carcinogenic to humans.

Table 6: IARC Group 3 PAHs and PAH derivatives[1]

Chemical	Animal Evidence
Acridine orange	inadequate
5-Aminoacenaphthene	inadequate
2-Aminoanthraquinone	limited
Anthanthrene	limited
Anthracene	inadequate
Benz[*a*]acridine	inadequate
Benz[*c*]acridine	limited
Benzo[*g*,*h*,*i*]fluoranthene	inadequate
Benzo[*g*,*h*,*i*]perylene	inadequate
Benzo[*c*]phenanthrene	inadequate
Benzo[*e*]pyrene	inadequate
Carbazole	limited
Chrysene	limited
Cyclopenta[*c*,*d*]pyrene	limited
Dibenz[*a*,*c*]anthracene	limited
Dibenz[*a*,*j*]anthracene	limited
Dibenz[*a*,*e*]fluoranthene	limited
Dibenzo[*h*,*rst*]pentaphene	limited
3,7-Dinitrofluoroanthene	limited
3,9-Dinitrofluoroanthene	limited
1,3-Dinitropyrene	limited
Fluoranthene	inadequate
Fluorene	inadequate
1-Methylchrysene	inadequate
2-Methylchrysene	limited
3-Methylchrysene	limited
4-Methylchrysene	limited
6-Methylchrysene	limited
2-Methylfluoranthene	limited
1-Methylphenanthrene	inadequate
1,5-Naphthalenediamine	limited
9-Nitroacenaphthene	limited
9-Nitroanthracene	no adequate data
7-Nitrobenz[*a*]anthracene	limited
6-Nitrobenzo[*a*]pyrene	limited
3-Nitrofluoranthene	inadequate
1-Nitronaphthalene	inadequate
2-Nitronaphthalene	inadequate
3-Nitroperylene	inadequate
2-Nitropyrene	inadequate
Perylene	inadequate
Phenanthrene	inadequate
N-Phenyl-2-naphthylamine	limited
Pyrene	inadequate
Triphenylene	inadequate

Table 6 (continued): IARC Group 3 PAHs and PAH derivatives[1].

[1]Source: OEHHA (1993). Abstracted from IARC Supplement 7 (1987) and IARC Volume 46. (1989). Group 3 have either limited or inadequate evidence in animals and are not classifiable as to their carcinogenicity in humans due to no adequate data.

Table 7: US EPA groupings of PAHs[1]

Group B2	Group D
Benz[*a*]anthracene	Acenaphthylene
Benzo[*a*]pyrene	Anthracene
Benzo[*b*]fluoranthene	Benzo[*e*]pyrene
Benzo[*j*]fluoranthene	Benzo[*g,h,i*]perylene
Benzo[*k*]fluoranthene	Fluorene
Chrysene	Naphthalene
Dibenz[*a,h*]anthracene	Phenanthrene
Indeno[1,2,3-*cd*]pyrene	

[1]Source: OEHHA (1993). Abstracted from US EPA (1993a). Group B2: possibly carcinogenic to humans. Group D is unclassifiable as to carcinogenicity.

If potency values have not been developed for specific compounds, a carcinogenic activity relative to BaP, rather than a true potency, can be developed. These relative activity values are referred to by OEHHA as PEFs. For air contaminants, relative potency to BaP based on data from inhalation studies would be optimal. Otherwise, intrapulmonary or intratracheal administration, such as those published by Deutsch-Wenzel *et al.* (1983), would be most relevant, since such studies are in the target organ of interest. Next in order of preference is information on activity by the oral route and skin painting. Intraperitoneal and subcutaneous administration rank at the bottom of the *in vivo* tests considered useful for PEF development because of their lack of relevance to environmental exposures. Next in decreasing order of preference are genotoxicity data which exist for a large number of compounds. In many cases genotoxicity information is restricted to mutagenicity data. Finally, there are data on structure-activity relationships among PAH compounds. Structure-activity considerations may help identify a PAH as carcinogenic, but at this time have not been established as predictors of carcinogenic potency.

Using this order of preference, PEFs were derived for 21 PAHs and are presented in Table 8. The cancer potencies of four other PAH compounds are given in Table 9. Explanation of the derivation of each PEF, type of data used in the derivation, and the relevant references are given below.

Table 8: OEHHA PEF weighting scheme for PAHs[1]

PAH or derivative	PEF
benzo[*a*]pyrene	1.0 (index compound)
benz[*a*]anthracene	0.1
benzo[b]fluoranthene	0.1
benzo[*j*]fluoranthene	0.1
benzo[k]fluoranthene	0.1
dibenz[*a*,*j*]acridine	0.1
dibenz[*a*,*h*]acridine	0.1
7H-dibenzo[c,*g*]carbazole	1.0
dibenzo[*a*,*e*]pyrene	1.0
dibenzo[*a*,*h*]pyrene	10
dibenzo[*a*,*i*]pyrene	10
dibenzo[*a*,*l*]pyrene	10
indeno[1,2,3-*cd*]pyrene	0.1
5-methylchrysene	1.0
1-nitropyrene	0.1
4-nitropyrene	0.1
1,6-dinitropyrene	10
1,8-dinitropyrene	1.0
6-nitrochrysene	10
2-nitrofluorene	0.01
chrysene	0.01

[1]Source: OEHHA (1993)

Table 9: Potencies of PAHs and derivatives

Chemicals	Cancer potency factors $(mg/kg\text{-}day)^{-1}$	Unit risks $(\mu g/m^3)^{-1}$
benzo[*a*]pyrene[1]	11.5	1.1×10^{-3}
dibenz[*a*,*h*]anthracene[1]	4.1	1.2×10^{-3}
7,12-dimethylbenzanthracene[1]	250	7.1×10^{-2}
3-methylcholanthrene[1]	22	6.3×10^{-3}
Naphthalene[2]	0.12	3.4×10^{-5}
5-nitroacenaphthene[1]	0.13	3.7×10^{-5}

Source: [1]OEHHA (1993), [2]OEHHA (2004): It is assumed that unit risks for inhalation have the same relative activities as cancer potencies for oral intake.

Potency and Potency Equivalency Factors (PEFs) for Selected PAHs

1. Benzo[*a*]pyrene. Benzo[*a*]pyrene (BaP) was the index compound for relative potency and for Potency Equivalency Factors (PEF) for PAHs and derivatives. It has a cancer potency of 11.5 $(mg/kg\text{-}day)^{-1}$ and inhalation unit risk of 1.1×10^3 $(\mu g/m^3)^{-1}$. For the potency equivalency scheme, it was assigned a PEF of 1.

2. Dibenz[*a*,*h*,]anthracene. An expedited potency of 4.1 $(mg/kg\text{-}day)^{-1}$ was derived using the linearized multistage model with the only dose-response data set available - a drinking water study (Snell and Stewart, 1962) which reported alveolar carcinomas of the lung in male DBA/2 mice due to dibenz[*a*,*h*]anthracene (incidence = 14/21 at 28.3 mg/kg-day versus 0/25 in controls). An inhalation unit risk can be obtained from a potency under the assumption that the chemicals are equally absorbed and are equally potent by oral and inhalation routes and that a 70 kg person inhales 20 cubic meters of air per day. When the potency in units of $(mg/kg\text{-}day)^{-1}$ is divided by 3500 (70 kg * 1000 µg/mg/20 m^3), an inhalation unit risk is obtained in units of $(\mu g/m^3)^{-1}$.

3. 7,12-Dimethylbenzanthracene. An expedited potency of 250 $(mg/kg\text{-}day)^{-1}$ was derived. The only study listed in the Gold *et al.* cancer potency (TD50) database (Gold *et al.*, 1984; 1986; 1987; 1989; 1990) is the feeding study by Chourolinkov *et al.* (1967) in female albino mice. Significant increases in malignant angioendotheliomas of the mesenteric intestine and papillomas of the forestomach were observed in animals treated with 0.39 mg/kg-day of 7,12-dimethylbenzanthracene. Cancer potency is based on mesenteric intestine angioendothelioma incidence (incidence = 49/75 versus 0/40 in controls).

4. 3-Methylcholanthrene. An expedited potency of 22 $(mg/kg\text{-}day)^{-1}$ was derived. Results of 3 studies in male Long Evans rats, one study in an unspecified strain of female rats, and 10 studies in female Wistar rats were included in the Gold *et al.* database. All studies in female rats found highly significant increases in tumors of the mammary gland. The cancer potency for 3-methylcholanthrene was taken as the geometric mean of cancer potencies estimated from 9 of the 10 studies in female rats (Shay *et al.*, 1962; Gruenstein *et al.*, 1964; Shay *et al.*, 1961). The upper bound on potency could not be estimated from one of the studies by Shay *et al.* (1961), because 100% of the treated animals developed mammary gland tumors.

5. 5-Nitroacenaphthene. An expedited potency of 0.13 $(mg/kg\text{-}day)^{-1}$ was derived based on the combined incidence of benign and malignant tumors of the ear canal in female rats. Usable studies were feeding studies by Takemura *et al.* (1974) in female Syrian golden hamsters and by the National Cancer Institute (1978) in male and female $B6C3F_1$ mice and F344 rats. The compound 5-nitroacenaphthene induced increases in tumor incidences at multiple sites in rats and female mice. Rats were the most sensitive species; the sensitivity of males were similar to that of females.

6. Benzo[*b*]fluoranthene. Benzo[*b*]fluoranthene was assigned a PEF of 0.1. Clement Associates (1988) applied both a two stage model and the multistage model to various data sets for several PAHs. The two models generally gave similar results for relative potency. In order to verify the results, OEHHA staff (OEHHA, 1993) used GLOBAL86 to fit the multistage model to the tumor data used by Clement Associates and obtained relative cancer potencies similar to those obtained by Clement Associates. Clement Associates (1988) used the mouse skin carcinogenesis data obtained by Habs *et al.* (1980) and the intrapulmonary administration to rats by Deutsch-Wenzel *et al.* (1983) to estimate a cancer potency for benzo[*b*]fluoranthene relative to BaP. As an example of the type of data used,

Deutsch-Wenzel *et al.* obtained pulmonary tumor incidences of 0, 2.9, and 25.7% after intrapulmonary administration of 0.1, 0.3, and 1 mg benzo[*b*]fluoranthene, respectively, whereas they obtained 11.8, 60.0, and 94.3% tumor incidence after the same doses of benzo[*a*]pyrene. Clement Associates estimated a relative cancer potency for benzo[*b*]fluoranthene of 0.140 after fitting the two stage model to the data and 0.105 after fitting the multistage model. Using the data of Habs *et al.* a relative cancer potency of 0.167 was obtained with the two stage model and 0.201 with the multistage model. The results from the multistage model were averaged, then rounded (down) to 0.1 to obtain the PEF. OEHHA obtained a relative potency of 0.208 for benzo[*b*]fluoranthene fitting the multistage model to the data from Habs *et al.* OEHHA staff were also able to reproduce the calculations for the two stage model in the accepted model for cancer risk assessment in California; results from the multistage model have been used to obtain PEFs although the two models usually gave the same PEF.

7. Benzo[*j*]fluoranthene. Benzo[*j*]fluoranthene was assigned a PEF of 0.1. Clement Associates (1988) used the mouse skin carcinogenesis data obtained by Habs *et al.* (1980) to estimate a cancer potency relative to BaP of 0.0648. OEHHA staff estimated 0.065 using the same data. This was rounded to 0.1 to obtain the PEF. Clement Associates did not use the data of Deutsch-Wenzel *et al.* (1983) on benzo[*j*]fluoranthene to calculate a relative potency but Deutsch-Wenzel *et al.* found that it was very similar in tumorigenic activity to benzo[*k*]fluoranthene.

8. Benzo[*k*]fluoranthene. Benzo[*k*]fluoranthene was assigned a PEF of 0.1. Clement Associates (1988) used mouse skin carcinogenesis data obtained by Habs *et al.* (1980) to obtain a cancer potency relative to BaP of 0.0235 and the intrapulmonary administration to rats by Deutsch-Wenzel *et al.* (1983) to estimate a PEF of 0.085. Because the latter was obtained by the pulmonary route it was chosen to be the basis of the PEF. The value was rounded to 0.1 to obtain the PEF.

9. Benz[*a*]anthracene. Benz[*a*]anthracene was assigned a PEF of 0.1. In the case of benz[*a*]anthracene, mouse skin carcinogenesis data obtained by Bingham and Falk (1969) were used by Clement Associates (1988) to calculate potencies for benz[*a*]anthracene. For this chemical the multistage model gave a relative potency of 0.0137. Using the two stage model a higher cancer potency of 0.145 relative to BaP was obtained. In the Wislocki *et al.* (1986) report, in which lung adenomas were induced in newborn mice, benz[*a*]anthracene (2.8 micromoles) was less carcinogenic (12/71 or 17% versus 7/138 or 5% in controls) relative to 0.56 micromoles BaP (24/64 or 38% versus 7/138 in controls). The relative potency was 0.08, which rounds to 0.1. Since the US EPA was using a PEF of 0.1 for this PAH (US EPA, 1993b) and the data from the Wislocki study were consistent with a PEF of 0.1, a value of 0.1 was selected by OEHHA.

10. Dibenz[*a,j*]acridine. Dibenz[*a,j*]acridine was assigned a PEF of 0.1. Warshawsky *et al.* (1992) compared the tumor-initiating ability of dibenz[*a,j*]acridine to BaP in mouse skin. Two hundred nanomoles of each compound were applied to groups of 30 mice, then the skin lesion was promoted with a phorbol ester for 24 weeks. Twenty-seven out of 30 BaP mice (90%) had skin papillomas, while 17 of 30 (57%) of the dibenz[*a,j*]acridine mice

had skin papillomas. The multistage model was fit to both sets of data and the ratio of upper 95% confidence limits on the linear coefficient was 0.36. This was rounded to a PEF of 0.1.

11. Dibenz[*a*,*h*]acridine. Dibenz[*a*,*h*]acridine was also assigned a PEF of 0.1. Its carcinogenic classification by IARC was based on studies published in 1940 and earlier and the studies did not appear appropriate for estimation of a PEF. Since its structure is similar to dibenz[*a*,*j*]acridine, it was assigned the same PEF as dibenz[*a*,*j*]acridine until usable compound-specific bioassay data becomes available.

12. 7H-Dibenzo[*c*,*g*]carbazole. 7H-dibenzo[*c*,*g*]carbazole was assigned a PEF of 1.0. Warshawsky *et al.* (1992) compared the tumor-initiating ability of 7H-dibenzo[*c*,*g*]carbazole to BaP in mouse skin. Two hundred nanomoles of each compound were applied to 30 mice, then promoted with a phorbol ester for 24 weeks. Twenty-seven out of 30 BaP-treated mice (90%) had skin papillomas, while 26 of 30 (87%) of the dibenzo[*a*,*j*]acridine-treated mice had skin papillomas for a relative tumorigenic activity of 0.97. This was rounded to a PEF of 1.

13. Dibenzo[*a*,*l*]pyrene. Dibenzo[*a*,*l*]pyrene was assigned a PEF of 10. Cavalieri *et al.* (1989; 1991) studied the tumor-initiating and dose-response tumorigenicity of dibenzo[*a*,*l*]pyrene in mouse skin and rat mammary gland. BaP was used as a reference compound in some experiments. Dibenzo[*a*,*l*]pyrene was the most potent member of the group. Several levels of PAHs were tested. When results from 33.3 nanomoles of dibenzo[*a*,*l*]pyrene as a skin tumor initiator (with promotion by a phorbol ester) were compared to results using the same amount of BaP, dibenzo[*a*,*l*]pyrene induced skin tumors in 23/24 (96%) of the animals while BaP induced tumors in 10/23 (43%) which resulted in a relative potency of 5.8. Dibenzo[*a*,*l*]pyrene induced approximately 5 times as many tumors per tumor-bearing animal. In a second experiment 4 nanomoles of each chemical were compared. Ninety-two percent (22/24) of the dibenzo[*a*,*l*]pyrene-treated mice had tumors but only 4% (1/24) of the BaP animals, which yielded a relative potency of 25.1. In a third experiment 100 nM were compared without promotion. Twenty-nine percent (7/24) of the dibenzo[*a*,*l*]pyrene-treated mice had tumors but only 4% (1/24) of the BaP animals, for a relative potency of 4. Finally, with direct application to the mammary gland, 0.25 and 1.0 nanomoles dibenzo[*a*,*l*]pyrene led to tumors in all the rats treated (19 and 20 per group, respectively) whereas only one animal in the 0.25 micromoles BaP group showed a tumor for a relative potency greater than 100. Based on its much greater tumorigenic activity than BaP in the above tests, dibenzo[*a*,*l*]pyrene was assigned a PEF of 10.

14. Dibenzo[*a*,*h*]pyrene. Dibenzo[*a*,*h*]pyrene was assigned a PEF of 10 since, in the experiments by Cavalieri *et al.* (1989) in which all four dibenzo[a]pyrenes were studied, its tumor causing activity was similar to dibenzo[*a*,*l*]pyrene. For example, when used to initiate tumors in mouse skin, 18 of 24 (75%) of mice treated with dibenzo[*a*,*h*]pyrene had tumors compared to 22 of 24 (92%) with dibenzo [*a*,*l*]pyrene. Controls showed skin tumors in 2 of 23 mice (9%).

15. Dibenzo[*a*,*i*]pyrene. Dibenzo[*a*,*i*] pyrene was assigned a PEF of 10 since, in the experiments by Cavalieri *et al.* (1989) in which all four dibenzo[*a*]pyrenes were studied, its tumor-causing activity was similar to dibenzo[a,l]pyrene. For example, when used to initiate tumors in mouse skin, 15 of 24 (63%) of mice treated with dibenzo[a,i]pyrene had tumors compared to 22 of 24 (92%) with dibenzo-[*a*,*l*]pyrene. Controls showed skin tumors in 2 of 23 mice (9%).

16. Dibenzo[*a*,*e*]pyrene. Dibenzo[*a*,*e*]pyrene was assigned a PEF of 1.0. Dibenzo[*a*,*e*]pyrene was the least potent of the four dibenzo[*a*]pyrenes studied by Cavalieri *et al.* (1989; 1991). In the experiments in which all four dibenzo[*a*]pyrenes were compared (Cavalieri *et al.*, 1989), its tumor-causing activity was approximately one-tenth to one-twentieth that of dibenzo[*a*,*l*]pyrene.

17. Indeno[1,2,3-*cd*]pyrene. Indeno[1,2,3-*cd*]pyrene was assigned a PEF of 0.1. Clement Associates (1988) used the mouse skin carcinogenesis data obtained by Habs *et al.* (1980) and by Hoffman and Wynder (1966) and the lung tumor data obtained by Deutsch-Wenzel *et al.* (1983) after intrapulmonary administration to estimate cancer potencies relative to BaP of 0.0302, 0.0292, and 0.246, respectively. These were averaged and rounded to obtain a PEF of 0.1.

18. 5-Methylchrysene. 5-Methylchrysene was assigned a PEF of 1.0. The activity of 5-methylchrysene relative to BaP has been studied by Hecht *et al.* (1976) using skin tumor initiation with phorbol ester (tetradecanoy1 phorbol acetate) promotion as well as skin tumor induction in mice. In the skin tumor induction test the tumorigenic activities of 5-methylchrysene and BaP were comparable enough so that a PEF of 1.0 was selected for 5 methylchrysene. Weekly application of 0.01% 5-methylchrysene led to skin carcinomas in 10 of 15 mice treated for up to 62 weeks, while 0.01% BaP led to skin carcinomas in 14 of 18 mice. The results for 0.005% of the 2 chemicals were 6 of 9 and 7 of 10, respectively.

19. 1-Nitropyrene. 1 Nitropyrene has been assigned a PEF of 0.1. In the Wislocki *et al.* (1986) report, in which lung tumors were induced in newborn mice, 1-nitropyrene (0.7 micromoles) was weakly carcinogenic in males (6/34 or 18% versus 4/45 or 9% in controls) and not carcinogenic in females (3/50 or 6% versus 2/34 or 6% in controls) relative to 0.56 micromoles BaP (13/37 or 35% in males versus 1/28 or 4% in control males and 13/27 or 48% in females versus 0/31 in control females). The relative potency was 0.348 in males and 0.076 in females. A PEF of 0.1 was assigned based on the experiment.

20. 4-Nitropyrene. 4-Nitropyrene was assigned a PEF of 0.1. Wislocki *et al.* (1986) compared the lung tumorigenicity of nitrated derivatives of pyrene to BaP in a newborn mouse assay. The background incidences were 4% in males and 0% in females. The administration of 2.8 micromoles of 4-nitropyrene gave a net incidence of 34% tumors in males and 31% in females, while 0.56 micromoles BaP gave 31% tumors in males and 48% in females. The potency of 4-nitropyrene relative to BaP was 0.23 in males and 0.12 in females. These were averaged and rounded to a PEF of 0.1.

21. 1,6-Dinitropyrene. 1,6-Dinitropyrene was assigned a PEF of 10. In the Wislocki *et al.* (1986) report, 1,6-dinitropyrene (0.2 micromoles) was weakly carcinogenic in inducing lung tumors in females (2/29 versus 0/31 in controls) and essentially not carcinogenic in males (1/25 versus 1/28 in controls) relative to 0.56 micromoles BaP (see 1-nitropyrene above for BaP data). The weak response combined with the low dose of 1,6-dinitropyrene (0.2 micromoles) relative to BaP (0.56 micromoles) resulted in a relative potency of 0.52 in females and 0.54 in males. In an intratracheal injection experiment (Takayama *et al.*, 1985) hamsters were given 26 weekly instillations of 0.5 mg BaP. All 10 males and 9 of 10 females developed respiratory tract tumors. A unit risk of 2.9×10^{-2} $(\mu g/m^3)^{-1}$ obtained from the female data which is 6.4 times the unit risks obtained from intratracheal studies using BaP and 26 times that using inhalation data. In a study by Iwagawa *et al.* (1989) using several doses of 1,6-dinitropyrene or BaP implanted directly into the lungs, a relative potency of 5.1 was obtained from the resulting lung cancer data. In light of the two experiments showing high relative potency and of 1,6-dinitropyrene's strong mutagenicity, a PEF of 10 appeared to be more appropriate than 1.0.

22. 1,8-Dinitropyrene. 1,8-Dinitropyrene was assigned a PEF of 1.0. In the Wislocki *et al.* (1986) report, 1,8-dinitropyrene (0.2 micromoles) was weakly carcinogenic in females (2/29 versus 0/31 in controls) and not carcinogenic in males (1/31 versus 1/28 in controls) relative to 0.56 micromoles BaP. However, due again to the low dose of 1,8-dinitropyrene chosen, the relative potency was 0.46 in females and 0.41 in males. In view of the high PEF of 1,6-dinitropyrene derived above and the very high mutagenicity of 1,8-dinitropyrene, the default PEF of 1.0 was assigned to 1,8-dinitropyrene until better *in vivo* data becomes available to derive a PEF.

23. 6-Nitrochrysene. 6-Nitrochrysene was assigned a PEF of 10. In the Wislocki *et al.* (1986) report, 0.7 micromoles of 6-nitrochrysene gave a net incidence of 76% lung tumors in males (28/33 versus 4/45 in controls) and 84% in females (36/40 versus 2/34 in controls). The potency of 6-nitrochrysene relative to BaP was 3.27 in males and 2.50 in females. In the newborn mouse assay of Busby *et al.* (1988), "(t)he ED50 for total lung tumors was 0.02 µmol for 6-NC and 0.2 µmol for BaP, thus showing a 10-fold higher potency for 6-NC compared with the 25-fold difference noted with tumor multiplicity." In a subsequent report (Busby *et al.*, 1989), 0.03 micromoles of 6-nitrochrysene caused lung adenomas and adenocarcinomas in 19/26 males and 13/22 females (versus controls of 13/91 in males and 7/101 in females) while 0.24 micromoles BaP caused lung adenomas and adenocarcinomas in 13/28 males and 19/27 females (against the same controls). The relative potencies were 17.51 for males and 6.17 for females. Based on the several experiments a PEF of 10 was selected.

24. 2-Nitrofluorene. 2-Nitrofluorene was assigned a PEF of 0.01. Miller *et al.* (1955) fed 2-nitrofluorene at a level of 1.62 mmol(215 mg)/kg diet to rats. This is estimated to give an animal dose of 33.1 mg/kg-day and a human equivalent dose of 4.7 mg/kg-day. In one experiment 17 of 20 male rats (85%) developed forestomach tumors by 12 months. In another experiment 4 of 9 female rats (44%) developed mammary tumors by 10 months. These experiments yielded cancer potencies of 0.25 and 0.62 $(mg/kg\text{-}day)^{-1}$, approximately

0.02 and 0.05 that of BaP obtained in this risk assessment. The values of 0.02 and 0.05 were averaged and rounded down to obtain a PEF of 0.01.

25. Chrysene. Chrysene was assigned a PEF of 0.01. Clement Associates (1988) used the mouse skin carcinogenesis data obtained by Wynder and Hoffman (1959) to estimate a cancer potency relative to BaP of 0.0132. This was rounded to obtain a PEF of 0.01.

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BENZYL CHLORIDE

CAS No: 100-44-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	126.58
Boiling point	179°C
Melting point	-43 to -48°C
Vapor pressure	1 mm Hg at 22°C
Air concentration conversion	1 ppm = 5.26 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.9 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 1.7 E-1 $(mg/kg\text{-}day)^{-1}$
[Cancer potency factor derived by US EPA/IRIS (1989) from female rat C-cell thyroid tumor incidence data (Lijinsky, 1986) using a linearized multistage procedure, extra risk; adopted by RCHAS/CDHS (1991).]

III. CARCINOGENIC EFFECTS

Human Studies

Several studies report on cancer mortality in workers occupationally exposed to benzyl chloride.

Sakabe *et al*. (1976) studied cancer incidences among 41 workers exposed to chemicals including benzyl chloride over 18 years (ending in 1972) in a plant producing benzoyl chloride in Japan. Four cases of cancer were reported among the workers: two fatal cases of lung cancer, one fatal maxillary malignant lymphoma, and one squamous cell carcinoma of the lung (still surviving in 1973). The range of employment duration among the workers with cancer was 6 to 14 years. Both cases of lung cancer were in smokers. The expected number of lung cancer deaths among 41 Japanese males was 0.06. In addition to smoking, another potential confounding factor is the reporting of exposure to other compounds in the work environment including benzotrichloride, benzoyl chloride, toluene, chlorine gas, hydrogen chloride, benzal chloride, and other chlorinated toluenes and polymers. Exposure levels were not quantitated.

Sakabe and Fukuda (1977) also reported on cancer deaths among workers exposed to chemicals including benzyl chloride in another plant involved with the production of benzoyl peroxide and benzoyl chloride between 1952 and 1963. Two lung cancer deaths (one a smoker) were reported. Expected number of deaths and exposure levels were not reported, and workers were also exposed to other chemicals as listed in the description of the study by Sakabe *et al*. (1976).

Sorahan *et al*. (1983) studied cancer mortality among British workers occupationally exposed to a number of compounds including toluene, benzotrichloride, benzoyl chloride, benzyl chloride, and benzal chloride during the course of producing chlorinated toluenes. Five digestive system cancers and 5 respiratory system cancers were reported among 163 male workers employed more than 6 months between 1961 and 1970. Expected mortality rates from these tumors in England and Wales were 1.24 and 1.78, respectively, and the mortality ratio was significantly elevated. Smoking rates were not reported among the workers. Cumulative exposure and death from any cancer among workers employed before 1951 was shown to be significantly correlated by survival analysis using the Cox Proportional Hazard Model, although this was not the case when entry cohorts were combined.

Wong and Morgan (1984) studied cancer mortality among a cohort of 697 workers employed from 1 to more than 35 years in a chlorination plant in Tennessee. Workers were exposed to benzyl chloride, benzoyl chloride, and benzotrichloride. Deaths from respiratory cancers were reported for 7 workers, 5 of whom were exposed for more than 15 years. Expected mortality for U.S. males in a group of this size was 2.84 deaths (1.32 deaths for the subgroup exposed > 15 years). No data on smoking was reported.

Animal Studies

Lijinsky (1986) treated F344 rats (52/sex/dose) and B6C3F$_1$ mice (52/sex/dose) with benzyl chloride in corn oil by gavage. The rats were dosed with 0, 15, and 30 mg/kg/day benzyl chloride and mice with 0, 50 and 100 mg/kg/day benzyl chloride, with treatments 3 days/week for 2 years. Animals were histopathologically examined 3-4 weeks after the end of the treatment using the NCI bioassay protocol. Survival in both species was not significantly affected by treatment. The incidence of C-cell adenoma/carcinoma of the thyroid was significantly increased in female rats in the high-dose group compared to control animals (14/52 treated vs. 4/52 control; $p < 0.01$ by Fisher's exact test). In male mice in the high-dose group, significantly increased incidences were found for hemangioma/hemangiocarcinoma (5/52 treated vs. 0/52 control), forestomach carcinoma (8/52 treated vs. 0/51 control) and forestomach carcinoma/papilloma (32/52 treated vs. 0/51 control). In male mice in the low-dose group only, an increased incidence of hepatic carcinoma/adenoma (28/52 treated vs. 17/52 control) was reported. In female mice in the low- and high-dose groups, an increased incidence of forestomach carcinoma/papilloma (5/50 low-dose, 19/51 high-dose vs. 0/52 control) was reported.

Injection-site sarcomas developed in 3 of 14 BD-strain rats administered benzyl chloride in peanut oil subcutaneously weekly for 51 weeks at 40 mg/kg-week and 6 of 8 rats administered 80 mg/kg-week (Druckrey *et al*., 1970). Mean induction time was 500 days.

Poirier *et al*. (1975) treated A/H mice (20/dose) 3 times weekly over 24 weeks intraperitoneally with a total dose of 0.6, 1.5 or 2 g benzyl chloride/kg body weight in tricaprylin. Surviving animals were sacrificed at 24 weeks. Among the survivors, lung tumors were found in 4/15, 7/16, and 2/8 animals, respectively. Animals treated with tricaprylin alone had an average of 0.22 lung tumors/mouse and animals receiving no

treatment had 0.21 lung tumors/mouse. The incidence of lung tumors in treated animals was not found to be statistically significant from control animals.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Human studies do not provide adequate data for the development of a cancer potency value because of the presence of confounding factors in the studies (multiple compound exposures, no data on smoking status) and no reporting of exposure levels. The animal study by Lijinsky (1986) showing development of thyroid tumors in female rats, and forestomach papillomas and carcinomas in male and female mice provides data from which cancer potency values can be derived.

Methodology

Cancer potency values were derived by US EPA (1989) from the tumor incidence data presented in the study by Lijinsky (1986). The experimentally administered doses (15 and 30 mg/kg) were converted to time-weighted dosage based on the dosing schedule (3 times/week) and the experimental duration (107.5 weeks). The human equivalent dose (HED) was calculated based on an assumed experimental animal body weight (bw_a) of 0.35 kg and human body weight (bw_h) of 70 kg using the following relationship:

$$HED = \text{time-weighted dose} \times (bw_a/bw_h)^{1/3}$$

The calculated human equivalent doses in the Lijinsky (1986) study were 1.06 and 2.12 mg/kg-day. A linearized multistage procedure (CDHS, 1985) was applied to the tumor incidence data for thyroid tumors in female rats (4/52 controls, 8/51 low-dose, 14/52 high-dose), forestomach tumors in male mice (0/51 controls, 5/50 low-dose, 32/52 high-dose) and forestomach tumors in female mice (0/52 controls, 5/50 low-dose, 19/51 high-dose). This resulted in estimations of the upper 95% confidence bound of cancer potency (q_1^*) of 0.17, 0.056, and 0.12 $(mg/kg\text{-}day)^{-1}$, respectively. Selection of the cancer potency value is made in the most sensitive species and site; therefore, the cancer potency value [0.17 $(mg/kg\text{-}day)^{-1}$] derived from the female rat C-cell thyroid tumor data was chosen.

A unit risk value of 4.9 E-5 $(\mu g/m^3)^{-1}$ was derived by ATES/OEHHA assuming a human breathing rate of 20 m^3/day, a human body weight of 70 kg, and 100% fractional absorption after inhalation exposure.

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BERYLLIUM

CAS No: 7440-41-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	9.012
Boiling point	2970°C
Melting point	1287°C
Vapor pressure	10 mm Hg @ 1860°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.4 E-3 $(\mu g/m^3)^{-1}$
[Calculated by US EPA (1992) from the human inhalation exposure data of Wagoner *et al.* (1980).]

III. CARCINOGENIC EFFECTS

Human Studies

US EPA (1992) reviewed several studies that found increased incidences of lung cancer in beryllium processing workers. A cohort mortality study of 3055 white males employed at a single beryllium processing plant in Pennsylvania with a median duration of employment of 7.2 months demonstrated a statistically significant increased incidence of mortality due to lung cancer in the entire cohort, as well as in the 2068 cohort members followed for 25 years or more since initial employment (Wagoner *et al.,* 1980). Recalculation of the number of expected deaths using 1968-1975 lung cancer mortality data indicated that the increased incidence was significant only among workers followed for 25 years or more (Bayliss, 1980; MacMahon, 1977, 1978), and was not significant when the number of expected deaths was adjusted for smoking (US EPA, 1986).

Earlier studies of workers from the same beryllium processing plant alone or combined with workers from other beryllium plants reported a statistically significant increase in lung cancer mortality (Bayliss and Wagoner, 1977; Mancuso, 1970, 1979, 1980). These studies made no adjustment for smoking and had methodological constraints and deficiencies that precluded their use to establish a causal relationship between beryllium exposure and lung cancer.

Animal Studies

Slight, non-statistically significant increases in cancer incidence (all tumor types) were observed in male Long-Evans rats (52/sex/group) following lifetime exposure to 5 ppm beryllium sulfate administered in the drinking water (Schroeder and Mitchener, 1975a).

Tumors were observed in 9/33 treated and 4/26 control rats. High mortality during the study resulting from a pneumonia epidemic at 20 months greatly reduced the power of this study to detect any potential carcinogenic effect of beryllium exposure. A non-statistically significant increase in combined lymphoma and leukemia incidence was observed in female Swiss mice administered 5 ppm beryllium sulfate in drinking water for life (9/52 exposed, 3/47 controls) (Schroeder and Mitchener 1975b).

Male and female Wistar-derived rats were exposed to diet containing beryllium sulfate at concentrations of 0, 5, 50, or 500 ppm for life (Morgareidge *et al*., 1977). Reticulum cell carcinomas of the lung were observed in 10/49 male control animals, 17/35 low dose animals, 16/40 intermediate dose animals, and 12/39 high dose animals, respectively. Since the results were published only as an abstract, and since no response was seen at the highest dose, these results are considered to be only suggestive for the induction of cancer via this route.

Beryllium and beryllium compounds have been shown to cause statistically significant tumor increases in male and female rhesus monkeys and several strains of rats via inhalation and intratracheal installation, and the induction of osteosarcomas in rabbits by intravenous or intramedullary injection. Studies describing the induction of lung tumors (adenomas, adenocarcinomas) by beryllium via inhalation during exposure periods of up to 72 weeks are listed in Table 1. Intratracheal instillation of beryllium also resulted in the induction of lung tumors and extrapulmonary lymphosarcomas and fibrosarcomas in rats (Groth *et al*., 1980; Ishinishi *et al*., 1980).

Table 1. Induction of lung tumors in animals exposed to beryllium via inhalation

Study	Species/strain	Compound
Reeves *et al*., 1967	male, female Sprague-Dawley rats	beryllium sulfate
Schepers, 1961	male, female Sherman and Wistar rats	beryllium phosphate, beryllium fluoride, zinc beryllium silicate
Wagner *et al*., 1969	male Charles River CR-CD rats	beryl ore
Vorwald, 1968	male, female rhesus monkeys	beryllium sulfate

Beryllium compounds were shown to induce osteogenic sarcomas in rabbits by intravenous injection in 12 studies and by intramedullary injection in 4 studies (US EPA, 1991)

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Wagoner *et al*. (1980) studied a cohort of 3055 white males employed at a single beryllium processing plant in Pennsylvania (exposed to beryllium metal, oxide or hydroxide) sometime between January 1, 1942 and December 31, 1967 with a median duration of employment of 7.2 months. A significantly increased incidence of mortality due to lung

cancer was observed in the entire cohort (47 observed versus 34.29 expected, $p < 0.05$), as well as in the 2068 cohort members followed for 25 years or more since initial employment (20 observed versus 10.79 expected, $p < 0.01$). When the number of expected deaths was recalculated using 1968-1975 lung cancer mortality data, significance was lost for the cohort overall (38.2 expected), but not for the subgroup followed for 25 years or more (13.36 expected, $p \approx 0.05$) (Bayliss, 1980; MacMahon, 1977, 1978). However, significance was lost for the subgroup when the number of expected deaths was adjusted for smoking (14.67 expected) (US EPA, 1986).

The data of Wagoner *et al*. (1980) was used for the quantitation of cancer potency due to inhalation exposure despite study limitations. Human inhalation exposure is usually to beryllium oxide rather than other beryllium salts. Animal studies utilizing beryllium oxide have used intratracheal instillation instead of inhalation exposure. The use of the available human data therefore avoids uncertainties due to cross-species extrapolation, and uses the most relevant route of administration and beryllium species.

Methodology

A risk assessment was performed based on the occupational exposure study of Wagoner *et al*. (1980). The narrowest range for median exposure that could be obtained on the basis of available information was 100 to 1000 $\mu g/m^3$. Effective dose was calculated by adjusting for the duration of daily (8 of 24 hours) and annual (240 of 365 days) exposure, and the fraction of the lifetime at risk (time from start of employment to study termination). Smoking-adjusted expected lung cancer deaths were found to range from 13.91 to 14.67 (based on exposure range) compared to 20 observed. Relative risk estimates of 1.36 and 1.44 were calculated and the 95% confidence limits of these estimates used to calculate the lifetime cancer risk (Table 2). These estimates were based on one data set and a range of estimated exposure levels and times. To account for estimation uncertainties, unit risks were derived using two estimates each of concentration, fraction of lifetime exposed and relative risk. The listed unit risk factor [2.4 E-3 $(\mu g/m^3)^{-1}$] is the arithmetic mean of the 8 derived unit risks. US EPA has stated that this unit risk may not be appropriate if the air concentration exceeds 4 $\mu g/m^3$ and should not be used under those circumstances.

Table II. Effective dose, upper-bound estimate of relative risk and unit risk of carcinogenicity due to human beryllium exposure via inhalation (US EPA, 1992).

Beryllium concentration in workplace ($\mu g/m^3$)	Fraction of lifetime	Effective dose ($\mu g/m^3$)	95% upper-bound estimate of relative risk	Unit risk/ ($\mu g/m^3$)
100	1.00	21.92	1.98	1.61E-3
			2.09	1.79E-3
	0.25	5.48	1.98	6.44E-3
			2.09	7.16E-3
1000	1.00	219.18	1.98	1.61E-4
			2.09	1.79E-4
	0.25	54.79	1.98	6.44E-4
			2.09	7.16E-4

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BIS(2-CHLOROETHYL)ETHER

CAS No: 111-44-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	143.02
Boiling point	176-178.5°C
Melting point	-24.5°C
Vapor pressure	0.7 mm Hg @ 20°C
Air concentration conversion	1 ppm = 5.8 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 7.1 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 2.5 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no human carcinogenicity studies available for bis(2-chloroethyl)ether (BCEE).

Animal Studies

Two studies address the carcinogenicity of bis(2-chloroethyl)ether by the oral route of exposure. Innes *et al.* (1969) administered 100 mg/kg body weight bis(2-chloroethyl)ether by oral gavage to two F_1 generation strains of mice termed X (C57BL/6 × C3H/Anf) and Y (C57BL/6 × AKH) (18/sex/strain) from day 7 to 28 of life, without adjusting the initial dose to account for weight gain. After 28 days, BCEE was added to feed at a concentration of 300 ppm for 76 weeks. Surviving animals were sacrificed at 80 weeks. Ninety animals of each strain were included as controls. Tumor incidence in surviving animals is summarized in Table 1. A statistically significant increase in hepatomas ($p < 0.05$) was noted in both males and females of strain X and in males of strain Y. No other tumor type showed significant increases in incidence.

Charles River CD rats (26/sex/group) were treated with 0, 25 or 50 mg/kg-day bis(2-chloroethyl)ether by gavage for 18 months by Weisburger *et al.* (1981). Animals were observed for 2 years. No carcinogenic effects were observed, although the authors report increased mortality among the high-dose females and reduction in mean weight among high-dose males and females.

Van Duuren *et al.* (1972) report on two experimental approaches to evaluate the carcinogenicity of bis(2-chloroethyl)ether; a subcutaneous injection study and an initiation study by dermal application. ICR/Ha Swiss mice (30 females) were injected weekly with 1 mg BCEE for 68 days. No tumors remote from the injection site were observed. Two sarcomas were noted at the injection site (2/30) but were not found to be statistically different from controls (0/30) ($p > 0.05$ by Fisher's Exact Test).

Van Duuren *et al.* (1972) also treated ICR/Ha Swiss mice (20 females/group) with a single dose of 1 mg BCEE applied to the skin followed by three applications/week of the tumor promoter phorbol myristate acetate (PMA) in acetone for life. Control groups included animals not treated with BCEE and animals treated with BCEE but without the promoter. Skin papillomas were noted among animals treated with both BCEE and PMA, but the incidence was not significantly higher than among control animals (3/20 treated, 2/20 controls; $p>0.05$ by Fisher's Exact Test). No tumors were observed among animals treated only with BCEE.

Theiss *et al.* (1977) injected A/St mice (20 males) intraperitoneally with 8, 20, or 40 mg/kg BCEE 3 times/week for 8 weeks. After 24 weeks all surviving mice were sacrificed and examined only for lung tumors. The incidence of tumors among treated animals was not found to be significantly higher than among controls.

Table 1. Incidence of tumors in rats treated with bis(2-chloroethyl)ether[*] (Innes *et al.,*1969).

		Tumor Incidence			
		Strain X		Strain Y	
Tumor Type/Treatment		female	male	female	male
hepatomas	treated	4/18[**]	14/16[**]	0/18	9/17[**]
	control	0/87	8/79	1/82	5/90
pulmonary tumors	treated	0/18	0/16	0/18	2/16
	control	3/83	5/79	3/92	10/90
lymphomas	treated	0/18	2/16	0/18	0/17
	control	4/87	5/79	4/82	1/90

[*] F_1 generation mice were administered 100 mg/kg body weight bis(2-chloroethyl)ether by oral gavage from day 7 to 28 of life and subsequently in feed at a concentration of 300 ppm for 76 weeks (calculated dose is 39 mg/kg-day). Surviving mice were sacrificed at 80 weeks.

[**] statistically significant increase in incidence ($p < 0.001$ by Fisher's exact test)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

In the absence of studies in humans useful in evaluating the carcinogenicity of bis(2-chloroethyl)ether, a single animal study (Innes *et al.*, 1969) has been identified as appropriate for the development of a cancer potency value. The most sensitive endpoint from this study is the development of hepatomas in treated male strain X rats. Other studies either do not show development of tumors (Weisburger, 1981) or experimental duration/dosing limited the interpretation of negative data (Van Duuren, 1972; Theiss, 1977).

Methodology

Lifetime average dose estimates from the Innes *et al.* study (1969) have been calculated to be 39 mg/kg-day bis(2-chloroethyl)ether (US EPA, 1980). A linearized multistage procedure polynomial was applied to the tumor incidence data (CDHS, 1985; Anderson, 1983). The upper 95% confidence bound on the cancer potency estimate is termed q_1^*. Using the data presented in Table 1, the following cancer potencies were derived from groups showing significant increases in hepatoma incidence:

animal group	q_1^* (mg/kg-day)$^{-1}$
Strain X - males	0.086
Strain X - females	0.013
Strain Y - males	0.031

The selection of the cancer potency value has been based on the q_1^* value from the most sensitive sex and strain in this case, 0.086 (mg/kg-day)$^{-1}$ in Strain X males derived from Innes *et al.*(1969). Calculation of the cancer potency in animals (q_{animal}) can be made from the following relationship, where T is the natural lifespan of the animal (104 weeks) and T_e is the experimental duration (80 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

The resulting q_{animal} is 0.19 (mg/kg-day)$^{-1}$. Conversion to human cancer potency (q_{human}) is based on the following relationship, where bw_{animal} is the assumed body weight for the test species (0.03 kg - mice; US EPA, 1980) and bw_{human} is the assumed human body weight (70 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The estimate of q_{human} based on this relationship is 2.5 (mg/kg-day)$^{-1}$. A unit risk value based upon air concentrations was derived by OEHHA/ATES assuming a human breathing rate of 20 m^3/day, 100% fractional absorption, and average human body weight of 70 kg. The calculated unit risk value is 7.1 E-4 ($\mu g/m^3$)$^{-1}$.

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BIS(CHLOROMETHYL)ETHER

CAS No: 542-88-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	114.96
Boiling point	106°C
Melting point	-41.5°C
Vapor pressure	30 mm Hg at 22°C
Air concentration conversion	1 ppm = 4.75 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-2 $(\mu g/m^3)^{-1}$
Slope Factor: 4.6 E+1 $(mg/kg\text{-}day)^{-1}$
[Calculated from potency value derived by RCHAS, cross-route extrapolation (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Increases in the incidence of lung cancer have been reported in a number of studies of workers exposed to both bis(chloromethyl)ether (BCME) and chloromethyl methyl ether (CMME). Some of these studies involve workers primarily exposed to CMME contaminated with 1-8 % BCME. Exposure to CMME, a known human carcinogen, is a confounding variable in these studies. However, there are several studies in which individuals were known to have been exposed to BCME, but exposure to CMME was not known to have occurred and appears unlikely.

Theiss *et al*. (1973) (reviewed by IARC, 1973) reported a retrospective study of a small group of BCME workers exposed between 1956 and 1962. Six cases of lung cancer were found in 18 men employed in a testing facility; 5 of the 6 men were smokers. Two additional lung cancer cases were found in a group of 50 production workers. Five of the 8 total cases were oat-cell carcinomas. Exposure periods were 6-9 years, and tumor latency was 8-16 years.

Sakabe (1973) reported on lung cancer cases occurring in 32 workers exposed to BCME in a Japanese dyestuff factory in the period 1955-1970. Five cases of lung cancer were reported compared to 0.024 expected cases ($p < 0.001$). One case was reported to be oat-cell carcinoma; the others were of mixed histological types. Duration of exposure to BCME ranged from 4 to 7 years; cancer mortality latency ranged from 8 to 14 years after initial exposure. It was noted that all the workers that developed lung cancer were also smokers, and that 4 of the 5 cases were also exposed to other industrial chemicals.

Lemen *et al*. (1976) conducted a retrospective cohort study of cancer incidence in a group of 115 white male anion-exchange resin manufacturing workers in San Mateo County, California. Worker tobacco smoking status was evaluated and used to adjust expected tumor incidence rates. Five cases of lung cancer were observed compared to 0.54 cases expected ($p < 0.01$), representing a nine-fold increased lung cancer risk. The histological type of lung cancer primarily observed was small cell-undifferentiated; exposure ranged from 7.6 to 14 years (mean of 10 years). The mean induction-latency period was 15 years. No quantitative worker exposure evaluation was performed.

The studies described above demonstrated a significant increase in lung cancer incidence, predominantly small-cell-undifferentiated carcinoma. This histologic type is not the one generally associated with smoking (squamous cell carcinoma).

Animal Studies

Male Sprague-Dawley rats and golden Syrian hamsters (50/exposure group) received 1, 3, 10 or 30 exposures (6 hours/exposure) to 1 ppm BCME by inhalation (Drew *et al*., 1975). After exposure, the animals were exposed for the remainder of their lifetime. Median survival time for hamsters receiving 0, 1, 3, 10 or 30 exposures was 675, 620, 471, 137 and 42 days, respectively. Median survival time for exposed rats was 467, 457, 168, 21 and 23 days, respectively. One rat in the 3 exposure group developed a squamous-cell carcinoma of the skin; additionally, one hamster in the 1 exposure group developed an undifferentiated nasal tumor. These tumor incidences were not statistically significant. However, the study treatment durations were short, and survival of the treated animals was poor.

Kuschner *et al*. (1975) exposed male Sprague-Dawley rats and golden Syrian hamsters to BCME by inhalation. Groups of 100 hamsters and 70 rats were exposed to 0.1 ppm BCME 6 hours/day, 5 days/week. Control group sizes were not stated. Exposure was generally for the life of the animals. After 80 exposures, 57/70 rats were still alive; 20 rats were then removed from the exposure schedule and observed for the remaining life of the animals. Mortality at 60 weeks was approximately 90% for rats (both animals exposed for their entire lifetime and animals receiving 80 exposures) and hamsters; corresponding control mortality at 60 weeks was approximately 40% and 15% for rats and hamsters, respectively. Two rats in the group receiving 80 exposures developed tumors; the tumor types were a nasal esthesioneuroepitheloma and a keratinizing squamous cell carcinoma of the lung. Additionally, one hamster developed an undifferentiated carcinoma of the lung. No corresponding tumors were reported in control rats or hamsters. Additional groups of rats were given 0, 10, 20, 40, 60, 80 or 100 6-hour exposures to 0.1 ppm BCME (group sizes 240, 50, 50, 20, 20, 30, and 30, respectively), then observed for the life of the animals. Mortality of the exposed animals in all exposure groups was equivalent to that of controls. Nasal and lung tumors were noted in the exposed animals. Nasal tumor types included esthesioneuroepithelomas, unclassified malignant olfactory tumors, squamous cell carcinomas involving the turbinates and gingiva, poorly differentiated epithelial tumors and adeno-carcinomas of the nasal cavity. Lung tumors included squamous cell carcinomas and adeno-carcinomas. Tumor incidence data for combined respiratory tract tumors is listed in Table 1.

Table 1. Bis(chloromethyl)ether-induced respiratory tract tumors in male Sprague-Dawley rats (Kuschner *et al*., 1975)

Number of exposures (6 hours, 0.1 ppm)	Human equivalent[1] $(mg/kg/day)^{-1}$	Tumor incidence[2]
0	0	0/240
10	0.00027	11/41
20	0.000541	3/46
40	0.00105	4/18
60	0.00184	4/18
80	0.00347	15/34
100	0.00373	12/20

1. Calculated by US EPA (1991)
2. Incidence of respiratory tract cancers in animals surviving beyond 210 days.

Male Sprague-Dawley rats (Spartan substrain) (120/group) and Ha/ICR mice (144-157/group) were exposed to 0, 1, 10 or 100 ppb BCME by inhalation for 6 hours/day, 5 days/week for 6 months (Leong *et al*., 1981). The animals were then observed for the duration of their lifespan. No significant increases in mortality were associated with BCME exposure, except for the 100 ppb exposure group; all animals in this group were dead by 19 months. Significant treatment-related increases in the incidence of respiratory tract tumors were noted. Tumor types included nasal esthesioneuroepithelomas and carcinomas, and pulmonary adenomas. Tumor incidence data is listed in Table 2.

Table 2. Bis(chloromethyl)ether-induced nasal tumors in male Sprague-Dawley rats (Leong *et al*., 1981)

Concentration[1] (ppb)	Tumor Incidence[2]
0	0/112
1	0/113
10	0/111
100	97/112

1. Animals were exposed to 0, 1, 10, 100 ppb BCME for 6 hours/day, 5 days/week for 6 months.
2. Incidence of nasal tumors as reported by CDHS (1988).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency factors for BCME were derived from male Sprague-Dawley rat respiratory tract tumor data (Kuschner *et al*., 1975; Leong *et al*., 1981). Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that the value derived from that data set is not appropriate (CDHS, 1985). The Kuschner *et al.* (1975) study used relatively high exposure levels of BCME. The exposure levels used in the Leong *et al*. (1981) study were lower, and the dose-response exhibited is highly non-linear. Therefore, a cancer potency estimated from the Leong *et al*. (1981) data set may be more representative of low-dose rate potency. For low dose exposures to BCME (below 1 ppb), the potency value was calculated from dose-response data published by Leong *et al*. (1981); for periodic high dose exposures (at or above 1 ppb BCME), the potency was derived from the study by Kuschner *et al*. (1975) (CDHS, 1988).

Methodology

Cancer potency factors (q_1^*) were derived using a linearized multistage procedure (CDHS, 1985) with the dose-response data for male Sprague-Dawley rat respiratory tract tumors (Kuschner *et al.*, 1975) and nasal tumors (Leong *et al*., 1981). Absorbed doses were calculated assuming complete absorption of inhaled BCME, using an inspiration rate of 0.29 m^3/day for Sprague-Dawley rats. The dose from a continuous exposure to 1 ppb BCME (4.7 µg/m^3) would therefore be 1.36 µg/day, or 2.6 µg/kg-day. The cancer potency factors (q_1^*) derived from the Leong *et al*. (1981) and Kuschner (1975) data sets were 8.9 $(mg/kg/day)^{-1}$ and 47 $(mg/kg/day)^{-1}$, respectively. Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors, using the relationship ($q_{human} = q_{animal} * (bw_h / bw_a)^{1/3}$), where q_{human} is the human potency, q_{animal} is the animal potency, and bw_h and bw_a are the human and animal body weights, respectively. Body weight values used for humans and Sprague-Dawley rats were 70 kg and 0.52 kg, respectively. The human cancer potency factors (q_1^*) derived from the Leong *et al*. (1981) and Kuschner (1975) data sets were 45.6 $(mg/kg/day)^{-1}$ and 240 $(mg/kg/day)^{-1}$, respectively. The unit risk factor was derived by OEHHA/ATES from the low dose exposure cancer potency value using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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1,3-BUTADIENE

CAS No.: 106-99-0

I. PHYSICAL AND CHEMICAL PROPERTIES (from HSDB, 1998)

Molecular weight	54.09
Boiling point	-4.4° C
Melting point	-108.9° C
Vapor pressure	910 mm Hg at 20° C
Air concentration conversion	1 ppm = 2.21 mg/m^3 at 25° C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.7 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 6.0 E-1 $(mg/kg\text{-}day)^{-1}$
[Calculated from lung alveolar and bronchiolar neoplasms in female mice (Melnick *et al.*, 1990) using a linearized multistage procedure (OEHHA, 1992).]

III. CARCINOGENIC EFFECTS

Human Studies

Several studies have examined cancer mortality rates among industrial workers who were likely to have been exposed to butadiene. However, these studies generally considered workers likely to have had contemporaneous exposure to other potential carcinogens (most notable styrene). Nevertheless, studies of two work environments are sufficiently specific to butadiene exposure to provide limited supporting evidence for the carcinogenic effects observed in animal bioassays. These studies are a case-control study of rubber workers by Matanoski *et al.* (1989) and cohort studies of a butadiene manufacturing plant by Downs *et al.* (1987) and Divine (1990). In addition, Checkoway and Williams (1982) observed statistical associations of blood abnormalities with butadiene exposure at a facility where excess leukemia and lymphoma had been reported.

The first epidemiological study evaluating the possibility of an increased risk of carcinogenicity following occupational exposure to butadiene and other compounds was conducted by the National Institute of Occupational Safety and Health (NIOSH). A study conducted at the University of North Carolina (Spirtas, 1976) prompted NIOSH to examine the issue of styrene-butadiene exposures and a possible link to leukemia (NIOSH, 1976). Leukemia rates in the area surrounding the Port Neches plants, Texas, were found to be above national rates.

McMichael *et al.* (1976) examined deaths occurring from 1964 through 1973 in a male population which had been employed at a large tire manufacturing plant in Akron, Ohio. Standardized Mortality Ratios (SMRs) for the study population indicated that deaths due to several types of cancer exceed rates for the 1968 U.S. male population. Statistically

significantly elevated SMRs were found for stomach cancer (171) and lymphatic and hematopoietic cancers (136). Other solvents and monomers to which these workers were exposed included styrene, benzene, and toluene. Work for five years or more in the synthetic plant was associated with significantly elevated risk ratios for lymphatic and hematopoietic neoplasms (6.2), lymphatic leukemia (3.9), and stomach cancer (2.2).

Andjelkovich *et al.* (1976, 1977) reported the mortality experience of 8,418 white male workers in a large rubber manufacturing plant, also in Akron, Ohio. The cohort was initially divided into two age groups, those under 65 and those 65 or older. SMRs were elevated (but not necessarily significantly) in both age groups in both cohorts for cancers of the stomach, large intestine, and prostate as well as for lymphosarcoma. The SMR for monocytic leukemia (311) was significantly elevated for this entire cohort.

Another cohort of 13,570 white males who had worked for ≥ 5 years in a Goodrich plant in Akron, Ohio was examined for mortality outcome from 1940-1976 (Monson and Fine, 1978). External comparisons (SMR) of mortality, based on U.S. white males, and internal comparisons of incidence were performed in this study. Leukemia and lymphatic cancers were elevated in a number of job categories as was the incidence of gastrointestinal cancer. Solvents were suggested by the authors to have been responsible for the increased incidences; the elevation cannot be specifically attributed to butadiene.

In an investigation of the health effects of styrene exposure, Ott *et al.* (1980) studied 2,904 employees of Dow Chemical plants who had worked for at least one year over the years from 1937 to 1970. SMRs for leukemia (176) and for lymphatic and hematopoietic neoplasms (132) were elevated but not significantly. Therefore, as with the previous studies (McMichael *et al.*, 1976; Andjelkovich *et al.*, 1976, 1977; Monson and Fine, 1978), this report is suggestive of an increase in incidence of lymphatic and hematopoietic cancers in a cohort associated with multiple types of chemical exposures. The increase cannot be definitely attributed to butadiene exposure.

White male workers who had been employed for at least six months in two SBR plants in eastern Texas were studied for an excess of leukemia (Meinhardt *et al.*, 1982) and an attempt was made to correlate the results to occupational chemical exposures. There were 1,662 study subjects in plant A and 1,094 in plant B. Workers were followed from 1943-1976 at plant A from 1950-1976 at plant B. There were no significantly elevated SMRs observed from workers in plant B. In plant A, SMRs were elevated but not significantly for lymphatic and hematopoietic neoplasms (155) and for several subcategories within that classification including leukemia (203).

Divine (1990) found a significantly elevated SMR for lymphosarcoma among 2,582 workers in a butadiene manufacturing facility. The SMR for lymphosarcoma was even higher in those with routine exposure to butadiene. Matanoski *et al.* (1990) observed an excess of leukemia and lymphatic and hematopoietic cancers in black production workers and an elevated SMR for residual cancers of the lymphohematopoietic system for all production workers in several styrene-butadiene rubber (SBR) plants in the U.S. and Canada. Presumably, in SBR plants, production workers had the highest likelihood of

exposure to butadiene, although they may have been exposed to other substances that are, or may be, linked to some of these cancers. While it is difficult to establish a causal relation with butadiene exposure, the fact that cancers of the lymphohematopoietic system were reported in mice suggests that the association deserves close attention in future studies.

Animal Studies

Inhalation of butadiene has been shown to induce tumors in mice and rats at multiple sites. These sites include the heart, lung, mammary gland, ovaries, forestomach, liver, pancreas, Zymbal gland, thyroid, testes, and hematopoietic system. Butadiene is only one of two chemicals known to induce cancer of the heart in laboratory animals.

Mice

The most detailed evaluations of the carcinogenicity of butadiene are the mouse inhalation studies sponsored by the National Toxicology Program (NTP), mouse I (NTP, 1984), and mouse II (Melnick *et al.*, 1990). The nominal doses of study I were 0, 652 or 1,250 ppm administered 6 hours/day, 5 days/week for either 60 weeks (males) or 61 weeks (females). Fifty animals per sex/dose were used. Although the study was designed for 103 weeks, early deaths resulted largely from malignant neoplasms involving multiple organs (heart, hematopoietic lymphomas, lung, mammary gland, ovaries, forestomach, and liver). The incidences of total significant tumor bearing animals (i.e., the number of animals bearing one or more significant tumors) at control, middle, and high doses were 2/50, 43/49, and 40/45 in the males and 4/48, 31/48, and 45/49 in the females. Tumor incidence data are provided in Table 1.

In study II, lower exposure concentrations of butadiene (i.e., 0, 6.25, 20, 62.5, 200, and 625 ppm) were used than had been employed in the first study. Interim sacrifices at 40 and 65 weeks of exposure were also added to the original study design in order to follow progression of lesions. As in the previous study, hemangiosarcomas of the heart, hematopoietic lymphomas, squamous cell neoplasms of the forestomach, alveolar-bronchiolar neoplasms, and/or adenocarcinomas of the mammary gland were frequently observed in mice which died between weeks 40 and 65 of the study. Tumor incidence data used in the quantitative risk assessment are given in Table 2.

Table 1: Incidence of primary tumors in mice exposed to butadiene in the "Mouse I" study[a] (OEHHA, 1992).

Site /Lesion	Sex	Nominal Dose (ppm) in Air		
		0	625	1250
Heart / Hemangiosarcoma	M	0/50[d]	16/49[c]	7/49[c]
	F	0/49[b]	11/48[c]	18/49[c]
Hematopoietic System /	M	0/50[b]	23/50[c]	29/50[c]
Malignant Lymphoma	F	1/50[b]	10/49[b]	10/49[c]
Lung / Alveolar and Bronchiolar Adenoma	M	2/50	12/49	11/49
	F	3/49	9/48	20/49
Lung / Alveolar and Bronchial Neoplasm	M	2/50[b]	14/49[c]	15/49[c]
	F	3/49[b]	12/48[c]	23/49[c]
Mammary / Acinar Cell Carcinoma	F	0/50[b]	2/49	6/49[e]
Ovary / Granulosa Cell Neoplasm	F	0/49[b]	6/45[c]	13/48[c]
Forestomach / Papilloma and Carcinoma	M	0/49	7/40[c]	1/44
	F	0/49[b]	5/42[e]	10/49[c]
Liver / Adenoma	F	0/50	1/47	4/49
Liver / Adenoma and Carcinoma	F	0/50[d]	2/47	5/49[e]

[a] Tumor incidences based on U.S. EPA evaluation of NTP (1984) study.
[b] Increasing trend ($p < 0.01$); [c] Increase compared to control ($p < 0.01$).
[d] Increasing trend ($p < 0.05$); [e] Increase compared to control ($p < 0.05$).

Table 2: Incidence of Primary Tumors in Mice Exposed to Butadiene in the "Mouse II" Study[1] (OEHHA, 1992).

Site / Lesion	Sex	Nominal Dose (ppm) in Air					
		0	6.25	20	62.5	200	625
Heart / Hemangiosarcoma	M	0/70	1/49	1/50	5/38	20/35	6/11
	F	0/70	0/50	0/50	1/33	20/31	26/31
Hematopoietic system /	M	4/50	3/50	8/42	11/44	9/33	69/71
All malignant lymphomas	F	10/50	14/47	18/44	10/38	19/33	43/48
Lymphocytic lymphomas	M	2/50	1/50	2/40	4/40	2/29	62/65
	F	2/50	4/44	6/43	3/38	11/27	36/42
Lung / Alveolar and	M	22/48	23/48	20/44	33/46	42/48	12/16
bronchiolar neoplasm	F	4/50	15/44	19/43	27/44	32/40	25/30
Forestomach / Papilloma and carcinoma	M	1/70	0/50	1/60	5/38	12/33	13/17
	F	2/70	2/50	3/38	4/33	7/23	28/33
Ovary / Granulosa cell Neoplasm	F	1/69	0/59	0/59	9/38	11/25	6/14

[1] Source: Data of Melnick *et al.*, 1990. Figures adjusted for intercurrent mortality.

Rats

A two-year rat inhalation toxicity/carcinogenicity study (Hazleton Europe, 1981) was also evaluated. Groups of 100 per sex/dose were exposed to 0, 1,000, or 8,000 ppm butadiene for 6 hours/day, 5 days/week for 105-111 weeks. Unlike the mouse I study, survival of treated animals was not adversely affected in the first year of the study, but during the second year there was a statistically significant relationship between mortality and air concentration of butadiene. The published incidences (Owen, 1987) are slightly different form those given by U.S. EPA (1985). The total significant tumor incidences (number of animals bearing one or more significant tumors) in males based on U.S. EPA criteria and 1987 published incidences are 4/100, 5/100 and 20/100 for the control, low, and high dose groups (Leydig cell tumors, pancreatic exocrine tumors, and Zymbal gland tumors). Total female significant tumor incidences in the control, low and high dose groups were: 18/100, 19/100, and 41/100 (mammary carcinoma, thyroid follicular cell tumors, and Zymbal gland tumors). Tumor incidence data are shown in Table 3.

Table 3: Incidence of Primary Tumors in Rats Exposed to Butadiene[a] (OEHHA, 1992)

Site / Lesion	Sex	Nominal Dose (ppm) in Air		
		0	1000	8000
Mammary / Fibroadenoma	F	32	64	55
Mammary / Carcinoma	F	18	15	26
TOTAL		50[b]	79[c]	81[c]
Thyroid / Follicular cell adenoma	F	0	2	10
Thyroid / Follicular cell carcinoma	F	0	2	1
TOTAL		0[b]	4	11[c]
Uterus / Cervical stromal sarcoma	F	1	4	5
Testis / Leydig cell adenoma or carcinoma	M	0[d]	3	8[c]
Pancreas / Exocrine adenoma	M	3[d]	1	10[e]
Zymbal gland adenoma	M	1	1	1
	F	0	0	0
Zymbal gland carcinoma	M	0	0	1
	F	0	0	4
TOTAL	M	1	1	2
	F	0[d]	0	4

[a] Data of Hazleton Europe (1981) as published by Owen *et al.*, 1987. Number of rats examined: 100 males and 100 females.
[b] Increasing trend ($p < 0.01$); [c] Increase compared to control ($p < 0.01$)
[d] Increasing trend ($p < 0.05$); [e] Increase compared to control ($p < 0.05$)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

OSHA (1990) has classified butadiene as a "potential occupational carcinogen". U.S. EPA (1985) and IARC (1987) have concluded that the evidence for carcinogenicity of butadiene in animals is sufficient. These organizations have classified the chemical as Group B2 and 2B respectively in their schemes of ranking potential human carcinogens.

With respect to quantitative risk assessment, the epidemiological data base is still considered inadequate for predicting risks of community exposure to butadiene. Thus, the quantitative risk assessment presented in this document relies on data from animal bioassays rather than epidemiologic studies. Cancer potencies were calculated using tumor incidence data from NTP (1984), Melnick *et al.* (1990), and Hazelton Europe (1981).

Methodology

Cancer potency estimates were made for mice and rats using total significant tumor incidences and individual site incidences, three measures of dose, and the linearized multistage procedure of low dose extrapolation. The most sensitive tumor site was the lung alveolar and bronchiolar neoplasms in female mice (mouse II bioassay data of Melnick *et al.*, 1990). The continuous internal dose was considered to be the best measure of dose available. When interspecies equivalent units of mg/m^2 surface area were used, the resulting upper range of human cancer potency based on all rodent assays was 4.4×10^{-6} to 3.6×10^{-4} $(\mu g/m^3)^{-1}$. The range of upper bound risk is based on the two orders of magnitude difference between potency figures for the mouse and the rat. This difference has been the subject of much additional metabolic and kinetic investigation. In addition to a higher metabolic rate for butadiene in the mouse, limited detoxification and accumulation of the primary reactive genotoxic metabolite (BMO) may be a significant factor in the increased susceptibility of mice to butadiene-induced carcinogenesis. The most detailed evaluation of the carcinogenicity of butadiene has been conducted in the mouse.

The staff of the Office of Environmental Health Hazard Assessment concluded that, for use in risk assessment, the quality of the mouse II bioassay data is superior to that of the rat data. The primary reasons for this conclusion are: 1) the use of lower, more relevant dose levels in the mouse II study; 2) the use of five dose levels in the mouse II study, compared to two in the rat study; 3) the presence of two mouse studies; 4) the fact that the rat study has not been replicated; 5) the consistency in sites of carcinogenicity between the two mouse studies; 6) the greater detail in the available mouse data which allows in-depth analysis; and 7) suggestions from limited epidemiological observations that butadiene exposure may be associated in humans with lymphatic and hematopoietic cancers, effects that were seen in mice. The analysis above using lung alveolar and bronchiolar neoplasm incidences in female mice (mouse II bioassay data of Melnick *et al.*, 1990) resulted in a cancer potency of 6.0 $(mg/kg\text{-}day)^{-1}$, and a cancer unit risk of 1.7×10^{-4} $(\mu g/m^3)^{-1}$.

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CADMIUM

CAS No: 7440-43-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1998) except as noted)

Molecular weight	112.41
Boiling point	765 ºC
Melting point	321 ºC
Vapor pressure	1 mm Hg at 394 ºC
Air concentration conversion	1 ppm = 1.8 mg/m^3 (from NIOSH, 1994)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.2 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 1.5 E+1 $(mg/kg\text{-}day)^{-1}$
[Human occupational exposure lung cancer data (Thun *et al*., 1985), Poisson regression model fitted by CDHS (1986), resulting model parameters applied to California life table to calculate cancer risk, reevaluated by CDHS (1990).]

III. CARCINOGENIC EFFECTS

Human Studies

US EPA has reviewed the epidemiologic evidence on health effects due to cadmium exposure (US EPA, 1985). Most of the studies were occupational mortality studies in which cause-specific death rates were compared to expected rates based on a standard population, with the ratio of observed to expected deaths yielding a standardized mortality ratio (SMR). Outcomes examined in these investigations included cancer of the respiratory tract, prostate, bladder, kidney, and gastrointestinal tract. The results were not entirely consistent, but the evidence for an effect of cadmium exposure was strongest for lung cancer, prostate cancer and renal cancer.

Lemen *et al*. (1976) found an excess of prostate cancer deaths among 292 workers employed for greater than two years in a job with potential cadmium exposure. The excess was significant if the analysis assumed a 20-year latency period. However, a follow-up study of this cohort by Thun *et al*. (1985) uncovered no new deaths due to prostatic cancer. The authors suggested that given the generally nonfatal nature of the disease, mortality studies frequently may not be sensitive enough to detect a potentially real association with incidence of prostate cancer. Sorahan and Waterhouse (1983, 1985) followed up a 1967 report by Kipling and Waterhouse which had found a highly significant excess incidence of prostatic cancer. Both the incidence report (Sorahan and Waterhouse, 1985) and the mortality study (Sorahan and Waterhouse, 1983) found no significantly elevated risk if the original four index cases were excluded. However, inclusion of these cases in the analysis yielded a highly significant association. For mortality, using cumulative years of high

exposure to cadmium, the *p*-value was less than 0.05 when controlling for sex, year of study, employment, age at starting employment, and duration of employment. For morbidity, using more than one year of high exposure, the value of *p* was less than 0.001 (1.99 expected, 8 observed, *p*-value not given by authors but calculated by DHS staff based on a Poisson distribution). Tumor incidence was determined using the Birmingham Regional Cancer Registry. The authors do not provide information on completeness of ascertainment by this registry.

The SMR study by Andersson *et al*. (1984) and the matched case-control study by Ross *et al*. (1983) both failed to reject the null hypothesis of no effect on risk of prostate cancer. However, the SMR was considered "possibly" increased and the lack of statistical significance could have been due to deficiencies in the measure of exposure. Similarly in the study by Ross *et al*., the odds ratio (OR) for cadmium exposure among prostatic cancer cases as compared to controls was 2. The smallest OR which would have an 80% chance of being detected as statistically significant in a study this size is 4; therefore, the lack of significance should be interpreted cautiously. In general, the power of these studies was not sufficient to detect the small relative risks for prostate cancer deaths expected from cadmium exposure.

The evidence available at that time appeared to be inconclusive regarding the effect of cadmium exposure on prostatic cancer. Given the highly significant early reports, it may be that cadmium acts as a promoting agent, inducing earlier tumors in those already susceptible. This effect may have been reduced markedly in recent years due to the lowering of exposure levels, sometimes by an order of magnitude or more (Thun *et al*. 1985, Andersson *et al*. 1984, Sorahan and Waterhouse 1985). Therefore, those with earlier exposure may have been at highest risk, and the cohorts most recently studied, being heterogeneous with respect to their exposures, show only nonsignificant increases in prostate cancer incidence, e.g., a doubling or less, and no increase in mortality. Because the human studies repeatedly found some elevation in risk, albeit a nonsignificant one, the staff of DHS decided that the evidence does not permit a conclusive rejection of a possible effect of cadmium on prostate cancer.

Table 1 summarizes the epidemiologic evidence relating respiratory cancer SMR's to cadmium exposure. A significantly increased risk of respiratory cancer deaths was seen by Lemen *et al*. (1976), Thun *et al*. (1985), Sorahan and Waterhouse (1983), Varner (1983), and Armstrong and Kazantzis (1983), but not by Inskip *et al*. (1982) nor by Andersson *et al*. (1984). However, the assessment of exposure in the two towns investigated by Inskip *et al*. relied only on 1979 soil samples for exposure from 1939 to 1979. Even with a questionable exposure assessment, males in the exposed town had a lung cancer SMR which, while not statistically significant, was nearly double that of males in the unexposed town (101 vs. 55). The other negative study (Andersson *et al*., 1984) had low statistical power to detect a SMR of less than 200. In other studies, the range of SMR's for respiratory cancer was 120-230 (see Table 1). The staff of DHS concluded that the two negative studies for respiratory cancer are not convincing evidence of no effect, due to low statistical power in one study and poor exposure data in the other.

The study by Thun *et al*. (1985) showed a positive dose-response relationship where dose was expressed as cumulative mg-days/m^3. Varner (1983) reported the lung cancer PMR (proportional mortality ratio) to be elevated. Sorahan and Waterhouse (1983), in two separate analyses, found an elevated risk of respiratory cancer. The first analysis was based on the SMR and included all potentially exposed workers. The second analysis used the regression method of life tables (RMLT) and assessed exposure by cumulative years employed in a (1) high exposure job or (2) high or moderate exposure job or (3) high or moderate exposure job excluding welding. Measures (2) and (3) resu1ted in a significant effect of exposure on respiratory cancer, particularly for those with more than 30 years of follow-up.

Table 1: Association Between Cadmium Exposure and Respiratory Cancer Mortality

Authors	SMR	Significant at $p < 0.05$
Sorahan and Waterhouse 1983	127	Y
Lemen *et al*., 1976	235	Y
Thun *et al*., 1985	229	Y
Armstrong and Kazantzis 1983	126[a]	Y
Inskip *et al*., 1982	101[b]	N
Andersson *et al*., 1984	120	N

[a] For workers with >10 years exposure in the "always low" category (the number of workers with "ever medium" and "ever high" exposures was small).
[b] vs. SMR-55 for the unexposed town.

Heavier smoking among cadmium workers as compared to the general population could account for the small but statistically significant SMR for lung cancer (126) observed by Armstrong and Kazantzis (1983) for those exposed >10 years at the "always low" category. No smoking histories were available. Sorahan and Waterhouse (1983) also lacked data on smoking, but they argue that smoking was unlikely to have been a confounder for two reasons. First, their analysis showed an increasing association with duration of employment, while smoking habits are unlikely to be well-correlated with duration of employment. Secondly, deaths from other diseases of the respiratory system were not elevated, as they would have been if the cohort had included a disproportionate number of smokers. However, the effect of nickel hydroxide could not be disentangled from that of cadmium oxide in this cohort.

The strongest evidence for cadmium-induced carcinogenicity in humans is the study conducted by Thun *et al*. (1985). The characteristics of this study which make it particularly convincing are the quality of the exposure data and the analysis of potential confounding. Since the quantitative results of this study constituted the basis for the DHS risk assessment of cadmium, a full description of this study is presented below.

Thun *et al*. (1985) conducted a follow-up of the report by Lemen *et al*. (1976), who had found an increase in mortality from respiratory and prostate cancer and from nonmalignant lung disease in a cohort of cadmium smelter workers. Thun *et al*. (1985) expanded the cohort and extended the follow-up period. The final cohort included those hired after 1925

and employed 6 months or longer in production areas of the plant during the period 1940-1969. The cause-specific death rates were adjusted by the indirect method to yield standardized mortality ratios (SMRs) and by the direct method to yield standardized rate ratios (SRRs). The SMR for lung cancer in the overall cohort was 147, while for those with 2 or more years of employment it was 229, with a 95% confidence interval of (131,371).

Exposure data that had been collected since the 1940's allowed evaluation of the lung cancer SMR by dose. Industrial hygiene measurements for departments and job sites with potential cadmium exposure were available (Smith *et al*. 1980). These were combined with individual work histories for each member of the cohort in order to assign an exposure level to each work day. Interruptions of employment were taken into account and exposure levels were adjusted to reflect respirator usage in departments where these were worn. A cumulative exposure in mg-years/m^3 was then assigned to each person-year of follow-up for each worker. The range of cumulative exposures was divided into three categories and both SMRs and SRRs were calculated for each category. The results are shown in Table 2 using US white males as the comparison population, and in Table 3 using Colorado white males as the comparison population. (Thun presented the analysis using Colorado white males as the control group at the Fifth International Cadmium Conference, February 1986, in San Francisco. This analysis assumes that pre-1950 lung cancer rates equaled those in 1950, since cause-specific rates were not tabulated in that state before 1950.)

Table 2: Lung Cancer (ICD 162-163) Mortality By Cumulative Exposure White Male Cadmium Workers Hired on or After 1/1/26 Compared to U.S. Death Rates (Adapted from Thun *et al*. (1986), Table 7)

Exposure (cumulative mg/m^3)					
Range	Median	Person years at risk	Deaths	SMR	SRR
≤384	184.1	7005	2	53	0.48
385-1920	795.6	5825	7 (6)*	152 (130)*	1.55 (l.33)*
≥1921	2761.6	2214	7	280	3.45
U.S. WHITE MALES				100	1.00

* Numbers in parentheses exclude one lung cancer death which was originally miscoded as being due to another cause.

The data indicate a clear dose-response relationship between cumulative cadmium exposure and the risk of death due to lung cancer. Using the US population as the comparison group, both the SMR and the SRR rise from about 1/2 the expected at "low" cumulative exposure to about 3 times the expected at high cumulative exposure. Both of

these measures of risk are larger when the Colorado population is used as a standard, with the SRR rising from 0.7 to over 5.0.

Table 3: Lung Cancer (ICD 162-163) Mortality by Cumulative Exposure; White Male Cadmium Workers Hired on or After 1/1/26 Compared to Colorado Death Rates, 1950-79 (Adapted from Thun *et al.* 1985, Table 8).

Cumulative exposure (mg-days/m^3)	Person-years at risk	Deaths	SMR	SRR
≤384 385-1920 ≥1921	7005 5825 2214	2 7(6)* 7	76 212(182)* 387	.70 2.29(l.96)* 5.09
Colorado white males			100	1.00

* Numbers in parentheses exclude one lung cancer death which was originally miscoded as being due to another cause.

Thun *et al*. (1985) calculated the standardized rate ratio (SRR) for each of 3 exposure groups. (The person-years at risk, rather than individual workers, were classified by cumulative exposure to that point in time.) The SRR is suitable for subgroup comparisons, but not for external comparisons. A regression of the SRRs yielded a slope of 7.33×10^{-7} which differed from zero with a probability of 0.0001.

Selection criteria described by Thun *et al*. (1985) appear to have been unbiased: all retired, deceased, and active employees who had worked a minimum of 6 months in production areas of the plant were included in the cohort. In calculating cumulative exposure, dates of interruption of employment were accounted for. Since more than 80% of the workers were followed for 20 or more years it is likely that the follow-up was sufficient for many latent cadmium-induced cancers to become manifest and lead to death. Trained nosologists evaluated the death certificates. As indicated by Thun *et al*., one lung cancer death was originally miscoded as being due to another cause. Removal of this death from the lung cancer deaths (i.e. restoring it to the original, but incorrect coding) is necessary in order that the comparison with general population rates be unbiased (since miscodings also occur in the general population). However, the findings are not altered in any substantial way by this reclassification.

Exposure categories were chosen prior to the analysis. The cumulative exposure for all person-years was miscalculated by Thun *et al*. (1985) because they included non-workdays. This does not cause bias for purposes of. inference since the misclassification was equivalent for all exposure categories. It would, however, alter the dose-response relationship, and therefore DHS staff adjusted for this error in conducting their risk assessment, since an overestimate of exposure would result in an underestimation of potency. The corrected exposures are shown in Tables 2 and 3.

If the cadmium-exposed workers included a disproportionate number of individuals with exposures to other agents responsible for lung cancer, then the observed association might be spurious. The potential confounders with regard to lung cancer mortality in this cohort were smoking and arsenic exposure.

(a) Smoking:

Indirect evidence that smoking was not a confounder in this cohort is provided by the cardiovascular death rate in this cohort, which was 35% lower than expected based on U.S. white male death rates. If this cohort included a higher proportion of total smokers or heavy smokers as compared to the general population of white males in the same age categories, then one would expect an increase (or at least not a deficit) in the cardiovascular death rate as well.

Data on the smoking habits of these workers were provided to Thun *et al*. (1985) by the company. The data came from company medical records and from a questionnaire survey mailed to surviving workers or the next-of-kin in 1982. The results of this survey have elicited differing interpretations depending on the choice of measure of smoking and on the choice of the comparison group. The 1985 paper by Thun *et al*. reported data on 70% of the workers. For these workers, the data indicated that as of 1982, 77.5% were current or former smokers compared to 72.9% current or former smokers among U.S. white males 20 years or older reported in the 1965 Health Interview Survey (HIS) conducted by the National Center for Health Statistics. It is clear that these 2 figures are not comparable since data from 1982 for the exposed group were compared with data from 1965 for the control group.

In the updated report by Thun *et al*. (1986), presented at the Fifth International Cadmium Conference in San Francisco, February 6, 1986, the authors provided a more meaningful comparison by limiting the smoking analysis to the 49% of the cohort for whom lifetime smoking histories were available. These data indicated that as of 1965 a larger percentage of the cadmium-exposed cohort were nonsmokers and a smaller percentage were heavy smokers compared to general population rates available from the HIS. The year 1965 was chosen since this was the midpoint of the study.

The percent who "ever smoked" was 77.5% in the cadmium-exposed cohort, and 76% in the total HIS sample. The data on the cadmium workers represented information from only 36% of the cohort. Given that the cohort under study was considerably older than the HIS sample, that the HIS survey was done about 10 years earlier than the survey of the cadmium cohort, and that different information was reported from these two surveys, the differences between the smoking habits of the total HIS sample and those of the cadmium-exposed workers do not appear to be very large.

The magnitude of confounding from differential smoking habits can be assessed. A method to estimate the contribution of smoking to lung cancer mortality in the cohort is described by Axelson (1978). The method is applied to the lifetime smoking histories summarized by Thun *et al*. (1985). The calculations (summarized in Table 4) are based on information

regarding smoking habits in the exposed group, smoking habits in the comparison group, and the relative risk for lung cancer at each level of smoking. In view of the data indicating a deficit of smokers in this cohort compared to the general population, the baseline SMR for lung cancer would have been reduced 30%.

It is unknown, however, whether the smoking histories of the 49% sample were representative of the cohort as a whole, and whether the histories themselves were biased, since they were collected retrospectively. While smoking may have confounded the relationship between cadmium and lung cancer, it is unlikely that smoking was responsible for all of the excess. Furthermore, if the smoking habits in this cohort were correctly reported, i.e., if the observed deficit of smokers was real, then the excess of lung cancer deaths is larger than originally calculated. In other words, confounding due to smoking did not create the appearance of a nonexistent carcinogenic effect from cadmium; rather, the confounding reduced the apparent magnitude of cadmium's carcinogenicity.

Table 4: Technique Used to Adjust for Cigarette Smoking (Thun *et al*., 1986)

Population	Percent of Population, 1965			Rate Ratio of Overall Population Relative to Nonsmokers	Rate Ratio Relative to U.S.
	Nonsmokers[3] (1X)	Moderate[1] Smokers (10X)	Heavy [2] Smokers (20X)		
Exposed	48.4%	40.8%	10.8%	6.724	0.70
U.S.	27.1%	53%	20%	9.571	1.0

1. 1-24 cigarettes/day
2. 25+ cigarettes/day
3. The numbers in parentheses refer to the relative risk for lung cancer associated with each level of smoking.
4. Usable information available on 250 persons hired after 1926.

(b) Arsenic

The plant employing the workers in this cohort refined cadmium metals and compounds from 1926 onwards. Between 1918 and 1925 it had functioned as an arsenic smelter. Therefore, the analysis by Thun *et al*. excluded workers employed prior to January 1, 1926. (For those employed prior to 1926 the lung cancer SMR was 714). Nevertheless, it is possible that residues of arsenic contributed to the lung cancer excess for those first employed in 1926 or later.

To estimate the possible contribution of arsenic to lung cancer in this cohort, Thun *et al*.:

(1) identified the departments and job categories which were likely to have involved continued exposure to arsenic;

(2) calculated the proportion of person-years spent in areas with probable arsenic exposure based on personnel records (20%);

(3) evaluated industrial hygiene measurements to estimate air concentrations (range - 300 to 700 $\mu g/m^3$; Thun used midpoint - 500 $\mu g/m^3$);

(4) estimated the total years of employment for workers in the cohort (1728 years);

(5) based on (2), (3), and (4), estimated that total arsenic exposure amounted to 345.6 person-years of exposure to air levels of 500 $\mu g/m^3$;

(6) assumed a 75% respirator protection factor (i.e. inhaled exposures were 25% of air concentrations or 125 $\mu g/m^3$. This yielded a total exposure of 43,200 μg-years/m^3.

Using a risk assessment model developed by OSHA for arsenic carcinogenicity, Thun calculated that 43,200 $\mu g/m^3$ years of exposure to arsenic would contribute no more than 0.768 lung cancer deaths. This may represent an overestimate of the contribution of the arsenic exposure to the lung cancer excess. The reasons submitted by Thun are as follows:

1) Only a fraction of jobs in the "arsenic areas" had exposures as high as the furnace area (500 $\mu g/m^3$);

2) The high exposure jobs were frequently staffed with brief employment-entry (sic) level workers who are not in the study cohort;

3) Urinary arsenic levels on workers in the "high arsenic" areas from 1960-80 averaged only 46 $\mu g/l$ (equaling an inhaled arsenic of 14 $\mu g/m^3$);

4) Thus, assuming an average inhaled arsenic concentration of 125 $\mu g/m^3$ for these years overestimates the dose by 9-fold;

5) ASARCO has previously argued that the OSHA risk assessment overestimates "by a factor of three or more" the expected increase in mortality from respiratory cancer. (Thun, personal communication; cited in CDHS, 1986)

The last issue with respect to confounding concerns the combined effects of arsenic and smoking on lung cancer, which are more than additive, though probably less than multiplicative. Therefore, if any of the workers who were exposed to arsenic were smokers, there could also be confounding from the interactive effect of these two exposures. However, when relative risks are small (e.g., less than 1.3), there is very little difference between additive and multiplicative effects. Since it is unlikely that in this cohort the relative risk associated with either arsenic or smoking is larger than 1.3, the effect of any interaction is likely to be negligible. (If both relative risks are 1.3, multiplying yields 1.69, adding yields 1.6, difference = .09.)

In conclusion, given the low level of arsenic exposure and the evidence indicating a deficit of smokers in this cohort, DHS staff decided that the apparent association between cadmium exposure and lung cancer were not likely to be explained by confounding from smoking and/or arsenic exposure.

To summarize the DHS staff's findings with regard to the study by Thun *et al*. (1985) - the SMR of 2.3 in those with more than 2 years of cadmium exposure and the dose-response relationship are unlikely to be explained by chance, by bias, or by confounding from smoking and/or arsenic exposure. The staff of DHS concluded that the excess of lung cancer deaths in the study by Thun *et al*. (1985) is best explained by exposure to high levels of cadmium. The DHS staff further concluded that this study constitutes strong evidence of human carcinogenicity.

Animal Studies

Cadmium has been the subject of numerous studies in experimental animals to determine its carcinogenic potential. These studies have been extensively reviewed elsewhere (IARC 1973, 1976; EPA 1981, 1985); only the inhalation and intratracheal administration studies will be discussed here.

Sanders and Mahaffey (1984) examined the carcinogenic potential of cadmium oxide in male rats by intratracheal instillation. The rats were treated one, two or three times with 25 μg of cadmium oxide. The first administration was given at 70 days of age and then at 100 and 130 days of age depending on the total dose to be given (25, 50, or 75 μg). The animals were then followed for their lifetime. No differences were found in survival times or organ weights between treated and control groups. Using life-table and contingency table statistical analyses a significant increase in benign mammary fibroadenomas was observed in the high dose group. Additionally, there was a significant increase in the number of rats in the high dose group that had three or more tumor types.

Hadley *et al*. (1979) exposed a group of 61 male Wistar strain rats one time to an airborne cadmium oxide aerosol concentration of 60 mg/m^3 for 30 minutes. The mass median diameter of the particles was 1.4 μm with a geometric standard deviation of 1.9 μm. Seventeen animals were used as controls. Twenty-seven exposed animals died within three days from acute pulmonary edema. The remaining animals were then observed for one year. No morphological changes were noted in the lungs of exposed animals, although one animal did have a well-differentiated pulmonary adenocarcinoma. The authors observed that this tumor's relatively short latency period and the low spontaneous incidence (0.1%) of such tumors suggested that it resulted from cadmium exposure.

Both the Sander and Mahaffey (1984) study and the Hadley *et al*.(1979) study were not adequate to assess carcinogenic potency, since the animals were only exposed for short periods and, in the Hadley *et al*. (1979) study, were not followed for sufficient time. Without continuous exposure, effects in the lungs may not occur or the study may not be sensitive enough to detect adverse effects.

In the only long-term inhalation study available to the cadmium TAC document, Takenaka *et al*. (1983) exposed rats to several concentration of a cadmium chloride aerosol. Groups of 40 male Wistar rats were exposed to a continuous (23.5 hours/day) airborne concentration of 13.4, 25.7, or 50.8 µg of cadmium/m^3 of air for 18 months. A control group of 41 rats was exposed to filtered room air. The aerodynamic mass median diameter of the aerosol particles was 0.55 µm with a arithmetic standard deviation of 0.48 µm and a geometric standard deviation of 1.8 µm. The rats were followed for an additional 13 months before surviving rats were sacrificed.

There were no statistically significant differences seen in body weight or survival between exposed and control groups. The incidence of lung carcinomas was significantly increased ($p > 0.014$, Fisher's exact test) in all exposure groups. Three lung tumor types were identified, adenocarcinoma, epidermoid carcinoma, and mucoepidermoid carcinoma. The numbers of animals in each group that had these tumor types are given in Table 5. The first lung tumor was observed at 20 months. In the high-dose group, the first tumors were observed at 23 months and 23 out of 25 animals in this group dying or sacrificed after 27 months had lung tumors. Therefore, these appear to be late-developing tumors.

Table 5: Lung tumors in rats exposed to cadmium chloride aerosols (Takenaka *et al*., 1983)

Exposure Group	# rats with tumors				
	# rats examined histologically	Adenocarcinoma	Epidermoid Carcinoma	Mucoepidermoid Carcinoma	Total Carcinomas
Control	38	0	0	0	0
13.4 µg/m^3	39	4	2	0	6
25.7 µg/m^3	38	16	5	0	20[b]
50.8 µg/m^3	35	15	8	3	25[b]

a Airborne exposure concentrations are based on the cadmium, not cadmium chloride, concentration.

b One rat had both an adenocarcinoma and an epidermoid carcinoma.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

A quantitative cancer risk assessment for cadmium using the data from the occupational mortality study by Thun et al. (1985) and extrapolating to ambient levels in California was done by DHS staff. The exposure data in this study were based on industrial hygiene measurements and individual work histories. These measurements consisted of historical area monitoring samples and, when appropriate, were adjusted to reflect respirator protection in departments where respirators had been worn. For workers employed 6 months or longer in production areas of the plant the person-years of follow-up were

divided into 3 categories according to cumulative exposure in mg-days/m^3 (see Table 6). The risk of death from lung cancer for each exposure group was measured by the standardized mortality ratio (SMR). The data indicated a clear dose-response, with SMRs of 53, 152 and 280 for the low, moderate and high exposure groups. Because the study related quantified exposure levels to quantified measures of lung cancer risk, the data were suitable for a risk assessment.

Table 6: Cadmium Exposure Levels of Workers in Thun *et al*. (1985) Occupational Exposure Study

	Cumulative exposure in mg-days/m^3			Equivalent lifetime dose rate* in μg/m^3
	Range reported by Thun *et al*.	Median	Median adjusted for 240 workdays/year	Median
Low	≤584	280	184.1	2
Middle	585-2920	1210	795.6	11.8
High	≥2921	4200	2761.6	41.0

* Assumes 24 hour/day exposure and an estimated average lifetime of 61.5 years.

Methodology

A Poisson regression model was fitted to the data. In this model the observed deaths are a function of two variables: the dose and the expected deaths. The function has two parameters: one for the carcinogenic potency of cadmium, the other to account for the healthy worker effect.

Obs_i = observed deaths in exposure group i

Exp_I = expected deaths in exposure group i based on the indirect method of age adjustment

d_i = median dose received by group I

The model is then expressed as:

$E[\ Obs_i\ ] = (1 + \beta d_i) \times \alpha \times Exp_i$ where E[ ] represents the expectation of a random variable, α = healthy worker effect, and β = potency of cadmium per unit dose.

This model predicts that in the absence of cadmium exposure ($d_i = 0$), the observed deaths will equal the expected deaths times some factor which distinguishes the workers from the general population, a factor which can be termed the "healthy worker effect". The appropriateness of this model is indicated by the mortality experience of the low exposure group, which had an SMR for lung cancer of 53. (The cohort also had a low SMR for cardiovascular deaths.) This model therefore separates the carcinogenic effect of cadmium

from the opposing, healthy worker effect. Using a nonlinear regression procedure (NLIN), the parameters were estimated at:

$\hat{\alpha}$ = 0.500 (unitless parameter) and
$\hat{\beta}$ = 0.0017 (cumulative mg-days/m^3)$^{-1}$

the 95% (two-tailed) upper confidence limit for β was 0.0079, and the χ^2 goodness-of-fit statistic was 0.15 (1 df, p = 0.70). Lung cancer deaths predicted by the model were compared with the observed lung cancer deaths for the three exposure groups (Table 7).

Table 7: Lung Cancer Deaths Among Cadmium-Exposed Workers: Observed And Predicted (Data of Thun *et al*., 1985)

	Cumulative Exposure Groups		
	Low	Middle	High
Observed	2	6	7
Predicted*	2.94	5.99	7.44

* Linear relative risk model with healthy worker effect, U.S. controls.

With these estimates of the parameters, the model was then applied to the California population to predict the excess number of lung cancer deaths induced by cadmium exposure. First, a current life table was produced for California males and females separately, using five-year age intervals. The background hazard of lung cancer death for each five-year age interval was calculated using 1980 census data for California (Bureau of the Census, 1982) and age-specific death rates for California from 1979-80 vital statistics data (California Department of Health Services, 1982) by standard statistical techniques (Chiang, 1984). These were then summed over a lifetime.

Next, using the estimated value for β and setting α = 1 for the general population (i.e. no healthy worker effect), the hazard of lung cancer death given a continuous lifetime exposure to 1 μg/m^3 cadmium was calculated from the model. Using these hazard rates, a new life table was constructed. Subtracting the background probability of a lung cancer death from that obtained for an exposed population resulted in a range of risk for excess lifetime cancer from 2×10^{-3} to 1.2×10^{-2} (μg/m^3)$^{-1}$. CDHS also suggested that a "best" cancer unit risk value for regulatory purposes was 1.6×10^{-3} (μg/m^3)$^{-1}$ for cadmium in air.

CDHS (1990) reviewed the previous CDHS (1986) estimate of parameters generated from the fit of the Poisson regression model to the Thun *et al*. (1985) lung tumor data. The 97.5% upper confidence limit for β was calculated for a number of values of α that were in the range $0.5 < \alpha < 1.0$. All of the calculated 97.5% upper confidence limit for β were less than the corresponding values calculated from the statistical analysis program used previously by CDHS (1986).

CDHS (1990) decided that it is reasonable to restrict α to values between 0.5 and 1.0. If α were less than 0.5, the study cohort background incidence of respiratory cancer would be less than 50% of the incidence among males in the Colorado population. On the other hand, CDHS (1990) concluded that it was not appropriate to assume that the background incidence of respiratory cancer is higher ($\alpha > 1$) in the study cohort than it is in the control population. Because the lung cancer incidence for Colorado males is 72% of the rate for U.S. males, CDHS selected the value $\alpha = 0.7$ as a reasonable midrange estimate. With this choice, the values of the MLE and 95% UCL for 0 are 0.0017 and 0.0028 $(\text{mg-days/m}^3)^{-1}$, respectively. When the upper confidence limit estimate for β is used to estimate lifetime cancer risk from the data and life-table methodology used by CDHS (1986), the resulting cancer unit risk is 4.1×10^{-3} $(\mu\text{g/m}^3)^{-1}$. This value is within the range of unit risks (2×10^{-3} to 1.2×10^{-2} $(\mu\text{g/m}^3)^{-1}$) contained in the cadmium TAC document and approved by the Scientific Review Panel.

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CARBON TETRACHLORIDE

CAS No: 56-23-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1998) except as noted)

Molecular weight	153.8
Boiling point	76.7°C
Melting point	-23°C
Vapor pressure	91.3 mm Hg @ 20°C
Air concentration conversion	1 ppm = 6.3 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.2 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 1.5 E-1 $(mg/kg\text{-}day)^{-1}$
[Calculated from mouse liver tumor incidence data (Edwards *et al*., 1942) using a linearized multistage procedure, extra risk (US EPA, 1984); revised by CDHS (1987).]

III. CARCINOGENIC EFFECTS

Human Studies

Capurro (1979) reported a study on the residents in a rural valley polluted by vapors from a solvent recovery plant for at least 10 years. Chloroform, benzene, methyl isobutyl ketone, trichloroethylene and 26 other organic agents were detected in the air in addition to carbon tetrachloride (Capurro, 1973). The author reported four excess cases of lymphoma. Attributing these cancer cases to carbon tetrachloride alone would be inappropriate due to exposure to the other contaminants.

In a preliminary study of 330 laundry and dry cleaning workers, Blair *et al*. (1979) examined occupational exposure to carbon tetrachloride and other dry cleaning agents. Information from death certificates indicated an excess of deaths from lung, cervical and liver cancer, and leukemia. Katz and Jowett (1981) studied female laundry and dry cleaning workers in Wisconsin. Their results failed to show an overall increase in malignant neoplasms, but they did report an elevated risk for cancers of the kidney and genitals (unspecified), along with smaller excesses of bladder and skin cancer and lymphosarcoma. However, the use of carbon tetrachloride has been of only minor importance in dry cleaning since the 1950's and quantitative data on exposure to carbon tetrachloride were not presented in these studies.

Hernberg *et al*. (1984) reported a case-control study on primary liver cancer and exposure to solvents. Of 126 cases, two had a history of exposure to carbon tetrachloride, among

other solvents. They concluded that there was an association between primary liver cancer and exposure to "solvent" among women, but not for men.

Two reports were published on cancer mortality in a population of rubber workers (Checkoway *et al*., 1984; Wilcosky *et al*., 1984). Information on cause of death was reported earlier by McMichael *et al*. (1974). They reported a significantly elevated odds ratio relating carbon tetrachloride with lymphatic leukemia (OR = 15.3, $p < 0.0001$) and lymphosarcoma and reticulum cell sarcoma (OR = 4.2, $p < 0.05$). Attributing these outcomes to carbon tetrachloride alone is inappropriate since different solvents were used simultaneously in a given process area. A high degree of correlation also existed between exposure to several other solvents and the incidence of lymphatic leukemia (carbon disulfide, ethyl acetate, acetone, and hexane) and lymphosarcoma (xylenes, carbon disulfide and hexane). Although some of these solvents are not recognized carcinogens, these potentially confounding exposures, the lack of association of carbon tetrachloride exposures with these cancers in other studies, and the small number of cases (19/6678), preclude any causal inference from this study.

In summary, the epidemiological studies and human case reports are inadequate for use in a quantitative risk assessment.

Animal Studies

Mice

Edwards (1941) and Edwards and Dalton (1942) administered carbon tetrachloride by gavage to different strains of male and female mice (Strains A, C, CH3 and Y) two to three times a week for 8 to 23 weeks. To assess the tumor-producing ability of carbon tetrachloride, animals were necropsied 12 to 21 weeks after the last treatment. For those animals exposed to approximately 2100 mg/kg of carbon tetrachloride the incidence of hepatoma was 88.2 percent (strain CH3). Whether the carbon tetrachloride-induced hepatomas were malignant was not established histologically in the study. The animals were dosed on a non-daily schedule for a maximum of 16 weeks and sacrificed starting at 4 months of age. Since tumor expression is a function of both dosage and the latency period, any risk assessment based on these studies, with their short observational periods, will underestimate the true carcinogenic risk. In another experiment Edwards and Dalton (1942) administered 1, 2, or 3 doses of carbon tetrachloride (≈260 to 2100 mg/kg) followed by long-term observation in Strain A mice. The doses were hepatotoxic, but when the animals were examined 12 months later no tumors were observed.

Edwards *et al*. (1942) treated 56 male and 19 female L mice with 0.1 ml of 40% carbon tetrachloride 2 or 3 times/week over 4 months, for a total of 46 treatments. Animals were killed 3 to 3.5 months after the last treatment. The combined hepatoma incidence of treated male and female mice was 47% (34/73 vs. 2/152 in the untreated controls) (Table 1).

Eschenbrenner and Miller (1943; 1946) extensively examined carbon tetrachloride-induced tumor production in Strain A mice. In the first study they administered 30 doses

of carbon tetrachloride at intervals of one to five days (0, ≈160, 315, 625, 1250 and 2500 mg/kg). All animals were examined for tumors at 150 days following the first dose. Centrilobular liver necrosis was observed at all exposure levels. They reported that the incidence of hepatomas was increased as the time interval between doses increased.

In a second study Eschenbrenner and Miller (1946) administered the same total quantity of carbon tetrachloride, either in 30 doses at four-day intervals or in 120 doses on consecutive days. This study was conducted to determine the effect of liver necrosis on tumor development. They found that mice receiving the smaller dose over 120 days (a "non-necrotizing" dose) developed tumors at roughly the same or greater rate as those animals that received necrotizing doses (30 large doses at four-day intervals). The tumor incidence was not statistically significant. It appears that liver necrosis was not a required precondition for the production of tumors with carbon tetrachloride. This study showed that the total length of the exposure period (i.e., 120 versus 30 days), not the time between doses, may have been the major determining factor in the production of tumors.

Three NCI mouse bioassays used carbon tetrachloride as a positive control (NCI, 1976a,b; 1977; Weisburger, 1977) and excess mortality was a severe problem in the studies. Mice ($B6C3F_1$, males and females) were dosed by gavage (0, 1250 and 2500 mg/kg body weight) for 5 days/week for up to 78 weeks and they were to be sacrificed at 92 weeks. However, only 14% of the animals survived to 78 weeks and less than 1% survived to 92 weeks. This compares with 66% of the controls surviving the 92-week experiment. Hepatocellular carcinoma was found in almost every treated animal (Table 1). Carcinomas were observed as early as 16 weeks for the low-dose female group. The high mortality and virtual 100% tumor response are the more serious limitations of this study for use in quantitative risk assessment.

Table 1: Carbon tetrachloride-induced liver tumor incidence in mice.

Study	Strain	Dose (mg/kg-day)	Tumor incidence
Edwards et al., 1941	strain Y (male, female)	0	2/152 (2%)
		≈2100	34/73 (47%)
NCI 1976a,b; 1977	$B6C3F_1$ (male, female)	0	6/157 (4%)
		1250	89/89 (100%)
		2500	90/93 (97%)

Rats

Reuber and Glover (1970) compared the carcinogenicity of carbon tetrachloride in 12-week-old male rats (Japanese, Osborne-Mendel, Wistar, Black and Sprague-Dawley strains). The animals were subcutaneously injected (0, 2080 mg/kg body weight) twice a week for up to 105 weeks. Corn oil was administered to controls. All the Black and Sprague-Dawley strains died within 18 weeks. No carcinomas were observed. Hyperplastic nodules and hepatic carcinoma were reported in the other three strains (80%, 20%; 63%, 31%; 14%, 14% for Japanese, Osborne-Mendel and Wistar rats, respectively).

Other lesions reported were hemangiomas (13% and 8% for Japanese and Osborne-Mendel rats, respectively), carcinomas of the thyroid gland (20% and 23% for Japanese and Osborne-Mendel rats, respectively), and subcutaneous leiomyosarcoma (7% in Japanese rats). Cirrhosis was reported in all animals. Due to the small group size, poor survival of several strains and the incomplete reporting of the total dosage, and most importantly, the inappropriate route of exposure (subcutaneous injections), this study was not used in a quantitative risk assessment. As in the mouse studies, NCI used carbon tetrachloride as a positive control in rat bioassays for chloroform, 1,1,1-trichloroethane and trichloroethylene (NCI, 1976a,b; 1977; Weisburger, 1977). The Osborne-Mendel rats were administered a time-weighted average dose of carbon tetrachloride by gavage for 78 weeks (47, 97 and 80, 159 mg/kg body weight, respectively for males and females). Hepatic carcinomas were found at both doses in both sexes (4%, 4% and 8%, 2% in low and high dosage, males and females, respectively). A lower incidence was reported in the high-dose females, but this may have been a result of that dose group's high mortality rate prior to tumor expression. Tumors in other tissues were not discussed.

Male and female Syrian golden hamsters were administered carbon tetrachloride in corn oil weekly by gavage (190 and 380 mg/kg of body weight, respectively) for a total of 30 weeks (Della Porta *et al*., 1961). Following treatment, the animals were kept 25 weeks, sacrificed and examined. Only eight of the original 20 animals survived the full 55 weeks. Carcinomas were not observed in the animals that died prior to the 43rd week, but one or more liver-cell carcinomas were reported in all the surviving animals, indicating that tumors may be produced at lower levels in this species. Liver tumor incidence in carbon tetrachloride-treated animals (males and females combined) was 10/19 (53%) compared to 0/80 (0%) for controls.

In summary, carbon tetrachloride has been shown to produce liver tumors in mice, rats and hamsters by the oral and subcutaneous routes. No inhalation cancer bioassays have been conducted.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Carbon tetrachloride has been observed to induce liver tumors in male and female hamsters, mice and rats, as described above. CDHS (1987) decided that the tumor incidence data from studies by Della Porta *et al*. (1961) (hamster), Edwards *et al*. (1942) (mouse) and NCI (1977a, b) (mouse) were suitable for use in developing a quantitative risk assessment.

Methodology

A health assessment document for carbon tetrachloride was prepared by US EPA (1984). This document contained a quantitative cancer risk assessment for carbon tetrachloride. A linearized multistage procedure was applied to liver tumor incidence data (Della Porta *et*

al., 1961; Edwards *et al*., 1942; NCI 1976a, b; 1977 [rat, mouse]) to estimate a cancer unit risk.

The quantitative risk assessment of carbon tetrachloride conducted by US EPA (1984) using the linearized multistage procedure was modified by DHS (1987) by: 1) applying an absorption fraction of 50% instead of 40%; 2) omitting one rat bioassay US EPA used (NCI, 1976a, b; 1977); 3) assuming an average inhalation intake of 18 µg/day instead of 20 µg/day; and 4) presenting the range of resulting unit risks instead of the geometric mean. DHS chose not to include the NCI rat bioassay data in the unit risk estimation because when the data are adjusted for excess mortality there is no statistically significant association between dose and tumor response. Cross-route extrapolation was used to calculate inhalation unit risk values from oral exposure data. Using an absorption fraction of 50%, an estimated human weight of 60 kg and an estimated respiration rate of 18 m^3/day, the unit inhalation intake is 4.5 times the unit oral intake. Therefore, the US EPA 95% upper confidence limit oral cancer risk values calculated were multiplied by a factor of 4.5 to obtain the values of 1.5×10^{-4} $(\mu g/m^3)^{-1}$ (Della Porta *et al*., 1961), 4.2×10^{-5} $(\mu g/m^3)^{-1}$ (Edwards *et al*., 1942) and 9.9×10^{-6} $(\mu g/m^3)^{-1}$ (NCI, 1976a, b; 1977 [mouse]). The cancer unit risk of 4.2×10^{-5} $(\mu g/m^3)^{-1}$ was recommended by CDHS for continuous air exposures.

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CHLORINATED DIBENZO-*p*-DIOXINS
CAS No: 1746-01-6

CHLORINATED DIBENZOFURANS
CAS No: 5120-73-19

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1998) except as noted)

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

Molecular weight	322
Boiling point	decomposes (NIOSH, 1994)
Melting point	305-306 ºC
Vapor pressure	7.4×10^{-10} mm Hg at 25 ºC
Air concentration conversion	not available

2,3,7,8-Tetrachlorodibenzofuran

Molecular weight	305.99
Boiling point	not available
Melting point	not available
Vapor pressure	not available
Air concentration conversion	not available

II. HEALTH ASSESSMENT VALUES

Congener	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg/day)^{-1}$
PCDDs		
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	3.8 E+1	1.3 E+5
1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin	3.8 E+1	1.3 E+5
1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin	3.8 E+0	1.3 E+4
1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin	3.8 E+0	1.3 E+4
1,2,3,7,8,9-Hexachlorodibenzo-*p*-dioxin	3.8 E+0	1.3 E+4
1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin	3.8 E-1	1.3 E+3
1,2,3,4,5,6,7,8-Octachlorodibenzo-*p*-dioxin	3.8 E-3	1.3 E+1
PCDFs		
2,3,7,8-Tetrachlorodibenzofuran	3.8 E+0	1.3 E+4
1,2,3,7,8-Pentachlorodibenzofuran	1.9 E+0	6.5 E+3
2,3,4,7,8-Pentachlorodibenzofuran	1.9 E+1	6.5 E+4
1,2,3,4,7,8-Hexachlorodibenzofuran	3.8 E+0	1.3 E+4
1,2,3,6,7,8-Hexachlorodibenzofuran	3.8 E+0	1.3 E+4
1,2,3,7,8,9-Hexachlorodibenzofuran	3.8 E+0	1.3 E+4
2,3,4,6,7,8-Hexachlorodibenzofuran	3.8 E+0	1.3 E+4
1,2,3,4,6,7,8-Heptachlorodibenzofuran	3.8 E-1	1.3 E+3
1,2,3,4,7,8,9-Heptachlorodibenzofuran	3.8 E-1	1.3 E+3
1,2,3,4,5,6,7,8-Octachlorodibenzofuran	3.8 E-3	1.3 E+1

Congener		Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg/day)^{-1}$
PCBs (IUPAC #, structure)			
77	3,3',4,4'-Tetrachlorobiphenyl	3.8 E-3	1.3 E+1
81	3,4,4',5- Tetrachlorobiphenyl	3.8 E-3	1.3 E+1
105	2,3,3',4,4'- Pentachlorobiphenyl	3.8 E-3	1.3 E+1
114	2,3,4,4',5- Pentachlorobiphenyl	1.9 E-2	6.5 E+1
118	2,3',4,4',5- Pentachlorobiphenyl	3.8 E-3	1.3 E+1
123	2',3,4,4',5- Pentachlorobiphenyl	3.8 E-3	1.3 E+1
126	3,3',4,4',5- Pentachlorobiphenyl	3.8 E+0	1.3 E+4
156	2,3,3',4,4',5- Hexachlorobiphenyl	1.9 E-2	6.5 E+1
157	2,3,3',4,4',5'- Hexachlorobiphenyl	1.9 E-2	6.5 E+1
167	2,3',4,4',5,5'- Hexachlorobiphenyl	3.8 E-4	1.3 E+0
169	3,3',4,4',5,5'- Hexachlorobiphenyl	3.8 E-1	1.3 E+3
189	2,3,3',4,4',5,5'- Heptachlorobiphenyl	3.8 E-3	1.3 E+1

PCDDs = polychlorinated dibenzo-*p*-dioxins. PCDFs = polychlorinated dibenzofurans. PCBs = polychlorinated biphenyls. IUPAC = International Union for Pure and Applied Chemistry.

[Linearized multistage procedure (GLOBAL79), fitted to male mouse hepatic adenoma and carcinoma data (NTP, 1982), body weight scaling, cross-route extrapolation (CDHS, 1986).]

III. CARCINOGENIC EFFECTS

Human Studies

Comprehensive reviews of the human studies of dioxin exposure and cancer risk available at the time the document entitled *Health Effects of Chlorinated Dioxins and Dibenzofurans* was written for the Toxic Air Contaminant (TAC) program (CDHS, 1986) are found in US EPA (1984) and Veterans Administration (VA) (1981, 1984). A more recent review of human dioxin exposure and cancer risk studies can be found in ATSDR (1999).

Dioxins have never been intentional products. In human exposure studies, PCDDs (polychlorinated dibenzo-*p*-dioxins) and PCDFs (polychlorinated dibenzofurans) have only been present as contaminants of other toxic chemicals, such as herbicides. Hence all studies of human PCDD/PCDF exposures have been studies of exposure to chemical mixtures that may have contained PCDD and PCDF.

VA (1981, 1984) summarized what is known about the presence of PCDD and PCDF in commercially-used chemicals. In general, PCDDs and PCDFs may be present as contaminants in the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5T). Levels of 2,3,7,8-TCDD in 2,4,5-T have been found as high as six parts per million (Rappe *et al*. 1982). Another widely used herbicide, 2,4-dichlorophenoxyacetic acid (2,4-D) is generally regarded as uncontaminated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD). Cochrane

et al. (1982) did detect traces of di-, tri-, and TetraCDD as high as one part per billion in technical grade 2,4-D from Canada. However, the TetraCDD isomer found in these samples was the 1,3,6,8-TCDD isomer, not the more toxic 2,3,7,8-TCDD.

Agent Orange, which was a mixture of 2,4,5-T and 2,4-D, has been shown to contain 2,3,7,8-TCDD concentrations as high as 15-47 parts per million with an average of about 2 ppm (VA 1981). PCDDs and/or PCDFs have also been found in the parts per million range in commercially used polychlorinated biphenyls (PCB), trichlorophenol (TCP), tetrachlorophenol, and pentachlorophenol (PCP) (Rappe *et al*. 1982, Hardell 1983).

Several case/control studies have been conducted in Sweden and in New Zealand. In these countries, phenoxyacetic acids and chlorophenols were used extensively for agriculture and forestry. After clinical observations of several patients with soft-tissue sarcomas (STS) and a history of heavy exposure to phenoxyacetic acids, Hardell and Sandstrom (1979) conducted a case/control study of STS and herbicide exposure. Cases were drawn from a university hospital in Northern Sweden, and consisted of 52 adult males with STS diagnosed between 1970 and 1977. Controls were drawn from general population registries, at a 4:1.matching ratio, and matched to cases on sex, age, place of residence, and vital status (whether alive or deceased). The investigators considered only non-malignant deaths for deceased controls. Study subjects (or their next of kin) provided exposure histories by a mailed questionnaire with a telephone follow-up. The odds ratio (OR) for exposure to phenoxyacetic acids only (excluding subjects exposed to chlorophenols) was 5.3 (95% confidence interval (95% CI) 2.4-11.5). For exposure to chlorophenols only (excluding those exposed to phenoxyacetic acids) the OR was 6.6 (95% CI 2.1-20.9).

To confirm these findings, Ericksson *et al*. (1981) replicated this study in Southern Sweden, using cases from a cancer registry. Similar study methods were used, including matching controls from a population registry (at a 2:1 ratio), and determining exposure by mail and telephone questionnaires. The investigators calculated separate odds ratios for exposure to phenoxy acids known to be contaminated with PCDD and PCDF (OR-17.0; 95% CI 2.1-140.0) and for exposure to phenoxy acids thought to be free of PCDD and PCDF (OR-4.2; 95% CI 1.2-14.9). When exposure was dichotomized into categories of 30 days or less, or more than 30 days, the ORs were 5.7 and 8.5, respectively, possibly indicating a dose-response trend.

One of the drawbacks of this study is that, exposure histories were provided by the study subjects; therefore, the results may be influenced by recall bias. Cases (or their next of kin) may be more likely to recall an exposure than a healthy person. In order to investigate this possible bias, Hardell (1981) duplicated the study methods using cases of colon cancer. Here there was no significant association with exposure to herbicides. Therefore, Hardell concluded that the association with STS was not due to reporting differences between diseased cases and healthy controls.

Smith *et al*. (1984) reported a similar case/control study in New Zealand. Here, male cases of STS were gathered from a national cancer registry, with controls also being selected from the same registry. This method of control selection was designed to avoid differential recall. Unlike the Swedish studies, however, the New Zealand study showed no significant

associations with reported phenoxy herbicide spraying. The authors suggested that if dioxin were the necessary agent, that Swedish herbicides may have been more contaminated than New Zealand herbicides. However, Smith *et al*. (1984) note that the Swedish investigators also found a significant association between STS and non-dioxin-contaminated herbicides, indicating that if the association were true, dioxin would not be the sole agent.

Another case/control study reported in brief by Olsen and Jensen (1984) of cases from the Danish Cancer Registry failed to show an association between nasal cancer and chlorophenol exposure, although nasal cancer was associated with occupational exposure to wood dust.

In a letter to Lancet, Milham (1982) reported proportionate mortality data from Washington state indicating that farmers suffered a significantly larger proportion of deaths due to STS. No other group occupationally exposed (foresters, orchardists, tree farmers) showed an excess of STS; however, the exposure assessment was based on occupations taken from death certificates. Furthermore, Milham indicated that 2,4-D was the predominant herbicide used, and 2,4-D is not generally contaminated with 2,3,7,8-TCDD.

A cohort study of phenoxy acid herbicide applicators in Finland was reported by Riihimaki *et al*. (1983). A historical cohort of 1926 herbicide applicators was assembled from the records of four large employers, including the Finnish Highway Authority and State Railways. These male workers had used chlorinated phenoxyacids for at least two weeks between 1955 and 1971. Their mortality between 1972 and 1980 was studied by comparing their names against population registers. National mortality figures provided expected age-standardized numbers of deaths. Deaths from all causes, and for all cancers, were less than expected. The power of this study to detect an increase in STS was poor, however, as only 0.1 case of STS was expected based on general population rates. Furthermore, as deaths in the cohort were studied only after 1972, 45 deaths that occurred in this group before 1972 were not tallied. (Even for post-1971 deaths, however, the follow-up period may also have been too short for a sufficient tumor latency period to have elapsed.)

There have been four potentially exposed occupational cohorts studied in the United States. Zack and Suskind (1980) reported the follow-up of Monsanto employees in Nitro, West Virginia, who were involved in a 1949 accident during the processing of trichlorophenol. A sudden violent reaction released fumes and residues into a building interior. Apparently, the released chemical mixture was not analyzed, but the authors assumed that it contained TCDD, as exposed workers developed chloracne. A historical cohort of 121 white male employees was assembled from company records on the basis of their having exhibited skin disorders "attributed to the 1949 TCP process accident." Their vital status was traced through 1978, providing a maximum of 29 years of follow-up per person. The standardized mortality ratio (SMR) for all causes of death in this cohort (relative to US white males) was significantly decreased (32 observed deaths vs. 46.4 expected). One cancer site showed an excess: lung cancer (5 observed vs. 2.85 expected), although this SMR of 1.75 was not statistically significant. Interestingly, there occurred one STS, a fibrous histiocytoma. However, the authors calculated SMRs (and expected numbers of deaths) only for causes with five or more observed deaths.

Zack and Gaffey (1983) described another cohort from this plant, composed of 884 male workers employed for at least one year between 1955 and 1977. It is not clear whether workers exposed in the 1949 accident were included. The same methods were used to calculate SMRs. Only 25 malignancies occurred, compared to 30.9 expected. However, two specific sites were notably elevated: lung cancer, with 14 observed vs. 9.9 expected (SMR 1.4; 95% CI 0.8-2.4), and bladder cancer, with 9 observed vs. 0.9 expected (SMR 9.9; 95% CI 4.5-18.8). One STS occurred in a worker judged to have been exposed to TCDD. One drawback to this study is that exposure histories were only constructed for the 163 decedents - and only 36% of these were judged to have had potential exposure to 2,4,5-T (and therefore TCDD). Therefore, the true exposed cohort may only have been one-third the size of the entire study group.

Cook *et al*. (1980) presented a similar historical cohort study of Dow chemical employees. In 1964, chloracne occurred in workers in a trichlorophenol manufacturing area. Industrial hygiene investigations concluded that TCDD was responsible and changes were made in the operations to decrease exposure. Levels of TCDD during this period were unknown because concentrations fell below the limit of detection at that time, 0.02 µg/ml of air (Cook 1981a); however, wipe samples were positive for TCDD. Cook *et al*. (1980) assembled a cohort of 39 workers thought to have high exposure potential, and 22 workers thought to have lower exposure. Among the high-exposure group, 87% had a history of chloracne, compared to 68% of the low-exposure group. Their vital status was determined through 1978. There were only four deaths (vs 7.8 expected based on US white males), although three of these deaths were due to neoplasms (vs 1.6 expected). One neoplasm was a fibrosarcoma.

Another Dow cohort was investigated by Ott *et al*. (1980). This cohort contained 204 white males involved in 2,4,5-T production between 1951 and 1971. The authors determined each worker's vital status through 1976, resulting in a median length of time since first exposure of about 20 years. Only one malignancy (a respiratory cancer) was recorded vs. 3.6 expected from US population rates. This cancer death occurred among the employees with 20 or more years of latency; in this group 0.9 deaths were expected.

Besides the small sample size, there are other problems with using this study for risk assessment. The exposure to TCDD may have been minimal. Environmental sampling of the breathing zone in 1969 revealed 2,4,5-T concentrations between 0.2 and 0.8 mg/m^3. Product specifications at that time called for a maximum TCDD concentration of 1 ppm. Assuming the maximum level of both 2,4,5-T in the breathing zone, and TCDD in the 2,4,5-T, the concentration of TCDD in the breathing zone would have been 10^{-6} of the concentration of 2,4,5-T, or 0.8 ng/m^3. Ott *et al*. also noted that 157 of the 204 workers (77%) were exposed for less than one year. Furthermore, a review of medical records of the cohort uncovered no cases of chloracne.

A further analysis of Dow employees was presented by Bond *et al*. (1983), who reported a morbidity survey on the combined cohorts previously described by Cook *et al*. (1980) and Ott *et al*. (1980). Bond *et al*. found few differences between the morbidity of these workers and a matched control group of workers from other locations in the plant. There were,

however, more ulcers and diseases of the digestive system (excluding liver) in the 2,4,5-T cohort, at roughly twice the prevalence in the controls. However, because the investigators only studied cohort members who participated in company medical programs between 1976 and 1978, only 69% of the original cohort was included. The study did not include workers who had died, retired, or left the company, raising the possibility that the most affected workers might have been missed.

Following the publication of the four US mortality studies, reports began to appear in Lancet of four additional cases of STS among these cohorts, bringing the apparent total to seven (Honchar and Halperin 1981, Cook 1981b, Moses and Selikoff 1981, Johnson *et al*. 1981). The proportion of deaths in these merged cohorts due to STS appeared to be far greater than would be expected (Fingerhut and Halperin 1983), although there is great difficulty in estimating expected rates of STS using general population statistics (Cook and Cartmill 1984). Fingerhut (cited in VA 1984) had the diagnoses of the seven cases reviewed by two pathologists. The pathologists could only agree on a diagnosis of STS for three of the seven, another three being reclassified, and the last diagnosis being disputed. Of the three definite cases, only two had frank chloracne to corroborate exposure. The VA review (1984) concluded that the occurrence of even two cases of STS among these relatively small cohorts warranted continued surveillance.

Other cohort studies of occupational exposures have come from Great Britain, West Germany, and the Netherlands. May (1973 and 1982) only briefly described the aftermath of a 1968 accidental release of TCP with a "higher than normal" concentration of TCDD. A total of 79 cases of chloracne were recorded, but May did not specify how many workers were exposed, so that an attack rate cannot be calculated. A survey of 46 of these workers, who were still with the company 10 years later, revealed that roughly half still had some chloracne (May, 1982). There were no other clinical problems reported, and no cases of cancer (although clearly few if any would be expected in a group this small).

Thiess *et al*. (1982) published a carefully-reported study of 74 workers exposed to dioxins during a 1953 reactor accident in a German 2,4,5-T plant. After a 23-year follow-up, this cohort exhibited seven deaths due to malignancies (vs. 4.09 expected from West German population rates), including three deaths due to stomach cancer (vs. 0.7 expected). The latter was statistically significant at a one-sided 95% level. No cases of STS occurred, although less than 0.1 would have been expected.

A mortality study of workers present at an explosion in an herbicide factory in Amsterdam was summarized by Dalderup and Zellenrath (1983). Between 200 and 500 g of TCDD were thought to have been liberated. The investigation traced 141 of 145 workers potentially exposed, and 69 (49%) had developed chloracne. After 20 years of follow-up, 8 of the workers had died with cancer (vs. 6.9 expected), yielding an SMR of 1.2 (95% CI 0.5-2.3). No STS deaths were seen. Unfortunately, the authors did not calculate SMRs separately for the group with frank chloracne (an indicator of stronger exposure), as the crude mortality for this chloracne group was 20%, and for the non-chloracne group 15%.

At the time the dioxin TAC document was prepared (CDHS, 1986), reports were starting to appear in the literature on the effects of Agent Orange herbicide exposure in Vietnam. However, most of those reports were at the time primarily anecdotal, or interim results. Agent Orange was composed of equal parts 2,4-D and 2,4,5-T, and about 90,000 tons of herbicides were sprayed in Vietnam between 1962 and 1971. Hay (1983) mentioned evidence from Vietnamese studies that "suggests a link" between herbicide exposure and liver cancer, but provided no details. Sarma and Jacobs (1982) reported three patients with STS who claimed Agent Orange exposure while serving in Vietnam.

The US Air Force's Ranch Hands study (summarized by VA, 1984) had released some initial results at the time the dioxin TAC document was prepared. This was a cohort study of some 1200 military personnel who worked on Operation Ranch Hand, the herbicide spraying operation. These subjects were matched (in a 5:1 ratio) with personnel who flew only cargo missions in Vietnam. As of 1983, the total mortality rates were nearly identical between the two groups. Only four cases of cancer had occurred among the exposed, and none were STS. The investigators stressed the preliminary nature of the data, the relatively low power of a study of this size to detect rare tumors such as STS, and the relatively short latency period up to that time (12-21 years).

A report by Greenwald *et al*. (1984) gave the results of a case/control study of STS in New York State. Cases of STS (n = 281) diagnosed between 1962 and 1980, who were between the ages of 18 to 29 during the war in Vietnam, were selected from the state cancer registry. Cases were individually age matched to living controls drawn from drivers' license files. The investigators gathered exposure information from subjects or next of kin by a telephone questionnaire. The questions focused on Vietnam service (and Agent Orange exposure in particular), but included other exposures such as chemical manufacturing and herbicide spraying in general. Only 3% of the cases and 4% of the controls had a history of Agent Orange, dioxin, or 2,4,5-T exposure. None of the various exposures proved statistically significant.

The power of this study can be criticized, with exposures as rare as they were. Also, the inclusion of cancer cases from the early 1960s can be questioned. These cases would not have had sufficient latency to have been caused by an exposure in Vietnam.

In 1983, an Australian Royal Commission began investigating the effects of Agent Orange exposure to Australian Vietnam veterans. However, their report, released in 1985, does not supply much information on the effects of PCDDs. The executive summary concluded that "only a very limited number of Australian servicemen were ever directly exposed," and further, that the dose received by the majority of Australian veterans was "so minute that it may, without doubt, be ignored," (e.g., it noted that no Australians developed chloracne). Not surprisingly, the Commission found no evidence of any cancer excess among the "exposed" servicemen (Royal Commission, 1985).

There are only a few cases where dioxin exposure of the general population has been documented; the Seveso incident in Italy, is one of them. In 1976, a chemical plant producing 2,4,5-trichlorophenol, exploded and released into the air several chemicals including TCDD in the vicinity of Seveso. The Seveso incident represents a unique event

in the sense that exposure to the toxic chemical was not limited to occupational exposure by workers but the whole population was affected by the TCDD release in the area surrounding a pentachlorophenol manufacturing facility that experienced an explosion and fire releasing dioxins into the atmosphere. Children, woman and men of various age were exposed to different degrees depending on the distance and direction from the origin of the plume.

Abate *et al*. (1982) summarized the series of studies following the 1976 accidental release of TCDD from a TCP-producing plant in Seveso, Italy. The investigators looked at mortality rates for 11 municipalities for four years after the accident and reported no increase in cancer mortality. These studies served mainly to provide baseline rates for future studies, because clearly not enough time had elapsed to provide the minimum 10 to 20 years required for an increased cancer risk to become manifest (Bruzzi, 1983).
Fifteen years after the industrial accident, Bertazzi et al. (1997) examined the cancer mortality among residents (20 to 74 years old) of Seveso by comparing populations living in dioxin contaminated areas (divided into three zones: highest, lower and lowest zone of exposure to dioxin, zone A, B, and R, respectively) with population from neighboring noncontaminated areas (zone nonABR). No increase for all-cancer mortality, or major specific sites like respiratory cancer among males and breast cancer among females, was found. However, other specific cancer mortality was observed and could be associated with dioxin exposure. Table 1 represents cancer mortality for men and women living in zone B.

Increased mortality from stomach cancer (RR = 2.4; 95% CI = 0.8-5.7) was reported 10 years after the accident in women living in zone B. In men, increased mortality from rectal cancer (RR = 6.2; 95% CI = 1.7-15.9) was observed. Leukemia in men represented one of the highest risks seen in zone B for hematologic neoplasms and was statistically significant (RR = 3.1; 95% CI = 1.3-6.4). Multiple myeloma in women (RR = 6.6; 95% CI = 1.8-16.8), and Hodgkin's disease in both genders (RR = 3.3; 95% CI = 0.4-11.9 in men; and RR = 6.5; 95% CI = 0.7-23.5 in women) were also noted in that zone. In the young population (20,000 subjects aged 0 to 19 years old), some cases of cancer were also found (Pesatori et al., 1993). Cancer cases noted included two ovarian cancers and Hodgkin’s lymphoma; myeloid leukemia represented the most evident increase although not statistically significant (RR = 2.7; 95% CI = 0.7-11.4). Two cases of thyroid cancer were also reported (RR = 4.6; 95% CI = 0.6-32.7). This observation represents an important result because of its magnitude and its correlation with experimental observations. None of the elevated cancer incidences in zone A, the area with the highest exposure, were statistically significant; however, this area also had the smallest population. Additionally, it should be noted that the Seveso population was exposed to 2–3 orders of magnitude times the level of dioxin normally experienced by the general population of industrialized countries. In 1997, individuals living in the contaminated area at the time of the accident still experienced high level of plasma TCDD 20 years after the industrial accident in Seveso. Geometric means for plasma TCDD concentration for individuals who lived in zone A, B and nonABR (control zone) in 1976 were 53.2, 11.0 and 4.9 ppt, respectively. Women in these three groups represented the gender with the highest plasma TCDD contamination (Landi et al., 1997). The authors concluded that the results indicate a

positive association between dioxin exposure and certain cancers, but further study is needed to clarify this association.

Table 1. Female and male deaths in zone B for selected causes, 1976-1991, ten years or more since first exposure (latency) and duration of exposure (length of stay in contaminated area) (Adapted from Bertazzi et al., 1997).

		Latency > 10 years		Length of stay > 10 years	
		Female	Male	Female	Male
All cancers	OBS	23	31	20	29
	RR	1.4	1.0	1.4	1.1
	(95% CI)	(0.9 –2.1)	(0.7 –1.4)	(0.8 –2.1)	(0.7 – 1.6)
Digestive cancer	OBS	10	12	9	12
	RR	1.5	1.0	1.6	1.2
	(95% CI)	(0.7 – 2.7)	(0.5 – 1.8)	(0.7 – 2.9)	(0.6 – 2.1)
Stomach cancer	OBS	5	X	4	
	RR	2.4	X	2.3	
	(95% CI)	(0.8 – 5.7)		(0.6 – 6.0)	
Lymphatic and hemopoietic	OBS	4	4	3	4
	RR	2.8	2.5	2.4	2.5
	(95% CI)	(0.7 – 7.1)	(0.7 –6.4)	(0.5 – 7.1)	(0.7 –6.4)
Multiple myeloma	OBS	3		2	
	RR	15.9		11.0	
	(95% CI)	(3.2 – 46.5)		(1.2 – 39.6)	
Rectal cancer	OBS		4		4
	RR		6.2		7.2
	(95% CI)		(1.7 – 15.9)		(1.9 - 18.4)
Leukemia	OBS		2		2
	RR		3.4		3.9
	(95% CI)		(0.4 – 12.3)		(0.4 – 14.1)

OBS = observed deaths RR = relative risk CI = confidence interval

Animal Studies

Van Miller *et al*. (1977a,b) reported the results of a study in which rats were fed diets containing from 1 ppt to 1 ppm of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) for 78 weeks. Surviving rats were killed after 95 weeks. Laparotomies were performed on all surviving rats at 65 weeks and all tumors were biopsied. Rats in the three highest dose groups, receiving 50 ppb or more, died early. A variety of tumors were found in rats receiving 5 ppt to 5 ppb while no-neoplasms were found in the control or low-dose groups. The absence of tumors in these two groups is unusual in this strain of rats. In addition, because of the small number of animals in each group (10) the study was inadequate to determine the carcinogenic potential of TCDD.

Toth *et al*. (1979) administered TCDD to male Swiss/H/Riop strain mice by gavage once a week for a year, then followed them for their lifetime. The weekly doses were 0.007,

0.7, and 7.0 µg/kg. Analysis of the results from this study focused on the incidence of liver tumors. A significant increase in the incidence of liver tumors was observed in the intermediate-dose group compared to the four separate control groups. The high-dose group, however, had an incidence of liver tumors that was similar to the control group. This finding may be explained by the early mortality in the high-dose group. The average life span was 424 days for this group, compared to average life spans of between 577 and 651 days for the control groups. If the treated animals had lived it is possible that more tumors may have formed.

Kociba *et al*. (1978) conducted a two-year feeding study in male and female Sprague-Dawley rats given diets containing 2200, 210, or 22 parts per trillion (w/w) TCDD for two years. Consumption of these diets resulted in daily doses of 0.1, 0.01, and 0.001 µg/kg body weight, respectively. There were 50 male and 50 female rats in each treatment group and 86 animals of each sex in the control group. There was a statistically significant ($p < 0.05$) increase in cumulative mortality for the high-dose female group in the latter half of the study. Body weights of the male and female high-dose groups were significantly ($p < 0.05$) reduced for the last three quarters of the study; however, food intake was not altered. The combined incidence of hepatocellular carcinomas and hepatocellular neoplastic nodules in the intermediate and high-dose groups of female rats was increased above the control group. Statistically significant increased incidences of stratified squamous cell carcinomas of the hard palate and/or nasal
turbinates were observed in both male and female high-dose groups. The male group also had an increased incidence of squamous cell carcinoma of the tongue, while the female group had an increased incidence of keratinizing squamous cell carcinoma of the lung.

US EPA (1981) reviewed this study and had an independent pathologist, Robert Squire, review the tissue pathology. The incidences of significant tumors reported by Kociba *et al*. (1978) and by Squire (US EPA, 1981) are given in Table 2 for male and female rats. The results of Squire's review did not differ greatly from those reported by Kociba *et al*. (1978).

CDHS staff members concurred with earlier reviewers (IARC 1982, EPA 1984) that the study reported by Kociba *et al*. (1978) was an adequately conducted chronic carcinogenicity bioassay of TCDD, with significant effects observed at the two higher dose levels.

Table 2: Tumor incidences in Osborne-Mendel rats receiving 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in the diet for two years (US EPA, 1984)

Tumor type, sex	Dose level (µg/kg-day)			
	0	0.001	0.01	0.1
	Tumor incidence[a]			
Tongue, stratified squamous cell carcinoma				
male	0/76 (0/77)	1/49 (1/44)	1/49 (1/49)	4/42 ($p = 0.015$) (3/44) ($p = 0.046$)
Nasal turbinates/hard palate, squamous cell carcinoma				
male	0/51 (0/55)	1/34 (1/34)	0/27 (0/26)	4/30 ($p = 0.017$) (6/30) ($p = 0.002$)
female	1/54 (0/54)	0/30 (0/30)	1/27 (1/27)	5/24 ($p = 0.009$) (5/22) ($p = 0.001$)
lung, keratinizing squamous cell carcinoma				
female	0/86 (0/86)	0/50 (0/50)	0/49 (0/49)	7/49 ($p < 0.001$) (8/47) ($p < 0.001$)
Liver, hepatocellular hyperplastic nodules, carcinomas				
female	9/86 (16/86)	3/50 (8/50)	18/50 ($p < 0.001$) (27/50) ($p < 0.001$)	34/48 ($p < 0.001$) (33/47) ($p < 0.001$)

P values determined using Fisher's exact test.

[a] Number of animals with tumor over number of animals examined (incidence reported by Kociba *et al*., 1978). Numbers in parentheses give the incidence reported by Squire (US EPA, 1984).

The National Toxicology Program (NTP 1982a) conducted an oncogenicity bioassay of TCDD in male and female Osborne-Mendel rats. They were administered TCDD in a 9:1 corn oil:acetone vehicle by gavage at dose levels of 0.005, 0.025, or 0.25 µg/kg twice a week for 104 weeks. The treatment groups consisted of 50 rats of each sex and a vehicle control group that was made up of three subgroups of 25 rats of each sex. An untreated control group, also made up of three subgroups of 25 rats of each sex, was included in the study, but not in the statistical analysis of the results by NTP. At the dose levels used, TCDD did not have a significant effect on survival of any treatment group. The high-dose group of male rats did have a statistically-significant increased incidence of subcutaneous tissue fibromas, but it was not considered biologically significant because of the variability found. All male treatment groups had significantly ($p < 0.05$) increased incidences of thyroid follicular cell adenomas or adenomas and carcinomas, although the low- and intermediate-dose level group incidences were not significant when compared to the untreated control group by CDHS staff. The female high-dose group had significantly ($p < 0.05$) increased incidences of several tumor types, including subcutaneous tissue fibrosarcomas, liver neoplastic nodules or hepatocellular carcinomas, and adrenal cortical adenomas. Of these 3 tumors, NTP considered only the liver tumors to be related to TCDD

administration. The incidences of these tumors are given in Table 3. Toxic hepatitis was found in 14 male and 32 female high-dose level rats.

Table 3: Tumor incidences in male and female Osborne-Mendel rats given 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) by gavage for two years (NTP, 1982a)

Sex, tumor type	Dose level (µg/kg-week)			
	0	0.01	0.05	0.5
	Tumor incidence[a]			
Males				
Thyroid				
Follicular cell adenoma	1/69	5/48 ($p = 0.042$)	6/50 ($p = 0.021$)	10/50 ($p = 0.001$)
Follicular cell adenoma/carcinoma	1/69	5/48 ($p = 0.042$)	8/50 ($p = 0.004$)	11/50 ($p < 0.001$)
Females				
Subcutaneous tissue, fibrosarcoma	0/75	2/50	3/50	4/49 ($p = 0.023$) [3][b]
Liver				
Neoplastic nodules/ hepatocellular carcinoma	5/75	1/49	3/50	14/49 ($p = 0.001$)
Adrenal				
Cortical adenoma or adenoma NOS	11/73	8/49	4/49	14/46 ($p = 0.039$)

[a] Number of animals with tumor over number of animals examined.
[b] Number of animals with hepatocellular carcinoma.
NOS = Not otherwise specified. *P* values determined using Fisher's exact test.

NTP (1982a) also conducted a carcinogenicity bioassay with TCDD in male and female B6C3F$_1$ hybrid strain mice. The protocol was similar to that used in the rat study with male mice receiving the same doses of TCDD. Female rats, however, received larger doses of 0.02, 0.1 or 1.0 µg/kg twice a week. These dose levels did not have a statistically significant effect on survival of any treatment group. Male mice in the highest dose group had a significantly increased incidence of hepatocellular carcinomas. The high-dose female group had significantly increased incidences of subcutaneous tissue fibrosarcomas, hepatocellular adenomas or carcinomas, and thyroid follicular-cell adenomas. NTP considered only liver tumors and thyroid tumors to be related to TCDD administration. NTP also considered histiocytic lymphomas to have been increased in the high-dose female group; however, the staff of DHS did not consider that these lymphomas were increased when the incidences in all control subgroups were considered. The observed tumor incidences in both male and female mice are given in Table 4. Toxic hepatitis was observed in 44 male and 34 female high-dose group animals. It was also observed in several animals of the other treatment groups.

Table 4: Tumor incidences in male and female B6C3F$_1$ mice given 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin (TCDD) by gavage for two years (NTP, 1982a).

Sex, tumor type	Dose level (µg/kg-week)[a]			
	0	0.01 (0.04)	0.05 (0.2)	0.5 (2.0)
	Tumor incidence[b]			
males				
liver (hepatocellular carcinoma)	8/73	9/49	8/49	17/50 ($p = 0.002$)
Hepatocellular adenoma or carcinoma	15/73	12/49	13/49	27/50 ($p < 0.001$)
females				
Subcutaneous tissue, fibrosarcoma	1/74	1/50	1/48	5/47 ($p = 0.032$)
liver, hepatocellular carcinoma	1/73	2/50	2/48	6/47 ($p = 0.014$)
hepatocellular adenoma or carcinoma	3/73	6/50	6/48	11/47 ($p = 0.002$)
thyroid, follicular cell adenoma	0/69	3/50	1/47	5/46 (p - 0.009)

P values determined using Fisher's exact test.
[a] Dose administered to male mice; dose administered to female mice in parentheses.
[b] Number of animals with tumor over number of animals examined.

Both rat and mouse carcinogenicity bioassays conducted by NTP appear to have been done in an adequate manner. The number of treatment groups and the large dose range used in the studies are not typical of NTP bioassays, although it was similar to that used by Kociba *et al*. (1978). However, it may not have been large enough to include a dose level which produced no effect. Most significantly increased tumor incidences only occurred in the high-dose level groups, but a statistically significant dose-related trend was found in all groups.

NTP (1982b) also conducted a dermal oncogenicity bioassay on TCDD in male and female Swiss-Webster mice. TCDD in an acetone suspension was applied to the skin three days per week for 104 weeks. The male rats received 0.001 µg per application and the females received 0.005 µg per application. Separate groups of male and female mice were treated with one application of 50 µg 7,12-dimethylbenz(*a*)anthracene (DMBA) one week prior to the start of TCDD treatments. The only significantly ($p = 0.01$) increased incidences of tumors observed were among female mice. Both the TCDD- and DMBA/TCDD-treated groups had a similar incidences of fibrosarcoma in the integumentary system (8/27 and 8/29, respectively), compared to the vehicle control of 2/41. In NTP's judgment, the results of this experiment indicated that TCDD was carcinogenic.

HexaCDDs have been tested for carcinogenicity by NTP (1980a) in both Osborne-Mendel rats and B6C3F$_1$ mice. The bioassay tested a mixture of HexaCDDs containing 31 percent 1,2,3,6,7,8-HexaCDD and 67 percent 1,2,3,7,8,9-HexaCDD. Lower chlorinated PCDDs made up the remaining 2% of the mixture, including 0.04 percent TetraCDDs. Male and female rats and male mice received weekly doses of 1.25, 2.5 or 5 µg/kg, administered by

gavage twice a week. The female mice were administered doses of 2.5, 5.0, or 10 μg/kg/week.

A dose-related "toxic hepatitis", which was noninflammatory and consisted of degenerative changes in the liver, was observed in treated rats. The treated groups of female rats had significantly increased incidences of liver neoplastic nodules. Four high-dose animals were diagnosed as having hepatocellular carcinoma. The mice also had a dose-related incidence of "toxic hepatitis" and the high-dose male and female mouse groups had statistically significant increased incidences of hepatocellular adenomas and combined incidences of hepatocellular adenomas and carcinomas. The incidences of these tumors are given in Table 5.

Several pathologists have independently evaluated the slides made from the female rat livers in this bioassay. The re-evaluations found fewer neoplastic nodules and carcinomas than did the original evaluation. Although the incidences of neoplastic nodules and carcinomas are probably lower than originally reported, the incidence is still significant in the high-dose group. The results of four separate evaluations of the liver pathology of the female rats are given in Table 6.

A dermal application carcinogenicity bioassay of the same mixture of HexaCDD in male and female Swiss-Webster mice was also conducted by NTP (1980b). This study was similar to the TCDD dermal oncogenicity bioassay in its protocol. Thirty mice of each sex were treated with 0.005 μg of the dioxin mixture three times per week for the first 16 weeks, which was increased to 0.01 μg thereafter. A similar group was initially treated once with 50 μg DMBA before being treated with the HexaCDD mixture. Thirty untreated and 45 vehicle-treated mice of each sex were used as controls. Although there was a slight increase in fibrosarcomas of the integumentary system, this was not considered by NTP to be a significant carcinogenic response. DMBA pretreatment had no additional effect.

DHS staff members agreed with IARC (1982) that there is adequate evidence to support a conclusion that TCDD is carcinogenic to rats and mice and that TCDD should be considered a potential carcinogen to humans. The NTP bioassays (NTP 1980a) of HexaCDDs also indicated that the mixture used was tumorigenic.

Table 5: Tumor incidences in female Osborne-Mendel rats and male and female B6C3F$_1$ mice given HexaCDD by gavage for two years (NTP, 1980a)

Sex, species, tumor type	Dose level (µg/kg-week)			
	0	1.25 (2.5)	2.5 (5.0)	5.0 (10)
	Tumor incidence			
female rat				
liver, neoplastic nodule or hepatocellular carcinoma	5/75	10/50 ($p = 0.026$)	12/50 ($p = 0.007$)	30/50 ($p < 0.001$)
male mice				
liver, hepatocellular adenoma	7/73	5/50	9/49	15/4 ($p = 0.003$)
liver, hepatocellular adenoma or carcinoma	15/73	14/50	14/49	24/48 ($p = 0.001$)
female mice				
liver, hepatocellular adenoma	2/73	4/48	4/47	9/47 ($p = 0.003$)
liver, hepatocellular adenoma or carcinoma	3/73	4/48	6/47	10/47 ($p = 0.004$)

P values determined using Fisher's exact test.
[a] Dose administered to male mice; dose administered to female mice in parentheses.
[b] Number of animals with tumor over number of animals examined.

Table 6: Incidence of liver tumors based on four separate pathological evaluations of female rats given HexaCDD by gavage for two years[a] (CDHS, 1986)

Pathologist and Diagnosis	dose level (µg/kg-week)			
	0	1.25	2.5	5
	Tumor incidence[b]			
NTP (1980) Neoplastic nodules or hepatocellular carcinoma	5/75	10/50 $p = 0.026$ p - 0.026	12/50 $p = 0.007$	30/50 (4)[c] $p < 0.001$
Squire (1983) Neoplastic nodules	1/75	4/50	7/50 $p = 0.007$	7/50 $p = 0.007$
Haberman and Schueler (Schueler 1983) Neoplastic nodules or hepatocellular carcinoma	NA	NA	NA	17/50 (3)[d]
Hildebrandt (1983) Neoplastic nodules or hepatocellular carcinoma	1/75	5/50 $p = 0.037$	7/50 $p = 0.007$	18/50(2) $p < 0.001$

[a] Chi-square test for trend in proportions for NTP, Squire, and Hildebrandt studies significant at $\alpha = 0.05$ level.
[b] Number of animals with tumor over number of animals examined.
[c] Number of animals diagnosed with hepatocellular carcinoma is shown in parentheses.
[d] The diagnosis for nine of the animals with neoplastic nodules was considered a matter of judgment by the pathologist.
NA = Not available.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Several human epidemiological studies of PCDD exposure reviewed in the dioxin TAC document (CDHS, 1986) reported results which suggested an increase in cancer incidence or mortality associated with PCDD exposure (Hardell and Sandstrom, 1979; Ericksson *et al*., 1981; Zack and Gaffey, 1983). However, these and the other studies described in the dioxin TAC document suffer from a number of limitations. The characterization of exposure to PCDD/PCDF were at best, uncertain. Usually the exposure occurred at a time when there were no sensitive measures of exposure levels. Exposure was often based on job title, self-reported use of substances which may have had PCDD contamination, or exposure to an event thought to have liberated PCDDs. Additionally, none of the human exposures described have been solely to PCDDs or PCDFs, but rather to a mixture of chemicals. PCDDs were only trace contaminants of other toxic chemicals. Many of the occupationally exposed subjects were exposed only briefly (e.g., during an accidental release), or worked in a possibly contaminated environment for a short time. For example, more than 75% of the workers studied by Ott *et al*. (1980) had been exposed for less than one year. Finally, many of the discussed studies, including the four US cohorts, have been hampered by small samples. Studies of only a few hundred subjects lack sufficient power to detect small increases in the risk of rare tumors. For these reasons, DHS staff members concluded that the epidemiologic data available at the time the dioxin TAC document was written provided insufficient information to conclude whether or not PCDDs or PCDFs are human carcinogens.

CDHS (1986) found that the most sensitive species, sex, and site for the induction of cancer by TCDD is the male mouse with hepatocellular adenomas or carcinomas (NTP, 1982a). This response is an order of magnitude greater than the least sensitive species, sex, and site examined, the female mouse subcutaneous fibromas. It is interesting to note that there is less than a four-fold difference in the unit risk between animal species for liver tumors. CDHS therefore developed an inhalation cancer unit risk value for TCDD based on the NTP (1982a) male mouse hepatocellular adenoma/carcinoma tumor data. CDHS also developed an inhalation cancer unit risk value for HexaCDD based on the most sensitive species, sex, and site for the induction of cancer. The data set chosen was the NTP (1980b) female rat liver neoplastic nodule or hepatocellular carcinoma incidence data as evaluated by Hildebrandt (1983).

Methodology

GLOBAL79 was used to fit a linearized multistage procedure to the NTP (1982a) male mouse hepatocellular adenoma/carcinoma tumor data for TCDD, and the NTP (1980b) female rat neoplastic nodule/hepatocellular carcinoma data for HexaCDD as evaluated by Hildebrandt (1983). This procedure provided point estimates of the extra risk for both the maximum likelihood estimate (MLE) and the linearized 95% upper confidence value (UCL). The UCL is calculated by maximizing the linear term of the procedure, or forcing a best fitting linear term if one is not present. This method of calculating the UCL is

consistent both with the expected low-dose linearity and the linear nonthreshold theory of carcinogenesis. The slope of the 95% UCL, q_1*, is taken as a plausible upper bound of cancer potency of TCDD at low doses.

The animal exposure data (NTP 1980a, 1982a) was converted into equivalent human exposures by applying appropriate scaling factors. The following assumptions were made: Oral and inhalation routes are equivalent, the concentration of TCDD in the air was assumed to be the daily oral dose, the route of exposure does not affect absorption, and there is no difference in metabolism and pharmacokinetics between animals and humans. The total weekly dose levels were averaged over the entire week to get the daily dose level. This procedure assumes that daily dosing of the animals in the NTP studies would have given the same results as did the actual twice weekly dosing schedule. Since the half-life of TCDD is relatively long, both dosing schedules should produce similar concentrations of TCDD in the animal tissues, and therefore would be expected to give similar results. The calculated daily doses are given in Table 7. Human equivalent exposures are listed in Table 8.

Because the animal dose levels for TCDD were converted to human equivalent exposure from inhalation, the 95% UCL, q_1*, is a measure of the greatest potential excess cancer risk for humans. If the lifetime daily exposure is expressed in $\mu g/m^3$, then q_1* is the excess risk associated with this exposure. Since q_1* for humans is a unit measure of excess lifetime cancer risk associated with exposure to TCDD, it is termed the unit risk. With the unit risk, the 95% UCL of excess risk may be calculated for any low-level exposure to TCDD by the equation R = unit risk × dose, where R is the 95% UCL of excess lifetime cancer risk. The cancer unit risks calculated by CDHS using the above procedure for TCDD and HexaCDD were 38 $(\mu g/m^3)^{-1}$ and 1 $(\mu g/m^3)^{-1}$, respectively.

Table 7: Calculated daily dose levels for NTP (1980a, 1982a) TCDD and HexaCDD chronic studies in rats and mice (CDHS, 1986)

Chemical	Animal	Reported Dose Level (µg/kg-week)	Calculated Dose Level (µg/kg-day)
TCDD	male and female rats, male mice	0.01 0.05 0.5	0.0014 0.0071 0.071
	female mice	0.04 0.2 2.0	0.0057 0.029 0.29
HexaCDD	female rats	1.25 2.5 5.0	0.18 0.36 0.71
	female mice	2.5 5.0 10	0.36 0.71 1.40

Table 8: Calculated equivalent human exposure to TCDD and HexaCDD based on daily animal dose levels from NTP (1980a, 1984a) carcinogenicity studies (CDHS, 1986)

Chemical	Animal	Daily Dose Level (µg/kg-day)	Airborne Concentration for Equivalent Human Exposure (ng/m^3)
TCDD	female rat (0.45)[a]	0.0014	0.93
		0.0071	4.6
		0.071	46
	male mice (0.048)	0.0014	0.44
		0.0071	2.2
		0.071	22
	female mice (0.04)	0.0057	1.7
		0.029	8.4
		0.29	84
HexaCDD	female rats (0.45) a	0.18	120
		0.36	230
		0.71	460
	female mice (0.04)	0.36	100
		0.71	210
		1.43	420

[a] Number in parentheses is animal body weight in kilograms.

CDHS recognized that total PCDD/PCDF in the air is composed of dozens of PCDD and PCDF homologues and isomers. The chemicals in such a mixture are difficult to quantitate analytically. As a result, usually only total PCDD and total PCDF are measured. In the Air Toxics Hot Spots program, certain dioxin sources are required to perform stack testing and speciate the 2,3,7,8-congeners. Thus, more data are becoming available to adequately characterize the risk from dioxin sources in California.

To estimate cancer risks from such mixtures requires information about: (1) the proportion of each PCDD and PCDF in the mixture, and (2) the carcinogenic potency of each. However, these data are not generally available. The proportion of isomers differs depending on the emission source, and only three isomers had been tested for carcinogenic potency (2,3,7,8-TCDD and a mixture of 1,2,3,6,7,8- and l,2,3,7,8,9-HexaCDD). It was also recognized that not all 2,3,7,8-isomer PCDDs and PCDFs are equally carcinogenic. The results of the bioassays on TCDD and HexaCDD suggested that carcinogenic potency may decline in homologues more chlorinated than TCDD. It was therefore assumed that PCDDs and PCDFs that are not chlorinated on the 2,3,7,8 positions or do not have at least one ring position open are noncarcinogenic. Additionally, it was also considered that the 2,3,7,8-isomer PentaCDD has a carcinogenic potency equivalent to TCDD, and that 2,3,7,8-isomer HeptaCDD is equivalent in carcinogenic potency to 2,3,7,8-isomer HexaCDD. The potencies for the homologous PCDDs were also used for the PCDFs. Using this approach, the potency of a given concentration of PCDDs would be 2% of the potency of TCDD. The potency of a mixture of PCDFs would be 3% of the potency of TCDD.

Another toxicity equivalency factor (TEF) scheme was developed after 1986 during an international symposium (NATO/CCMS, 1988a,b), and it was adopted by US EPA (US EPA, 1989) and the Department of Toxic Substances Control (DTSC) (DTSC, 1992). The international scheme, referred to as ITEFs, is based on experimental cancer and noncancer data for many 2,3,7,8-PCDDs and 2,3,7,8-PCDFs and on the assumption that the mechanism of all PCDD/PCDF-related biologic effects are based on initial binding to a specific protein, the *Ah* receptor. Because the ITEF scheme incorporated more experimental data from cancer and noncancer studies for more PCDDs/PCDFs than does the CTEF scheme, the replacement of the CTEFs by the ITEFs was considered appropriate for use in risk assessment. This approach also increases uniformity among Cal/EPA guidelines. The TEFs contained in the dioxin TAC (CDHS, 1986) document and the ITEFs are listed in Table 8. The cancer unit risks and potency factors for chlorinated dibenzo-*p*-dioxins and dibenzofurans listed in the 1999 chemical summary and Hot Spots Unit Risk and Cancer Potency Values table (OEHHA, 1999) were generated by applying the appropriate ITEFs to the cancer unit risk and potency factor for 2,3,7,8-TCDD calculated in the dioxin TAC document.

As TEFs for PCDDs and PCDFs were developed, considerable efforts went into the study of quantitative structure activity relationships (QSAR) for polychlorinated biphenyls (PCBs). PCB congeners substituted in the para and at least 2 of the meta positions but not at any of the ortho positions can adopt structural conformations most resembling that of 2,3,7,8-TCDD, therefore have the greatest potency and exert their toxicity through the *Ah* receptor pathway. These coplanar PCB congeners are structurally similar to 2,3,7,8-tetrachorodibenzo-*p*-dioxin and therefore are termed dioxin-like PCBs. Introduction of one chlorine in the ortho position results in a decrease in toxic potency and PCBs with more than one chlorine in the ortho positions lack some effects exerted by non- and mono-ortho PCBs. These PCB congeners show a different spectrum of toxic effects (Safe, 1994).

In 1991, U.S. EPA considered using the TEF methodology for PCBs. They noted that only a small subset of the 209 PCB congeners elicits dioxin-like activity and meet the criteria for inclusion in the TEF methodology. In an attempt to harmonize TEF schemes for dioxin-like compounds, the World Health Organization - European Center for Environmental Health (WHO-ECEH) and the International Program on Chemical Safety (IPCS) generated a database consisting of almost 1,200 peer-reviewed publications, representing all the available toxicological data for PCBs up to the end of 1993. From a selected number of these publications and based on four inclusion criteria, the WHO-ECEH and the IPCS proposed TEF values for 13 dioxin-like PCBs (Ahlborg *et al.*, 1994). The inclusion criteria are:

1. The compound should show structural similarity to PCDDs and PCDFs.
2. It should bind to the *Ah* receptor.
3. It should induce dioxin-specific biochemical and toxic responses.
4. It should be persistent and accumulate in the food chain.

In addition, the first WHO PCB TEF consultation (Ahlborg *et al.*, 1994) recommended expanding the current database to include all relevant information on PCDDs, PCDFs and other dioxin-like compounds that satisfied the four inclusion criteria.

Some terminologies and definitions applicable to TEFs were reviewed prior to the second WHO-ECEH consultation (van Leeuwen, 1997). The term TEF, used in the past to describe any experimental end point to be compared with TCDD was reconsidered since not all end points are "toxic" end points. For example, end points such as binding to the *Ah* receptor and induction of ethoxyresorufin-O-deethylase (EROD) are mostly considered biological/biochemical responses. Therefore, experimental end points, for which numerical values are compared to the response to TCDD, should be termed "Relative Potency" values (REPs). These REPs could be the result of a single laboratory experiment looking at a single end point. REPs are derived from the available data either used as reported in each publication, or calculated by comparing dose-response curves or ratios of medium effective doses (ED_{50}), median lethal dose (LD_{50}), median effective concentration (EC_{50}) etc. A chemical's TEF is then derived from all available REPs examined for that compound. Thus, the term TEF is be restricted to describe an overall estimate of the order-of-magnitude of the toxicity of a compound relative to the toxicity of TCDD. This estimate is derived by consensus, using careful scientific judgment of all available data (van Leeuwen, 1997; van den Berg *et al.*, 1998). The derivation of TEF consensus using *Ah* receptor-specific end points gives more weight to toxic responses than to biochemical (e.g., enzyme induction) responses and it puts more weight on *in vivo* data than on *in vitro* results. In fact, the weighting order of contributing *in vivo* data was: chronic > subchronic > subacute > acute.

In its most recent consultation in 1997, the WHO-ECEH proposed amendments to the previous NATO/WHO I-TEF scheme (NATO/CCMS, 1989). For revision of the existing mammalian TEFs, the WHO-ECEH committee agreed that if the available information was considered insufficient to warrant a change, the existing value would remain. The suggested WHO_{97} TEFs for humans and mammals along with the CTEFs and ITEFs are presented in Table 9. Taking advantage of new data and understanding of the underlying mechanisms of toxicity of dioxin-like compounds, the WHO-ECEH's re-evaluation and extension of the TEF concept lead to the following amendments:

1) For 1,2,3,7,8-PeCDD, an increase in TEF value from 0.5 to 1.0 was recommended, based on new *in vivo* tumor promotion data and CYP 1A1/A2 induction potencies from subchronic studies.

2) For OCDD, the TEF value was reduced from 0.001 to 0.0001 based on a recalculation of the old data in which exposure versus tissue concentrations were compared (administered dose); originally the TEF was based on body burdens of the chemical following subchronic exposures.

3) For OCDF, the TEF value was changed from 0.001 to 0.0001 based on new *in vivo* EROD induction potency values (81) and an expected structural similarity with OCDD; thus, for the *in vivo* situation, a change in analogy with OCDD is recommended.

The Scientific Review Panel on Toxic Air Contaminants (SRP) reviewed and endorsed the use of the WHO_{97} TEFs in Hot Spots risk assessments at its June 20, 2003 meeting. The cancer unit risks and potency factors for chlorinated dibenzo-*p*-dioxins and dibenzofurans and polychlorinated biphenyls listed in this chemical summary and the Hot Spots Unit Risk and Cancer Potency Values table were generated by applying the appropriate WHO_{97} TEFs to the cancer unit risk and potency factor for 2,3,7,8-TCDD calculated in the dioxin TAC document.

Table 9: Toxicity equivalency factors for chlorinated dibenzo-*p*-dioxins and dibenzofurans (relative to 2,3,7,8-TCDD)

Congener	California TEF [a]	I-TEF [b]	TEF $_{WHO/97}$ [c]
PCDDs			
2,3,7,8-TCDD	1	1	1
1,2,3,7,8-PeCDD	1	0.5	1
1,2,3,4,7,8-HxCDD	0.03	0.1	0.1
1,2,3,6,7,8-HxCDD	0.03	0.1	0.1
1,2,3,7,8,9-HxCDD	0.03	0.1	0.1
1,2,3,4,6,7,8-HpCDD	0.03	0.01	0.01
1,2,3,4,6,7,8,9-OCDD		0.001	0.0001
PCDFs			
2,3,7,8-TCDF	1	0.1	0.1
1,2,3,7,8-PeCDF	1	0.05	0.05
2,3,4,7,8-PeCDF	1	0.5	0.5
1,2,3,4,7,8-HxCDF	0.03	0.1	0.1
1,2,3,6,7,8-HxCDF	0.03	0.1	0.1
1,2,3,7,8,9-HxCDF	0.03	0.1	0.1
2,3,4,6,7,8-HxCDF	0.03	0.1	0.1
1,2,3,4,6,7,8-HpCDF	0.03	0.01	0.01
1,2,3,4,7,8,9-HpCDF	0.03	0.01	0.01
1,2,3,4,6,7,8,9-OCDF		0.001	0.0001
PCBs (IUPAC #, Structure)			
77 3,3',4,4'-TCB			0.0001
81 3,4,4',5-TCB			0.0001
105 2,3,3',4,4'-PeCB			0.0001
114 2,3,4,4',5-PeCB			0.0005
118 2,3',4,4',5-PeCB			0.0001
123 2',3,4,4',5-PeCB			0.0001
126 3,3',4,4',5-PeCB			0.1
156 2,3,3',4,4',5-HxCB			0.0005
157 2,3,3',4,4',5'-HxCB			0.0005
167 2,3',4,4',5,5'-HxCB			0.00001
169 3,3',4,4',5,5'-HxCB			0.01
189 2,3,3',4,4',5,5'-HpCB			0.0001

Value introduced or changed

[a] CDHS, 1986 [b] NATO/CCMS, 1989. [c] van Leeuwen, 1997.

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CHLORINATED PARAFFINS (average chain length C12, 60% chlorine by weight)

CAS No: 108171-26-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1994) except where noted)

Molecular weight	411 (average) [NTP, 1986]
Boiling point	not available
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 17 mg/m^3 (approximate)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.5 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 8.9 E-2 $(mg/kg\text{-}day)^{-1}$
[NTP (1986) female mouse liver tumor data, contained in Gold *et* al. database (1990), expedited Proposition 65 methodology (OEHHA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of chlorinated paraffins are known to exist.

Animal Studies

Male and female $B6C3F_1$ mice and Fischer 344N rats (50/sex/group) were treated by gavage with a commercial-grade chlorinated paraffin product dissolved in corn oil 5 days/week; treatment duration was 103 and 104 weeks for mice and rats, respectively (NTP, 1986). Exposure levels were 0, 125 and 250 mg/kg body weight for mice, and 0, 312 and 625 mg/kg for rats. Significant increases in the incidence of liver tumors were noted in male and female mice; the incidence of alveolar and bronchiolar carcinoma was significantly increased in male mice, as was the combined incidence of thyroid follicular-cell adenomas and carcinomas in female mice. Tumor incidences in mice are listed in Table 1.

Significant increases in liver tumor incidence were noted in male and female rats. Significant increases were also noted in the incidence of leukemia in male rats, and in the incidence of thyroid follicular-cell tumors in female rats. Tumor incidences in rats are listed in Table 2.

Table 1. Tumors induced in B6C3F$_1$ mice by gavage administration of chlorinated paraffins (NTP, 1986)

Dose (mg/kg bw)	Hepatocellular adenomas	Hepatocellular adenomas and carcinomas	Alveolar/bronchiolar carcinomas	Thyroid follicular-cell tumors
Males				
0	11/50	20/50	0/50	
125	20/50	34/50	3/50	
250	29/50	38/50	6/50	
Females				
0	0/50	3/50		8/50
125	18/50	22/50		12/49
250	22/50	28/50		13/49

Table 2. Tumors induced in Fischer 344 rats by gavage administration of chlorinated paraffins (NTP, 1986)

Dose (mg/kg bw)	Hepatocellular carcinomas	Hepatocellular adenomas and carcinomas	Mononuclear cell leukemia	Thyroid follicular-cell tumors
Males				
0	0/50	0/50	7/50	
312	10/50	13/50	12/50	
625	16/48	16/50	14/50	
Females				
0	0/50	0/50		0/50
312	4/50	5/50		6/50
625	7/50	7/50		6/50

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NTP (1986) gavage study of chlorinated paraffins in male and female B6C3F$_1$ mice and F344 rats are listed in Gold *et al*. (1990). Benign and malignant liver tumors were observed in both sexes and species; significant elevations in tumor incidences at other sites were also observed. Estimates of cancer potency are similar for male and female mice and male rats. Cancer potency is based on dose-response data for benign and malignant liver tumors in female mice (see Table 1) (OEHHA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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CHLOROFORM

CAS No.: 67-66-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	119.49
Boiling point	61° C
Melting point	-63.5° C
Vapor pressure	200 mm Hg 25° C
Air concentration conversion	1 ppm = 4.9 mg/m^3 at 25° C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 5.3 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 1.9 E-2 $(mg/kg\text{-}day)^{-1}$
[Calculated by CDHS (1990) using a nonthreshold linear procedure. This unit risk is the arithmetic average of unit risks generated by CDHS and Bogen *et al.* (1989) for renal tumors observed in rats and mice reported by Jorgenson *et al.* (1985) and NCI (1976), and the geometric mean for supporting data sets (Roe *et al.*, 1979; Tumasonis *et al.*, 1985).]

III. CARCINOGENIC EFFECTS

Human Studies

There is no information currently available in the open literature which examines the potential relationship between exposure to chloroform in an occupational setting and human cancer. However, several studies are available which examine the relationship between trihalomethanes (THM) in drinking water and human cancer.

Many studies have concentrated on chlorination of water and concomitant production of halogenated carcinogens as a causative factor in human cancers. Cantor *et al.* (1978) compared age-adjusted cancer mortality rates by site and sex for whites in the years 1968-71 to measures of THM and the drinking water. A weighed linear regression model was used to predict cancer rates in 923 U.S. counties which were over 50% urban in 1970. Reasonably strong associations between bladder cancer and THM levels in drinking water were found after controlling for confounding by urbanization, ethnicity, social class, and county industrialization. The association was not changed by controlling for occupation in certain high-risk (for bladder cancer) industries nor by lung cancer rates used as a surrogate measure for cigarette smoking. The measure of THM most associated with bladder cancer in both white males and females was that of bromine-containing trihalomethanes (BTHM). Chloroform and total trihalomethanes (TTHM) were not as well associated. There were inconsistent associations between other cancer sites and THM levels. However, there was some evidence of and association of chloroform in drinking water with kidney cancer in males, which Cantor *et al.* believed warrants further study.

Hogan *et al.* (1979) examined the potential association between chloroform levels in finished drinking water supplies and various site-specific cancer mortality rates. The most consistent associations were between chloroform "exposure" and cancers of the bladder, rectum and large intestine. Hogan *et al.* stated that the results of this ecological study must be interpreted with caution and the association between chloroform levels in drinking water and certain types of cancer (e.g., bladder, large intestine and rectum) warrant further study.

Carlo and Mettlin (1980) analyzed 4,255 cases of cancer reported in Erie County, NY, between 1973 and 1976 for any relationship between cancer and type of water source, THM levels, and a variety of socioeconomic variables. No significant association between THM and cancers were noted in the regression analyses for the total population. When regression analyses were conducted for population stratified by race-sex, a significant association was found between THM levels in drinking water and pancreatic cancer in white males ($p <$ 0.05). The investigators caution that the lack of association between THM and pancreatic cancer in other sex-race groups and absence of association between THM and other cancer raises doubts as to the validity of this finding.

Brenniman *et al.* (1980) conducted a case-control study in Illinois to determine whether an association exists between chlorination of drinking water and gastrointestinal and urinary tract cancers. Cases (3,208) and controls (43,666) were classified according to residence in chlorinated and unchlorinated groundwater communities. Elevated risk was found for cancers of the gallbladder, large intestine, total gastrointestinal, and urinary tract for women. However, the investigators considered the results tenuous because, when the data were subclassified according to several control variables, the associations were not strengthened. Many confounding factors were not controlled including smoking, diet, ethnicity, and occupation.

Alavanja *et al.* (1980) conducted a case-control study on all gastrointestinal and urinary tract cancer deaths occurring from January 1, 1968 through December 31, 1970 in seven counties in New York. There was a statistically significant excess risk of stomach cancer in females, and of stomach, esophagus, large intestine, rectum, liver and kidney, pancreas, and urinary bladder in males residing in chlorinated water areas in the seven counties studied. The investigators concluded that the excess risk was associated with living in chlorinated areas of certain counties and was not due to a disparity in the age, race, or ethnic distribution, or to urban/rural classification, hazardous occupation, or a surface vs. ground water difference. Several confounding factors were not controlled including cigarette smoking and diet.

The association between site-specific cancer mortality and THM exposure, as estimated by chlorine dose, was investigated by Young *et al.* (1981). Cases were obtained from death certificates provided by the Wisconsin Bureau of Health Statistics and consisted of all white female deaths that occurred 1972-77 within 28 counties due to malignant neoplasms of esophagus, stomach, colon, rectum, liver, bile ducts, pancreas, urinary bladder, kidney, lung, breast, and brain. Only death from colon cancer was associated with chlorine dose (- < 0.05). The risk of colon cancer, calculated as odds ratios, was over twice as great when

the water source was affected by rural runoff. This variable was tested because of the assumption that rural runoff increased the organic precursors to THMs. While the association of colon cancer with chlorination and rural runoff factors is provocative, the findings of this study must be considered inconclusive due to the possible underestimation of risk associated with misclassification error and spurious contribution from unknown colon cancer risk factors (Young *et al.*, 1981).

Wilkins and Comstock (1981) conducted a nonconcurrent prospective study to investigate possible relationships between products of water chlorination and human cancer. Site and sex-specific incidence rates for malignant neoplasm of liver, biliary passages, kidney, and bladder were constructed from hospital records, a cancer registry, and death certificates. Incidence rates for cancer of the bladder among men and cancer of the liver among women were not significant relative to the other exposure groups among persons using water from the chlorinated surface supply. While the results were only weakly suggestive, Wilkins and Comstock noted that bladder cancer has been suggestively linked with chloroform and other indices of THM in drinking water in other studies.

Gottlieb and Carr (1982) studied the potential relationship between chlorination of drinking water and cancer in 20 south Louisiana parishes. Chlorinated surface water was associated with a significant risk for rectal cancer ($p = 0.012$). The odds ratio for rectal cancer in groups receiving high chlorination level (> 1.09 ppm chlorine) to groups with no chlorinations is 1.53 (95% CI=1.15-2.04) in surface water supplied areas. Gottlieb and Carr concluded that there appears to be some cancer risk associated with water chlorination, but definitive studies are needed with respect to the role of industrial confounders and the importance of co-contaminants.

Lawrence *et al.* (1984) used a case-control approach to study the association of chloroform exposure via drinking water to colorectal cancer in white female teachers in upstate New York. Analysis was based on 395 cases of colon and rectal cancer and 395 control noncancer deaths matched with respect to age and year of death. No effect of cumulative chloroform exposure on incidence of colorectal cancer deaths was observed.

Cantor *et al.* (1987) examined the association between use of chlorinated drinking water and bladder cancer by a case-control study design. The investigators interviewed 2,982 cases and 5,782 controls in 10 geographic areas of the U.S. Risk of bladder cancer was primarily associated with use of tap water rather than nontap beverages. Among white males, the coefficients for tap and nontap beverages were 0.176 ($p < 0.001$) and 0.037 ($p = 0.42$), and among white females, the coefficients were 0.123 ($p = 0.09$) and 0.089 ($p = 0.39$), respectively. It was suggested that nonvolatile components of tap water may be associated with risk of bladder cancer since both heated and nonheated tap water beverages were significantly associated with bladder cancer risk among males. The relative risk increased with increasing tap water intake. While this investigation was quite thorough in many respects, there is a need for confirmation of these findings. The contribution of chloroform in the etiology of human bladder cancer in men may be overshadowed by other nonvolatile chemicals present in the drinking water.

Overall, the present epidemiological evidence suggests an association between chlorinated drinking water consumption and human cancer, particularly bladder and gastrointestinal cancers. However, these relationships cannot be directly correlated to chloroform exposure because many other carcinogens are found in drinking water including other chlorinated halomethanes, brominated halomethanes, industrial pollutants, and nonvolatile halogenated compounds.

Animal Studies

The National Cancer Institute conducted carcinogenesis bioassays of chloroform in both sexes of Osborne-Mendel rats and B6C3F$_1$ mice (NCI, 1976). Mice and rats were given either corn oil or chloroform in corn oil by gavage, 5 days/week for 78 weeks. Time-weighted average doses for female rats were 100 and 200 mg/kg, and for male and female mice were 138 and 277 mg/kg, and 238 and 477 mg/kg, respectively. Tumor incidences are listed in Table 1.

A statistically significant increase ($p < 0.05$) in epithelial tumors of renal tubular origin was noted in the treated males. Ten carcinomas, two of which had metastasized, and three adenomas of renal tubular origin were found in 12 high dose male rats. In the low dose males, two carcinomas and two adenomas of tubular origin were observed in four out of 50 animals. Among the 48 high dose female rats, one tubular epithelial carcinoma and one renal squamous cell carcinoma were observed. No renal epithelial tumors were noted in matched or colony controls. The NCI reported that these type of tumors rarely occur spontaneously in Osborne-Mendel rats.

The incidence of thyroid tumors in female rats was statistically higher than controls in both treated groups ($p = 0.05$, Fisher exact test) but not in treated male rats. The incidence of hepatocellular carcinoma or neoplastic nodules was not increased in the chloroform-treated rats. Although inflammatory pulmonary lesions occurred in all test groups, the lesions were more severe and occurred more frequently in the chloroform-treated rats.

The incidence of hepatocellular carcinomas in mice was significantly elevated in all treatment groups ($p < 0.001$, Fisher exact test). The NCI reported that in their experience the spontaneous incidence of hepatocellular carcinomas in B6C3F$_1$ mice is about 5-10% in males and 1% in females. The NCI concluded that chloroform treatment was associated with increased incidences of hepatocellular carcinomas in male and female mice and renal epithelial tumors in male rats.

In addition, Reuber (1979), based on his examination of the histological sections from the NCI study, concluded that chloroform treatment was also associated with cancer of the liver in rats and an increased incidence of malignant lymphomas in mice. However, the NCI did not agree with his findings.

The carcinogenicity of chloroform given in drinking water was evaluated in male Osborne-Mendel rats and female B6C3F$_1$ mice (Jorgenson *et al.*, 1985). The chloroform used (technical grade), was found to contain 100 ppb diethylcarbonate, and trace amounts of

1,1-dichloroethane, dichloroethylene, carbon tetrachloride, and an unidentified C_5H_{10} hydrocarbon. Time-weighted average doses of chloroform calculated based on water consumption rates and body weight, ranged up to 160 and 263 mg/kg-day for rats and mice, respectively. Two control groups were used, an untreated control, and a control group of animals with restricted access to water.

Jorgenson *et al.* observed a dose-related significant increase in renal tubular cell adenomas and adenocarcinomas in male rats, but found no treatment-related increases in tumor incidence in the female mice (Table 1). The lack of liver tumors in female $B6C3F_1$ mice is in sharp contrast to the results of the NCI study. A major difference between the NCI study and the Jorgenson study is the mode of administration. Administration of chloroform to rats in a corn oil vehicle slowed the gastrointestinal absorption of chloroform relative to the absorption rate observed after administration as a bolus in water (Withey *et al*., 1983). In the Jorgenson *et al*. study, the rats received small doses of chloroform each time they drank water. The corn oil vehicle effect (Withey *et al.*, 1983) may have diminished the differences in absorption kinetics expected with the two different methods of administration. Therefore, any differences in peak blood concentrations between the NCI study and the Jorgenson study may not have been sufficient to account for the difference in liver tumor incidence. Physiologic or metabolic changes produced by corn oil consumption might interact with chemical carcinogens altering the production of liver tumors (Bull *et al.*, 1986; Newberne *et al.*, 1979).

A series of experiments was conducted by the Huntingdon Research Center to determine the effects of chronic ingestion of chloroform in a toothpaste base in mice, rats, and beagle dogs. In the first set of experiments (Roe *et al.*, 1979), doses of 17 and 60 mg chloroform/kg were administered by gavage in toothpaste to male and female ICI mice, 6 days/week for 80 weeks followed by a 16 week observation period (Experiment I). Controls (N=104) were treated with 1 ml chloroform-free toothpaste/kg-day. Aside from increased nonneoplastic liver lesions (moderate fatty degeneration), the only significant difference in pathology reported was an increase in the incidence of kidney tumors in high dose male mice, three were hypernephromas (tubular adenocarcinoma) and the remainder were adenomas (tumor incidences listed in Table 1). The incidence of renal tumors in high-dose male ICI mice was significantly greater than control mice ($p = 0.00012$, Fisher exact test). None of the female ICI mice examined developed renal tumors (Roe *et al.*, 1979). Roe *et al.* (1979) also investigated other components of the toothpaste base for carcinogenicity using male ICI mice. No lesion in this part of the study could be correlated with treatment.

In a third mouse experiment (Experiment III), Roe *et al.* (1979) compared the effects of toothpaste containing 3.5% chloroform on male mice of four different strains (C57BL, CBA, CF/1, and ICI). Treatment with chloroform was not associated with any increase in liver or lung neoplasms relative to vehicle-treated controls in any of the four strains tested but was associated with significantly higher incidences of moderate to severe kidney pathology in CBA and CF/1 mice relative to the controls ($p < 0.0001$, chi-square test).

Palmer *et al.* (1979) gave groups of 50 Sprague-Dawley rats (both sexes) 0 or 60 mg chloroform/kg-day, 6 days/week by gavage in a toothpaste base for 80 weeks, followed by a 15 week observation period. There were no differences in the incidences of tumors of any site examined, including brain, lung, liver, kidney, and mammary gland, between treated and control animals. Heywood *et al.* (1979) investigated the carcinogenicity of chloroform in a toothpaste base in beagle dogs. Groups of male and female dogs received toothpaste base with 0, 15 or 30 mg chloroform/kg-day, 6 days/week for 7.5 years (8-16 dogs/sex), followed by a 20-24 week recovery period. Treatment with chloroform at the high dose was associated with significant elevations in SGPT levels but no treatment-related tumors were observed.

Chloroform treatment of rats via drinking water was associated with hepatic neoplastic nodules and hepatic adenofibrosis (Tumasonis *et al.*, 1985). Chloroform was administered to male and female Wistar rats in the drinking water at about 220 mg/kg/day and 160 mg/kg/day for the female and male rats, respectively. The incidence of hepatic neoplastic nodules was significantly elevated in treated females compared to controls ($p < 0.03$, Fisher exact test). In males, the incidence of hepatic neoplastic nodules did not differ in control and chloroform-treated groups. Increased incidences of hepatic adenofibrosis were observed in chloroform-treated males and females relative to controls. In contrast to the NCI and the Jorgenson *et al.* studies, renal tumors were not associated with chloroform treatment. However, Tumasonis *et al.* indicated that kidneys were only examined when grossly observable lesions were evident. Hence, kidney tumors may have been missed by this protocol. Tumasonis *et al.* concluded that chloroform is a hepatocarcinogen in Wistar rats.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Chloroform is carcinogenic to rats and mice (NCI, 1976; Roe *et al.*, 1979; Jorgenson *et al.*, 1985). The International Agency for Research on Cancer (IARC) has classified chloroform as a possible human carcinogen (Group 2B). Similarly, the U.S. EPA has placed chloroform in Group B2 in their classification scheme, based on sufficient evidence of carcinogenicity in animals, but inadequate epidemiologic evidence. Current evidence and understanding of the carcinogenic process is insufficient to classify chloroform as either a genotoxic or epigenetic carcinogen, and it is possible that both types of effects are involved.

Table 1: Chloroform carcinogenicity bioassay tumor incidence data used to estimate cancer potency (CDHS, 1990)

Study	Strain/Species	Sex	Tumor Site	Lifetime Daily Dose (mg/kg-day)	Tumor Incidence
NCI (1976)	$B6C3F_1$ mouse	M	hepatocellular carcinoma	control 83 167	1/18 18/50 44/45
	$B6C3F_1$ mouse	F	hepatocellular carcinoma	control 143 287	0/20 36/45 39/41
	Osborne-Mendel rat	M	renal tubular adenoma or adenocarcinoma	control 45 90	0/19 4/38 12/27
Jorgenson *et al.* (1985)	Osborne-Mendel rat	M	renal tubular adenoma or adenocarcinoma	control 18 38 79 155	4/301 4/313 4/148 3/48 7/50
Roe *et al.* (1979)	ICI mouse (Experiment I)	M	renal tubular adenoma or adenocarcinoma	control 12 43	0/72 0/37 8/37
	ICI mouse (Experiment II)	M	renal tubular adenoma or adenocarcinoma	control 40	6/237 9/49
	ICI mouse (Experiment III)[a]	M	renal tubular adenoma or adenocarcinoma	control 42	1/49 5/47
	ICI mouse (Experiment III)[b]	M	renal tubular adenoma or adenocarcinoma	control 42	1/50 12/48
Tumasonis *et al.* (1985)	Wistar rat	F	cholangiocarcinoma	control 220	0/18 34/40
	Wistar rat	M	cholangiocarcinoma	control 160	0/22 17/28
Reuber *et al.* (1979) using NCI (1976)	Osborne-Mendel rat	F	cholangiocarcinoma and cholangiofibroma	control 50 100	0/20 3/39 11/39

[a] toothpaste base was used as the vehicle; [b] arachis oil was used as the vehicle

The estimation of cancer risk to humans from exposure to chloroform by CDHS (1990) is based on animal studies. Data were chosen based primarily on statistical significance, as discussed below.

Methodology

The following data sets were evaluated to estimate chloroform cancer potency: 1) Liver tumor data in male and female $B6C3F_1$ mice, and renal tubular cell tumors in male Osborne-Mendel rats from the NCI (1976) study were chosen because statistically significant increases in these tumor types were observed in chloroform treated animals relative to controls; 2) Renal tubular cell tumor data in male Osborne-Mendel rats from the Jorgenson *et al.* (1985) study and in male ICI mice in the Roe *et al.* (1979) study were used for risk estimation based on a statistically significant increase in kidney tumors in

chloroform treated animals relative to controls; 3) Liver cholangiocarcinoma ("adenofibrosis") data in female rats from Tumasonis *et al.* (1985), and from Reuber's reanalysis of the NCI (1976) slides (Reuber, 1979) were also analyzed with the linearized multistage model (GLOBAL86). Administered doses were transformed to lifetime doses by adjusting for the number of days exposed per week and the ratio of the length of exposure to the length of the experiment (exposure plus observation period).

Calculated q_1* values from the above studies ranged from 8.1×10^{-4} to 1.9×10^{-2} $(mg/kg\text{-}day)^{-1}$. These represent cancer potency estimates for rats and mice and must be converted to theoretical equivalent potency values for humans. This conversion is based on equivalency of dose per unit surface area according to Anderson *et al.* (1983). These "human" cancer potencies range from 4.2×10^{-3} to $2.6 \times l0^{-1}$ $(mg/kg\text{-}day)^{-1}$. Scaling factors ranged from 5.19 to 13.57.

The NCI (1976) and Jorgenson *et al.* (1985) studies were the most thorough studies in terms of the number of doses tested, sample size, histological examination of the animals, and other procedural and statistical methods presented. As such, CDHS placed more confidence in the potency slopes from these studies than in the other studies. The potency slopes derived from Roe *et al.* (1979) and Tumasonis *et al.* (1985) fall within the range of those from the NCI and Jorgenson studies.

Bogen *et al.* (1989) used a physiologically based pharmacokinetic (PBPK) model to estimate metabolized dose for chloroform to use in the analysis of cancer potency with the linearized multistage model to carcinogenicity bioassay data from NCI (1976), Jorgenson *et al.* (1985), Roe *et al.* (1979), and Tumasonis *et al.* (1985). In the application of the model, the liver was considered to metabolize chloroform through a saturable enzyme system following Michaelis-Menten kinetics. This approach is consistent with the evidence that chloroform metabolites are responsible for toxicity and probably for the carcinogenicity of chloroform. The potency estimates made from these studies ranged from 4.8×10^{-3} to 5.0×10^{-1} $(mg/kg\text{-}day)^{-1}$. These corresponded to unit risks of 4.5×10^{-6} to 4.7×10^{-4} $(ppb)^{-1}$. These potency estimates are incorporated into DHS staff's best estimate of cancer potency for chloroform.

There are no studies on the carcinogenicity of chloroform by the inhalation route. Therefore, estimation of the cancer risk from exposure to chloroform in the ambient air required extrapolation from the oral route. In so doing, it is assumed that chloroform is also carcinogenic by the inhalation route, and that the risk posed by an absorbed inhaled dose of chloroform is equivalent to that posed by the same dose absorbed after oral administration. In the final risk range, the DHS staff included tumor sites that did not appear to be vehicle-dependent. Therefore, the liver tumors were not included in the range of risks or the best estimate of risk, due to the possible potentiation of liver tumors by the corn oil vehicle.

The best estimate of unit risk was considered by CDHS (1990) to be the arithmetic average of unit risks generated by CDHS (1990) and Bogen *et al.* (1989) for rat renal tumors in Jorgenson *et al.* (1985) and NCI (1976) and of the geometric mean for supporting data sets

(Roe *et al.*, 1979; Tumasonis *et al.*, 1985). This unit risk, 5.3 E-6 $(\mu g/m^3)^{-1}$, represents the best estimate using a nonthreshold linear procedure and using most of the data on the carcinogenicity of chloroform. It included analysis by PBPK modeling of metabolized dose, as well as analysis of potency based on applied dose.

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4-CHLORO-*o*-PHENYLENEDIAMINE

CAS No: 95-83-0

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	142.60
Boiling point	not available
Melting point	76 °C (NCI, 1978)
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.83 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 1.6 E-2 $(mg/kg\text{-}day)^{-1}$
[Male rat urinary bladder tumor data (NCI, 1978), contained in Gold *et al.* (1990), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 4-chloro*o*-o-phenylenediamine in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice were fed diets containing 4-chloro-*o*-phenylenediamine (NCI, 1978). Dietary 4-chloro-*o*-phenylenediamine concentrations and treatment durations for rats and mice are listed in Table 1. Treatment group sizes were 50 animals/sex/species/group, except for low-dose male rats, where a group size of 49 was used.

At study termination, 84, 84 and 70% of male mice, and 72, 88 and 78% of female mice in the control, low-dose and high-dose groups, respectively, were still alive. Survival in treated rats was somewhat lower; 64, 80 and 56% of male rats and 72, 84 and 54% of female rats in the control, low-dose and high-dose groups, respectively, were still alive at study termination. Significantly increased treatment-related liver tumor (hepatocellular adenomas, carcinomas) incidences were noted in both male and female mice. These data are listed in Table 2. A significant dose-related trend was also noted in the increased incidence of urinary bladder carcinomas in male (transitional cell papillomas, carcinomas) and female (papillary or transitional cell carcinomas) rats (Table 2). Increases in the incidence of forestomach tumors also occurred in both male and female rats. The

forestomach tumor increases were not statistically significant; however, these tumors are rare in F344 rats.

Table 1. Study design summary for NCI (1978) carcinogenicity bioassay of 4-chloro-*o*-phenylenediamine in Fischer 344 rats and B6C3F$_1$ mice.

Sex/species	Treatment group	4-chloro-*o*-phenylenediamine concentration (mg/kg diet)	Observation period		Time-weighted average concentration (mg/kg diet)
			Treated (weeks)	Untreated (weeks)	
Male rats	control	0		105	
	low-dose	5000	78	27	
	high-dose	10000	78	28	
Female rats	control	0		106	
	low-dose	5000	78	28	
	high-dose	10000	78	28	
Male mice	control	0		97	0
	low-dose	10000 5000 0	33 45	 17	7000
	high-dose	20000 10000 0	33 45	 18	14000
Female mice	control	0		97	0
	low-dose	10000 5000 0	33 45	 18	7000
	high-dose	20000 10000 0	33 45	 18	14000

Table 2. Tumor induction in F344 rats and B6C3F$_1$ mice fed diet containing 4-chloro-*o*-phenylenediamine (NCI, 1978)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
Male rats	control low-dose high-dose	0 149 294	urinary bladder tumors	0/50 15/49 25/50
Female rats	control low-dose high-dose	0 184 368	urinary bladder tumors	0/50 5/50 22/50
Male mice	control low-dose high-dose	0 701 1390	liver tumors	15/50 28/50 34/50
Female mice	control low-dose high-dose	0 752 1500	liver tumors	0/50 11/50 10/50

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al.* (1984) list results of the NCI (1978) feeding study in male and female B6C3F$_1$ mice and F344 rats. Benign and malignant neoplasms of the liver were elevated in treated male and female mice. Forestomach tumors were also observed in treated rats; these tumors are relatively uncommon in this strain. In addition, substantial increases in the incidences of urinary bladder cancers were seen in rats of both sexes. Dose-response data are given in Table 2. Rats appear to be more sensitive than mice. Quantitative analysis of dose-response data for urinary bladder tumors indicate that male and female rats have nearly the same sensitivity. The upper confidence bound on potency for data on male rats is slightly higher, and this is the value used as a cancer potency for 4-chloro-*o*-phenylenediamine (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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p-CHLORO-*o*-*T*OLUIDINE

CAS No: 95-69-2

p-CHLORO-*o*-TOLUIDINE HYDROCHLORIDE

CAS No: 3165-93-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

***p*-Chloro-*o*-toluidine**

Molecular weight	141.61
Boiling point	241 °C
Melting point	30 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.79 mg/m^3

***p*-Chloro-*o*-toluidine hydrochloride**

Molecular weight	178.07
Boiling point	not available
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 7.3 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 7.7 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 2.7 E-1 $(mg/kg\text{-}day)^{-1}$
[Male and female mouse hemangioma and hemangiosarcoma tumor data (Weisburger *et* al., 1978; NCI, 1979), contained in Gold *et* al. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

IARC (1990) reviewed studies by Currie (1933) and Uebelin and Pletscher (1954) which investigated bladder tumor incidence in small groups of male workers exposed to *p*-chlor*o*-*o*-toluidine; one case of bladder carcinoma was discovered (Currie, 1933).

A cohort study by Ott and Langner (1983) investigated 342 male workers involved in the manufacture of organic dyes in the US between 1914 and 1958. One plant area involved 117 workers with potential exposure to *p*-chlor*o*-*o*-toluidine and other raw materials and intermediates, including *ortho*-toluidine. Followup of this subcohort from 1940 to 1975

indicated that a nonsignificant excess of total cancer deaths occurred (12 observed, 8 expected) and no bladder cancer was observed.
Two studies were conducted on a cohort of 355 male workers in *p*-chloro*-o*-toluidine manufacturing plants in the Federal Republic of Germany (FRG) who had been followed up for mortality from 1929 to 1982. No deaths due to bladder cancer were found in the first study (Stasik *et al*., 1985). The second study examined a subcohort of 116 workers exposed prior to 1970 (the implementation date of improved exposure controls) with presumed high *p*-chloro*-o*-toluidine exposure levels. Excluding 2 cases of urinary bladder carcinomas in the current work force, 6 cases of bladder carcinoma were found between January 1983 and June 1986 in hospital and other institution records. No cancer registry data was available for the area of the FRG where the plant was located; cancer registration rates for a different area of the FRG was therefore used as a basis of comparison. The expected number of tumors was 0.11 based on sex- and age-specific cancer rates. Two patients had hemorrhagic cystitis thought to be due to massive exposure to *p*-chloro*-o*-toluidine. Cigarette smoking was discounted as a confounding variable after reviewing patient smoking histories (3 patients were nonsmokers). Quantitative exposure data was unavailable, but the predominant chemical exposure was to *p*-chloro*-o*-toluidine; however, exposure to other amines could have occurred.

Animal Studies

Male and female random-bred CD-1 albino mice (derived from HaM/ICR mice) and male Charles River CD Sprague-Dawley-derived rats (25/sex/group) were fed diets containing *p*-chloro*-o*-toluidine hydrochloride (97-99% pure) as part of a larger carcinogenicity study of several compounds (Weisburger *et al*., 1978). Mouse exposure levels were 0, 750 or 1500 mg/kg diet and 0, 2000 or 4000 mg/kg diet for males and females, respectively; the mice were fed treated diet for 18 months, followed by an additional 3 month observation period. Rats were fed diet containing 2000 or 4000 mg/kg diet *p*-chloro*-o*-toluidine for 3 months; the doses were then reduced to 500 and 1000 mg/kg diet for 15 months. An untreated control group (25 males) was included. All rats were killed after 24 months. Tumor incidence differences between control and exposed rat groups were not statistically significant. Hemangiomas and hemangiosarcomas were observed in male and female mice; tumor incidence data is listed in Table 1. These tumor types were found in 5/99 male and 9/102 female pooled controls from the larger carcinogenicity study, but were not present in the simultaneous controls.

Diets containing *p*-chloro*-o*-toluidine hydrochloride (99% pure) were fed to groups of male and female B6C3F$_1$ mice and Fischer 344 (F344) rats (50 animals/sex/species/treatment group) (NCI, 1979). Exposure levels for mice were 3750 or 15000 and 1250 or 5000 mg/kg diet for males and females, respectively. Exposure levels for rats were 1250 or 5000 mg/kg diet. Untreated control groups (20 animals/sex/species) were included. Exposed animals were fed treated diet for the duration of the study. All surviving mice were killed at 99 weeks; however, all high-dose females had died by 92 weeks. All surviving rats were killed at 107 weeks.

Exposure to *p*-chloro-*o*-toluidine did not affect mortality of either male or female rats; a dose-related increase in mortality was noted for both male and female mice (NCI, 1979). However, sufficient numbers of mice of each sex were at risk for tumor development for determination of tumor incidence significance. The percentage of mice surviving to study week 52 was at least 95% for all sexes and treatment groups. No significant tumor incidence increase was observed in male or female F344 rats as a result of *p*-chloro-*o*-toluidine exposure. Significant treatment-related increases ($p < 0.001$) were observed in the incidence of both hemangiosarcomas and hemangiomas and hemangiosarcomas combined in both male and female mice. Tumor incidence data is listed in Table 1.

Table 1: Incidence of vascular tumors (hemangiomas and hemangiosarcomas) in male and female mice treated with *p*-chlor*o*-*o*-toluidine hydrochloride by dietary administration

Study	Sex/Strain	Dietary concentration (mg/kg diet)	Average Dose[1] (mg/kg-day)	Tumor Incidence
Weisburger *et al*. (1978)[2]	male CD-1	0 750 1500	0 90 180	0/14 12/20 13/20
Weisburger *et al*. (1978)[3]	female CD-1	0 2000	0 260	0/15 18/19
NCI (1979)[2]	male $B6C3F_1$	0 3750 15000	0 450 1800	0/20 6/50 41/50
NCI (1979)[3]	female $B6C3F_1$	0 1250	0 162	1/20 43/50

1. Doses as reported by Gold *et al*. (1984).
2. Decreased survival according to Gold *et al*.; a time-to-tumor analysis was performed using TOX_RISK (Crump *et al*., 1991; Cal/EPA, 1992).
3. Analysis of the data set using the computer program TOX_RISK (Crump *et al*., 1991) indicated that inclusion of the high dose group resulted in a *p*-value of = 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983; US EPA, 1986), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

On the basis of positive bioassay results, the hydrochloride salt of *p*-chlor*o*-*o*-toluidine was classified as a compound with sufficient evidence of carcinogenicity in animals by IARC

(1987). The results of feeding studies on by NCI (1979) using male and female $B6C3F_1$ mice and Fischer 344 rats and by Weisburger *et al.* (1978) using male and female CD-1 HaM/ICR mice and male Charles River CD rats are reported in Gold *et al*. (1984). In contrast to rats, mice are sensitive to *p*-chlor*o*-*o*-toluidine hydrochloride-induced carcinogenicity. Vascular tumors (hemangiomas and hemangiosarcomas) were induced in treated mice of both strains and sexes tested.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. The cancer potency for *p*-chlor*o*-*o*-toluidine is based on the bioassay results for the hydrochloride, adjusted for differences in molecular weight. An overall cancer potency was estimated by taking the geometric mean of the 4 values derived from dose-response data for vascular tumors from each of the mouse sex and strains tested (male and female CD-1 and $B6C3F_1$ mice) (Weisburger *et* al., 1978; NCI, 1979; see Table 1). Male $B6C3F_1$ mouse survival in the NCI (1979) study was poor; a cancer potency for that sex and strain was therefore derived using a time-to-tumor analysis (Crump *et al*., 1991; Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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CHROMIUM (HEXAVALENT)

CAS No: 18540-29-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	51.966
Boiling point	2642 °C
Melting point	1900 °C
Vapor pressure	1 mm Hg at 1616 °C
Air concentration conversion	not available

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.5 E-1 $(\mu g/m^3)^{-1}$
Slope Factor: 5.1 E+2 $(mg/kg\text{-}day)^{-1}$
[Human lung cancer mortality data (Mancuso, 1975), linearized multistage procedure, extra risk (US EPA, 1984), reevaluated by CDHS (1985).]

Oral Slope Factor: 4.2 E-1$(mg/kg\text{-}day)^{-1}$
[Calculated by CDHS (1991) from female mouse benign and malignant stomach tumor data (Borneff *et al.*, 1968), using a linearized multistage procedure.]

III. CARCINOGENIC EFFECTS

Human Studies

Several reviewers have summarized the epidemiologic studies examining the effects of chromium exposure on cancer morbidity and/or mortality (IARC, 1980; Hayes, 1982; US EPA, 1984). The chromium Toxic Air Contaminant (TAC) document (CDHS, 1985) included a summary table listing 14 occupational studies reporting an increase in cancer morbidity and/or mortality (primarily but not exclusively lung cancer). At the time the chromium TAC document was released, the relevant studies with exposure data were those by Pokrovskaya and Shabynina (1973, as cited in US EPA, 1984), Mancuso (1975) and Langard *et al*. (1980).

Pokrovskaya and Shabynina (1973) compared the cancer mortality of a group of ferroalloy workers in the Soviet Union to the local population for the time period 1955-1969. No specific cohort was defined nor were the number of cancer cases, individuals in the comparison groups, or person-years at risk given. Workers in the plant were reported to be exposed to low-solubility chromium compounds with concentrations of hexavalent chromium exceeding the allowable level of $0.01 mg/m^3$ by 2 to 7 times. In addition, some workers were exposed to smelting process fumes for the chromium ore, which included benzo[*a*]pyrene.

Age-specific cancer mortality ratios (SMR) were reported. The ratios for cancers in males aged 50-59 were significantly increased ($p < 0.001$) for all sites (SMR = 3.3), lung (SMR = 6.67), and esophagus (SMR = 2.0). Esophageal cancer mortality was also elevated among 60-69 year old males (SMR = 11.3, $p < 0.001$). However, the lack of methodological detail reporting as well as the absence of a defined worker cohort leave the results of this study open to question.

Mancuso and Hueper (1951) studied the lung cancer-chromium association in employees of the Painesville, Ohio chromate plant. A cohort of workers was defined as consisting of employees who had worked for at least one year during the period 1931-1949. The male population of the county in which the plant was located served as the comparison group. Denominator data were not reported; rather, the results were presented as proportionate mortality ratios (PMR). The PMR for cancer of the respiratory system was 18.2% (6/33) among chromate workers and 1.2% among the general male population. This difference is significant at $p < 0.01$. The authors also stated that about 96% of the workers were exposed predominantly to insoluble chromium (chromite ore; Cr(III)), suggesting that insoluble chromium, because of its relatively long pulmonary retention time may have played a causal role in carcinogenesis. However, since all work environments were contaminated with both trivalent and hexavalent chromium, (i.e., both insoluble and soluble chromium) the data are too limited to ascribe the carcinogenic form.

Mancuso (1975) followed up a segment of this population (new employees for the years 1931-37). A major concern of the author was to determine whether an association existed between lung cancer deaths and exposure to chromium of different oxidation states and solubilities. Data from a 1949 industrial hygiene study of the plant were used to derive weighted average exposures to insoluble, soluble and total chromium which were then applied to the worker cohort. Water-soluble chromium was considered to be hexavalent while insoluble chromium was assumed to be trivalent. The author noted that since the plant's inception in 1931, production had dramatically increased, possibly increasing chromium dust concentrations. This was likely to have continued until 1949, when the company instituted control measures, which markedly reduced the exposure. Thus, the 1949 exposure data probably represent an average exposure for the cohort; that is, the data underestimate exposure from 1931 to 1949 and overestimate it subsequently.

Of the 332 cohort employees, 173 (52%) had died by 1974, including 41 from lung cancer. No comparison to a reference group was made. The age-adjusted data showed an increase in lung cancer rates with increasing exposure to chromium, regardless of solubility (and hence oxidation state). No statistical evaluation of those trends was reported, but the staff of DHS tested the data and found a statistically significant positive trend ($p < 0.001$).

Langard *et al*. (1980) studied the incidence of cancer in male workers at a Norwegian ferroalloy plant (chromium and silicon alloys were produced). The cohort studied included all men who had worked at least one year in the period 1928-77, but the analysis focused on 976 workers who started before January 1, 1960. Both overall cancer mortality and incidence were lower than would have been expected based on national data. Lung cancer incidence was elevated; however, 7 cases were found among ferrochromium workers while

3.1 were expected ($p > 0.05$). The authors note that the expected rate may be inflated because the age-corrected lung cancer rate in the population of the county in which the plant is located is only 58% of the incidence in the whole country. Applying 58% to the expected rate results in a significant increase in the incidence ratio ($p < 0.01$). Furthermore, using non-ferrochromium workers as an internal referent population resulted in an 8.5-fold increase in lung cancer incidence ($p = 0.026$). Exposure data were based on a 1975 industrial hygiene survey of the plant. The total chromium content of dust was "with few exceptions" below 1 mg/m^3. This level probably underestimates past exposures. Water-soluble chromium (assumed to be hexavalent) ranged from 11-33% of the total. The presence of high levels of Cr(VI) in previous years was also confirmed by the finding of' 2 workers with nasal septum perforations. Exposure to asbestos and low levels of polycyclic aromatic hydrocarbons also occurred, but concentrations were not reported. However, since the 243 ferrosilicon workers studied were similarly exposed yet experienced no lung cancers, the
effect of these exposures may be minimal.

Table 1 Age, chromium exposure concentrations, lung cancer mortality and person-years of exposure for male chromate workers (Mancuso, 1975; as cited in US EPA, 1998).

Age (years)	Midrange ($\mu g/m^3$)	Deaths from Lung Cancer	Person Years
50	5.66	3	1345
	25.27	6	931
	46.83	6	299
60	4.68	4	1063
	20.79	5	712
	39.08	5	211
70	4.41	2	401
	21.29	4	345

Animal Studies

There have been at least eighty reported attempts to induce cancer in rodents by administration of chromium compounds by various routes. These have been reviewed by IARC (1980, 1982) and US EPA (1984). US EPA (1998) has stated that hexavalent chromium compounds were carcinogenic in animal assays producing the following tumor types: intramuscular injection site tumors in Fischer 344 and Bethesda Black rats and in C57BL mice; intraplural implant site tumors for various chromium VI compounds in Sprague-Dawley and Bethesda Black rats; intrabronchial implantation site tumors for various Cr VI compounds in Wistar rats; and subcutaneous injection site sarcomas in Sprague-Dawley rats.

It was noted in the chromium TAC document that at the time of document preparation, no chromium compound had been unequivocally shown to cause a significantly increased number of neoplasms in experimental animals after exposure by inhalation. At least 7 experiments involving dusts containing Cr(VI) and/or Cr(III) compounds had been conducted. Although Nettesheim et al. (1971) reported a significantly increased incidence of alveologenic (not bronchogenic) adenomas and adenocarcinomas in mice exposed to calcium chromate dust (13 mg/m3) over their lifetimes for 5 hr/day, 5 days/wk, this conclusion could not be confirmed on the basis of the data reported. The authors' statistical methodology was not reported. Fourteen treated animals (6 males and 8 females) developed tumors, whereas only 5 control animals (3 males and 2 females) did. However, the numbers of exposed and control animals were not reported, nor was the distribution of tumor types, so that the claim of a significant increase of treatment-related tumor incidence could not be validated. CDHS (1990) found that a later study (Glaser *et al*., 1986) reported increases in tumors of the lung, pharynx, pituitary, pancreas, and liver of male rats exposed for 18 months to aerosols of $Na_2Cr_2O_7$ at chromium concentrations of 100 mg/m^3. Statistical criteria used for the evaluation of tumor increases were not discussed by the authors. When analyzed by staff of CDHS, the incidence of respiratory tumors in the high-dose group, 4/19, was found to be significantly increased above the incidence, 0/37, in controls.

CDHS (1990) also described a oral chromium carcinogenicity bioassay done by Borneff *et al.* (1968). Male and female NMRI mice were exposed to 1 mg K_2CrO_4 per day (added to the regular diet); a control group of 79 females and 47 males was maintained on regular diet for three generations. During 880 days of observation, each generation was dosed for two years. Approximately two-thirds of the animals in both the treatment and the control group died during months 8-11. Necropsies were performed on 66 dosed females and 35 dosed males and on 79 female and 47 male controls. Two carcinomas of the stomach were found in dosed females, but no stomach carcinomas were found in dosed males or controls. In addition, benign stomach tumors (papillomas and hyperkeratomas) were seen in 9 females and 2 males given chromium and in 2 females and 3 males in the control group. The increased incidence of malignant stomach tumors was not significant when compared with controls, but the incidence of malignant or benign stomach tumors in dosed females, 11/66, was significantly increased above 2/79, the incidence in controls ($p = 0.003$).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Inhalation

A number of human occupational studies (relevant reviews listed above) have demonstrated that inhalation exposure to chromium results in an increased risk of lung cancer mortality in humans. An occupational exposure study by Mancuso (1975) was used by US EPA (1984) as the basis for an inhalation cancer unit risk for chromium. This study demonstrated the carcinogenicity of chromium in a cohort which was sufficiently large and

which was followed for an adequate time period. Data from an industrial hygiene study were used to derive weighted average exposures to insoluble, soluble and total chromium which were then applied to the worker cohort. Table 1 lists the age, exposure and lung cancer mortality study data.

Oral

Borneff *et al.* (1968) exposed male and female NMRI mice to 1 mg K_2CrO_4 per day for two years. A significantly increased incidence of stomach carcinomas were noted in female mice; a significantly increased incidence of benign stomach tumors (papillomas and hyperkeratomas) were noted in both male and female mice.

Methodology

Inhalation

US EPA (1984) used both multistage linearized "competing risks" and "crude" procedures to estimate human cancer risks associated with chromium inhalation exposure from the data set of Mancuso (1975). The resulting cancer unit risk (1.2 E-2 $(\mu g/m^3)^{-1}$) (US EPA, 1998) was a maximum likelihood estimate (MLE) derived from the "competing risks" procedure, calculated on the basis of total chromium exposure. It was also assumed that the smoking habits of chromate workers were similar to those of the U.S. white male population. CDHS (1985) adopted the US EPA linear nonthreshold procedure to estimate low-dose chromium inhalation cancer risk. A multistage linearized "crude" procedure was used to derive a cancer unit risk of 1.5 E-1 $(\mu g/m^3)^{-1}$, which was the 95% upper confidence limit for the estimate of the relative risk in the Mancuso (1975) study. The cancer mortality in Mancuso (1975) was assumed to be due to Cr(VI), which was further assumed to be no less than one-seventh of total chromium. This contrasts with the unit risk developed by US EPA (1984), which was calculated on the basis of total chromium exposure.

Oral

An oral cancer potency factor for chromium(VI) was derived from the benign and malignant mouse stomach tumor incidence data reported by Borneff *et al.* (1968). From the average weight of the treated mice, 31 grams, the dose of 1 mg/day of K_2CrO_4 (0.26 mg/day Cr) was calculated to be 8.39 mg/kg-day, and from the incidence of benign and malignant stomach tumors combined, the oral cancer potency of Cr(VI) was calculated using a linearized multistage procedure to be 3.17×10^{-2} $(mg/kg\text{-}day)^{-1}$ (CDHS, 1991). Surface-area scaling was used to extrapolate the animal cancer potency to human cancer potency. The scaling factor was calculated by taking the ratio, human body weight divided by animal body weight, raised to the one-third power. This extrapolation factor, $(70\ kg/0.031\ kg)^{1/3}$, was calculated to be 13.1. Multiplying the above potency estimate, 3.17×10^{-2} $(mg/kg\text{-}day)^{-1}$, made from the mouse study, by the extrapolation factor gives the estimate, 0.42 $(mg/kg\text{-}day)^{-1}$, for the carcinogenic potency of Cr(VI) ingested by humans.

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CREOSOTE (COAL TAR-DERIVED)

CAS No: 8001-58-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	complex mixture
Boiling point	194 - 400ºC
Melting point	not available
Vapor pressure	not available
Air concentration conversion	not available

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: Can be calculated using PEF factors contained in the benzo[*a*]pyrene Toxic Air Contaminant (TAC) document (OEHHA, 1993).

Slope Factor: Can be calculated using PEF factors contained in the benzo[*a*]pyrene TAC document (OEHHA, 1993).

III. CARCINOGENIC EFFECTS

Human Studies

Henry (1947) reviewed 3753 cases of cutaneous epitheliomata (epitheliomatous ulceration or cancer of the skin) reported to the British Medical Inspector of Factories from 1920 to 1945. Thirty five cases (12 of the scrotum) had creosote exposure. Henry (1946) also reported that the crude mortality rate for scrotal cancer during 1911-1938 for British brickmakers exposed to creosote oil was 29 per million men based on 9 verified cases as compared to a national average of 4.2 per million and rates of 1 per million or less for groups not exposed to suspected skin carcinogens.

A cohort study reported on 123 Swedish workers who treated wood with creosote and were exposed to both creosote and arsenic between 1950 and 1980 (Axelson and Kling, 1983; reviewed in IARC, 1985). Eight workers died of cancer compared to 6 expected. Three cancer deaths (leukemia, pancreas and stomach) were observed compared to 0.8 expected in a subgroup of 21 workers exposed only to creosote for five or more years.

A case-referent study of Swedish workers examined potential relationships between past occupational and radiation exposure and multiple myeloma (Flodin *et al*., 1987). Exposure assessment employed a mailed questionnaire that asked questions about occupational (including coal tar creosote) and radiation exposure. Data analysis using the Miettinen confounder score technique indicated that an increased prevalence of multiple myeloma was associated with occupational exposure to coal tar creosote (crude rate ratio = 6.0, p = 0.001). The rate ratio point estimate for creosote exposure increased to 9.0 after age

stratification. The power of this study was limited by differences between the case group and the referent group in the number of smokers and gender composition.

Creosote contains many of the same compounds present in other polycyclic aromatic hydrocarbon (PAH) mixtures (roofing tar pitch, coke oven emissions) known to be human carcinogens (US EPA, 1986; ATSDR, 1990).

Animal Studies

Female C57BL mice (10 animals/group) were exposed to blended creosote oil (a mixture of creosote, anthracene oils and naphthalene recovery residue oil) in toluene. One drop (8.7 - 9 µl) of a 20% or 80% solution was applied to the skin three times/week for the animals' lifetimes or until tumors developed (21 - 44 weeks and 18 - 35 weeks for the 20% and 80% solution exposure groups, respectively). All treated mice developed skin papillomas and 7 mice in each group developed epidermoid carcinomas, some of which metastasized to pulmonary or regional lymph nodes. None of the vehicle control animals developed skin tumors (Poel and Kammer, 1957).

Female Swiss mice (30/group) were treated twice weekly with one drop of a 2% solution of creosote in acetone applied dermally for 70 weeks. Skin tumors (including 16 carcinomas) were reported in 23 of 26 surviving mice. The average tumor latency period was 50 weeks. No vehicle control group was included; however, no animals in a control group of 50 mice receiving a single application of 1% 7,12-dimethylbenz[*a*]anthracene in mineral oil developed tumors after 80 weeks (Lijinsky *et al*., 1957).

Undiluted creosote applied topically twice weekly (25 µl) to 30 random-bred female mice for 28 weeks induced an average of 5.4 papillomas per animal; 82% of the mice had carcinomas. The average time to tumor for papillomas and carcinomas was 20 and 26 weeks, respectively. No vehicle control group was included in the study (Boutwell and Bosch, 1958). In a similar study, a group of 24 albino mice treated dermally with 25 µl creosote twice weekly for 5 months and housed in stainless steel cages exhibited 139 lung adenomas (5.8 tumors/mouse) after 8 months. A group of 29 mice born and housed in creosote-treated wood cages treated dermally with 25 µl creosote for 5 months demonstrated 315 lung adenomas (10.8 tumors/mouse) after 8 months. A control group (19 mice) housed in stainless steel cages demonstrated 9 lung adenomas (0.5 tumors/mouse) after 8 months (Roe *et al*., 1958).

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Creosote has been demonstrated to cause skin and lung tumors in mice after dermal exposure, and is predominantly composed of PAH; similar PAH-containing coal tar products (roofing tar pitch, coke oven emissions) have been shown to be human carcinogens (US EPA, 1986; ATSDR, 1990). Creosote has been given B1 and 2A classifications (probable human carcinogen) by US EPA (1987) and IARC (1985),

respectively. No creosote carcinogenicity bioassay study suitable for quantitative risk assessment exists. However, a cancer unit risk factor for the PAH benzo[*a*]pyrene (BaP) derived from an inhalation exposure study (Thyssen *et al*., 1981) has been developed, along with Potency Equivalency Factors (PEFs) for several related PAHs. (OEHHA, 1993).

Thyssen *et al*. (1981) exposed male Syrian golden hamsters (24/group) by inhalation to 0. 2.2, 9.5 or 46.5 mg BaP/m^3 in a sodium chloride aerosol (greater than 99% of the particle diameters were between 0.2 and 0.5 μm). The hamsters were exposed to BaP daily for 4.5 hours/day for the first 10 weeks of exposure; subsequent exposure was daily for 3 hours/day. Total treatment duration was 95 weeks. Animals dying in the first year of the study were replaced. The effective number of animals in the control, 2.2, 9.5 and 46.5 mg/m^3 exposure groups were 27, 27, 26 and 25, respectively. Survival time for the 46.5 mg/m^3 exposure group was significantly reduced (60 weeks) when compared to controls (96 weeks). Survival times for the other exposure groups were similar to controls. Respiratory tract (including nasal cavity, larynx and trachea) tumor incidence was significantly increased in a dose-dependent manner in the 9.5 and 46.5 mg/m^3 exposure groups (34.6% and 52%, respectively, compared to controls); those exposure groups also demonstrated an increase in upper digestive tract (including pharynx, esophagus and forestomach) tumor incidence (27% and 56%, respectively). This study was selected as the basis of a cancer potency factor for exposure to BaP by inhalation because it used the most sensitive species and sex demonstrating a dose response and using the most relevant exposure route.

Methodology

A linearized multistage procedure (GLOBAL86) (Howe and van Landingham, 1986) was used with the Syrian golden hamster respiratory tract tumor incidence data of Thyssen *et al*. (1981) to calculate a cancer potency factor. Data from the highest exposure group (46.5 mg/m^3) was not used due to the shortened lifespan of the hamsters in this group. Administered dose for the 2.2 and 9.5 mg/m^3 exposure groups based on an inspiration rate of 0.063 m^3/day and a body weight of 0.1 kg was 0.152 and 0.655 mg/kg/day, respectively. Surface area scaling was then used to extrapolate a human cancer potency factor and an inhalation unit risk factor (using assumptions of 70 kg body weight and 20 m^3/day inspiration rate). Creosote is approximately 91% PAH, nitro-PAH or hydroxy-PAH (Wright *et al*., 1985); a unit risk for creosote can be calculated using the unit risk value for BaP and the PEFs for related PAHs (OEHHA, 1993).

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p-CRESIDINE

CAS No: 120-71-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	137.20
Boiling point	235 °C
Melting point	51.5 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.611 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.3 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 1.5 E-1 $(mg/kg\text{-}day)^{-1}$
[Female mouse urinary bladder tumor data (NCI, 1979), contained in Gold *et* al. (1984), expedited Proposition 65 methodology, with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *p*-cresidine in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice (50 animals/sex/species/group) were fed diets containing *p*-cresidine (NCI, 1979). The study design is outlined in Table 1. Dose levels for male and female mice were reduced after 21 weeks; the study report did not describe the rationale for the dose reduction.

Mortality in mice was dose-related and associated with the development of bladder tumors; mortality in rats was also dose-related and was related to development of urinary bladder and nasal cavity tumors. Survival percentages after 75 weeks of treatment are listed in Table 2. Significant incidence increases were seen for urinary bladder tumors in male and female rats (squamous-cell or transitional-cell carcinomas) and mice (transitional-cell carcinomas), for liver tumors in female mice (hepatocellular adenomas or carcinomas) and male rats (neoplastic liver nodules, hepatocellular carcinomas or cholangiocarcinomas), and for nasal cavity tumors (primarily nasal cavity tumors) in male and female rats. These data are listed in Table 2. Nonsignificant increases in nasal cavity tumors were also observed in male and female mice.

Table 1. Study design summary for NCI (1979) carcinogenicity bioassay of *p*-cresidine in Fischer 344 rats and $B6C3F_1$ mice.

Sex/species	Treatment group	*p*-cresidine dietary concentration (mg/kg diet)	Observation period	
			Treated (weeks)	Untreated (weeks)
Male rats	control	0		106
	low-dose	5000	104	1
	high-dose	10000	104	1
Female rats	control	0		106
	low-dose	5000	104	2
	high-dose	10000	104	2
Male mice	control	0		97
	low-dose	5000	21	
		1500	83	
		0		2
	high-dose	10000	21	
		3000	71[a]	
Female mice	control	0		97
	low-dose	5000	21	
		1500	83	
		0		2
	high-dose	10000	21	
		3000	83	
		0		2

a. All animals in this group were dead by the end of week 92.

Table 2. Mortality and tumor incidences associated with dietary exposure of Fischer 344 rats and B6C3F$_1$ mice to *p*-cresidine (NCI, 1979)

Sex/species	Treatment group	Average Dose[1] (mg/kg-day)	Survival after 75 weeks (%)	Tumor type	Tumor incidence[2]
male mice	controls	0	98	urinary bladder tumors	0/50
	low-dose	260	50		40/50
	high-dose	552	10		31/50
female mice	controls	0	90	urinary bladder tumors	0/50
	low-dose	281	78		42/50
	high-dose	563	28		45/50
	controls			liver tumors	0/50
	low-dose				14/50
	high-dose				6/50
male rats	controls	0	94	urinary bladder tumors	0/50
	low-dose	198	96		30/50
	high-dose	396	62		44/50
	controls			liver tumors	0/50
	low-dose				13/50
	high-dose				2/50
	controls			nasal cavity tumors	0/50
	low-dose				2/50
	high-dose				23/50
female rats	controls	0	96	urinary bladder tumors	0/50
	low-dose	245	98		31/50
	high-dose	491	76		43/50
	controls			nasal cavity tumors	0/50
	low-dose				0/50
	high-dose				11/50

1. Doses as reported by Gold *et al*. (1984).
2. Tumor incidences as reported by Gold *et al*. (1984)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NCI (1979) feeding study in male and female B6C3F$_1$ mice and Fischer 344 rats are listed in Gold *et al*. (1984). Urinary bladder tumors as well as tumors at other sites were observed in both sexes of mice and rats. The most sensitive site appears to be the urinary bladder. Both sexes of both species show similar sensitivities at this site. The potency derived from dose-response data on female mice (benign and malignant urinary bladder tumors) is slightly greater than those for the other groups and is taken as the best estimate here (see Table 2).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Because female mouse survival was poor, the potency was derived using a time-to-tumor analysis (Crump *et al*., 1991; Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

California Environmental Protection Agency (Cal/EPA) 1992. Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, Berkeley, CA.

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Hazardous Substance Data Bank (HSDB) 1994. National Library of Medicine, Bethesda MD (CD-ROM Version). Micromedix, Inc., Denver CO, Edition 22.

National Cancer Institute (NCI) 1979. Bioassay of *p*-Cresidine for Possible Carcinogenicity. CAS No. 120-71-8. Carcinogenesis Technical Report Series No. 142. NCI-CG-TR-142 DHEW Publication No. (NIH) 78-1355. U.S. Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

CUPFERRON (N-hydroxy-N-nitroso-benzenamine, ammonium salt)

CAS No: 135-20-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	155.16
Boiling point	not available
Melting point	163-164 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 6.346 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.3 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 2.2 E-1 $(mg/kg\text{-}day)^{-1}$
[Male rat hemangiosarcoma data (NCI, 1978), contained in Gold *et* al. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of cupferron in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F_1 mice were exposed to diets containing cupferron (NCI, 1978). A summary of the experimental design is outlined in Table 1. Treatment periods were followed by an observation period during which animals were fed control diet. Male and female mouse dose levels were reduced after 35 weeks. Group sizes were 50 animals/sex/species/group except for the high-dose male mouse group, which consisted of 49 animals.

Cupferron induced significantly increased incidences of forestomach squamous-cell carcinomas, hepatocellular neoplastic nodules and carcinomas in male and female rats, hemangiosarcomas in male and female rats and mice, auditory sebaceous gland tumors in female mice and rats, hepatocellular carcinomas in female mice and Harderian gland adenomas in male and female mice. Hemangiosarcoma incidence data is listed in Table 2.

Table 1. Experimental design for carcinogenicity bioassay of cupferron using male and female Fischer 344 (F344) rats and B6C3F$_1$ mice (NCI, 1978)

Sex/species	Group	Cupferron concentration (%)	Experiment duration (weeks)		Time-weighted average concentration[1]
			treatment period	observation period	
male rats	control	0	0	110	
	low dose	0.15	78	26	
	high dose	0.3	78	19	
female rats	control	0	0	110	
	low dose	0.15	78	28	
	high dose	0.3	78	28	
male, female mice	control	0		98	0
	low dose	0.3	35		0.2
		0.1	43	18	
	high dose	0.6	35		0.4
		0.2	43	17	

1. Time-weighted concentration $= \dfrac{\sum (\text{concentration} \times \text{weeks received})}{\sum (\text{weeks receiving chemical})}$

Table 2. Cupferron-induced hemangiosarcoma incidence in male and female F344 rats and B6C3F$_1$ mice (NCI, 1978)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor incidence[2]
Male rat	control	0	0/50
	low dose	45	38/50
	high dose	96.5	35/49
Female rat	control	0	0/50
	low dose	55.2	28/50
	high dose	110	37/50
Male mouse	control	0	1/50
	low dose	185	3/50
	high dose	374	7/50
Female mouse	control	0	1/50
	low dose	200	5/50
	high dose	405	6/50

[1]Doses as reported by Gold *et al*. (1984).
[2]Tumor incidences as reported by Gold *et al*. (1984)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NCI (1978) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats are listed in Gold *et al*. (1984). Benign and malignant vascular tumors as well as tumors at other sites were observed in mice and rats of both sexes treated with cupferron. Cancer potency is based on the data for vascular tumors in the male rat (see Table 2) because the rat is the more sensitive of the species tested, and the male appears to be slightly more sensitive than the female (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Analysis of the data set using the computer program TOX_RISK (Crump *et al*., 1991) indicated that inclusion of the high dose group resulted in a p-value of = 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

Anderson, EL and the Carcinogen Assessment Group of the U.S. Environmental Protection Agency 1983. Quantitative approaches in use to assess cancer risk. Risk Anal 3:277-295.

California Environmental Protection Agency (Cal/EPA) 1992. Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, Berkeley, CA.

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National Cancer Institute (NCI) 1978. Bioassay of Cupferron for Possible Carcinogenicity. CAS No. 135-20-6. Carcinogenesis Technical Report Series No. 100. NCI-CG-TR-140. DHEW Publication No. (NIH) 78-1350. U.S. Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

2, 4-DIAMINOANISOLE

CAS No: 615-05-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	138.17
Boiling point	not available
Melting point	67-68 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.651 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 2.3 E-2 $(mg/kg\text{-}day)^{-1}$
[Male rat thyroid tumors (NCI, 1978), contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 2,4-diaminoanisole in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F_1 mice were fed diets containing 2,4-diaminoanisole (DAA) sulfate (NCI, 1978). Mice were fed diets containing 1200 or 2400 mg/kg DAA sulfate for 78 weeks and were observed for an additional 18-19 weeks. Rats were fed diets containing 5000 mg/kg DAA sulfate for 78 weeks, or diet containing 1250 mg/kg DAA sulfate for 10 weeks, then 1200 mg/kg diet for 68 weeks, followed by a 29 week observation period. Matched control groups were provided for each dose group. Group sizes were 50 animals/sex/species/group with the exception of the male rat high-dose control group (49 animals). Mortality of control and treated rats and mice were similar by the end of the study. Significantly increased incidences of thyroid tumors were seen in both mice (males - follicular cell adenomas; females - follicular cell adenomas, carcinomas) and rats (follicular cell adenocarcinomas, carcinomas, papillary adenocarcinomas and cystadenocarcinomas). Increased skin tumor incidences (squamous-cell carcinomas, basal-cell carcinomas, sebaceous adenocarcinomas) were observed in male rats. Male and female rats both had increased incidences of preputial or clitoral gland adenomas, papillomas or carcinomas and Zymbal gland tumors (males - squamous cell carcinomas, sebaceous adenocarcinomas; females - sebaceous adenocarcinomas). Tumor incidence data is listed in Table 1.

Table 1: Tumor induction in Fischer 344 rats and B6C3F$_1$ mice by dietary administration of 2,4-diaminoanisole (NCI, 1978)

Sex/species	Dose group	Average Dose[1] (mg/kg-day)	Tumor type	Tumor Incidence[2]
Male mouse	control	0	thyroid	1/100
	low dose	116		0/50
	high dose	234		11/50
Female mice	control	0	thyroid	0/100
	low dose	126		0/50
	high dose	253		8/50
Male rats	control	0	thyroid	2/99
	low dose	35.2		2/50
	high dose	146		17/50
	control	0	preputial gland	0/99
	low dose	35.2		2/50
	high dose	146		8/50
	control	0	skin	0/99
	low dose	35.2		2/50
	high dose	146		9/50
	control	0	Zymbal gland	0/99
	low dose	35.2		1/50
	high dose	146		6/50
Female rats	control	0	thyroid	3/100
	low dose	44		1/50
	high dose	182		10/50
	control	0	clitoral gland	3/100
	low dose	44		5/50
	high dose	182		8/50
	control	0	Zymbal gland	0/100
	low dose	44		0/50
	high dose	182		4/50

1. Doses reported by Gold *et al*., 1984.
2. Tumor incidences reported by Gold *et al*., 1984.

Diets containing 2,4-diaminoanisole at concentrations of 0, 1200, 2400 or 5000 mg/kg diet were fed to female F344 rats (40 - 60/group) for up to 82-86 weeks (Evarts and Brown, 1980). An additional 15 rats were fed diet containing 5000 mg/kg diet for 10 weeks, then fed control diet and observed for up to 87 weeks. Thyroid tumor incidences (follicular-cell adenomas or carcinomas or C cell carcinomas) were 1/37 in controls, 2/47 in the low-dose group, 3/33 in the mid-dose group and 31/40 in the high-dose group; in addition, 3/12 animals exposed to the 5000 mg/kg diet for 10 weeks had thyroid tumors. Clitoral gland tumors (squamous-cell, sebaceous-cell or squamous-sebaceous-cell carcinomas) were

noted in 0/37 controls, 8/47 of the low-dose group, 15/33 of the mid-dose group and 9/40 of the high dose-group, as well as in 1/12 of the animals in the 10 week high-dose group.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency for 2, 4-diaminoanisole was derived from that for the sulfate using a molecular weight conversion (Cal/EPA, 1992):

$$q_h\,(\text{base}) = q_h\,(\text{sulfate}) \times \frac{\text{MW(sulfate)}}{\text{MW(base)}}$$

where q_h is the human potency and MW is the molecular weight. This conversion assumes that the intake of equivalent moles of the two forms of the chemical results in equivalent concentrations of the active species *in vivo*. Gold *et al.* (1984) list the results of the NCI (1978) feeding studies in male and female F344 rats and $B6C3F_1$ mice, and the feeding study by Evarts and Brown (1980) in female F344 rats. Cancer potency is based on dose-response data for benign and malignant thyroid tumors in male rats, the most sensitive sex and species (see Table 1) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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Evarts RP and Brown CA. 1980. 2,4-diaminoanisole sulfate: early effect on thyroid gland morphology and late effect on glandular tissue of Fischer 344 rats. J Natl Cancer Inst 65:197-204.

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Hazardous Substance Data Bank (HSDB) 1994. National Library of Medicine, Bethesda MD (CD-ROM Version). Micromedix, Inc., Denver CO, Edition 22.

National Cancer Institute (NCI) 1978. Bioassay of 2,4-Diaminoanisole for Possible Carcinogenicity. CAS No. 615-05-4. Carcinogenesis Technical Report Series No. 84. DHEW Publication No. (NIH) 78-1334. U.S. Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

2, 4-DIAMINOTOLUENE

CAS No: 95-80-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	122.17
Boiling point	292 °C
Melting point	99 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.997 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 4.0 E+0 $(mg/kg\text{-}day)^{-1}$
[Female rat mammary gland tumors (NCI, 1978), contained in Gold *et* al. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the carcinogenic potential of 2,4-diaminotoluene in humans are known to exist.

Animal Studies

IARC (1978) reviewed a study by Umeda (1955) in which 20 rats of mixed strain and sex were injected subcutaneously with 0.5 ml of a 0.4% solution of 2,4-diaminotoluene at weekly intervals. No tumor induction was noted in 11 rats that died in the first 8 months of the study. All 9 surviving rats, which received 29-44 weekly injections, developed subcutaneous sarcomas. No concurrent control group was included in this study; however, another group of 12 rats exposed to 11 subcutaneous injections of xanthene in propylene glycol over 10 months did not develop local sarcomas.

Male Wistar rats were fed diets containing 0, 0.06% or 0.1% 2,4-diaminotoluene for 30-36 weeks (12 animals/treatment group, 6 animals/control group) (Ito *et al.*, 1969). Exposure to 2,4-diaminotoluene caused an increased incidence of hepatocellular carcinomas in the treated animals (0/6, 7/11, and 9/9 in the control, low-dose and high-dose groups, respectively).

Male and female Fischer 344 (F344) and $B6C3F_1$ mice were fed diets containing 2,4-diaminotoluene (NCI, 1979). Treatment group sizes were 50 animals/sex/species/group; matched control group sizes were 20 animals/sex/species/group. The study design is

outlined in Table 1. Male and female rat low- and high-dose levels were reduced after 40 weeks.

Table 1. Experimental design of 2,4-diaminotoluene carcinogenicity bioassay using male and female F344 rats and B6C3F$_1$ mice (NCI, 1979)

Sex/species	Study group	dietary 2,4-diaminotoluene (ppm)	Study time (weeks)	Time-weighted average dose[c] (ppm)
Male rat	matched control	0	103	0
	low dose	125	40	
		50	63	79
	high dose	250	40	
		100	39[a]	176
Female rat	matched control	0	103	0
	low dose	125	40	
		50	63	79
	high dose	250	40	
		100	44[b]	171
Male,female mouse	matched control	0	101	
	low dose	100	101	
	high dose	200	101	

a. Test diet administration was terminated at the time indicated and all high-dose males were killed because of morbidity.

b. Test diet administration was terminated at the time indicated and all high-dose females except four were killed because of morbidity.

c. Time-weighted average dose $= \dfrac{\sum (\text{dose in ppm} \times \text{weeks at that dose})}{\sum (\text{weeks receiving each dose})}$

Significantly increased tumor incidences were observed in treated rats; hepatocellular adenomas, carcinomas and neoplastic nodules in male and female rats, mammary gland adenomas and carcinomas in female rats, and subcutaneous fibromas in male rats. Significant increases in tumor incidence were also noted in female mice; hepatocellular carcinomas in the low- and high-dose groups, and lymphomas in the low-dose group. No significant tumor induction was noted in male mice. Tumor incidence data is listed in Table 2.

Table 2. 2,4-Diaminotoluene-induced tumor incidence in F344 rats and $B6C3F_1$ mice (NCI, 1978)

Sex/species	Study group	Average dose[a] (mg/kg-day)	Tumor type	Tumor incidence[b]
Male rats	matched controls	0	liver tumors[c]	0/20
			subcutaneous fibromas	0/20
	low dose	3.2	liver tumors[c]	5/50
			subcutaneous fibromas	15/50
	high dose	7.0	liver tumors[c]	10/50
			subcutaneous fibromas	19/50
Female rats	matched controls	0	liver tumors[c]	0/20
			mammary gland tumors	0/20
	low dose	3.95	liver tumors[c]	0/50
			mammary gland tumors	11/50
	high dose	8.55	liver tumors[c]	6/50
			mammary gland tumors	14/50
Female mice	matched controls	0	liver tumors	0/20
			lymphomas	2/20
	low dose	13.0	liver tumors	13/50
			lymphomas	29/50
	high dose	26.0	liver tumors	18/50
			lymphomas	11/50

a. Doses as reported by Gold *et al*. (1984).
b. Tumor incidences as reported by Gold *et al*. (1984)
c. Includes hepatocellular neoplastic nodules, adenomas and carcinomas

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NCI (1978) feeding studies of 2, 4-diaminotoluene in male and female $B6C3F_1$ mice and F344 rats are listed by Gold *et al*. (1984). Significant increases in tumors were seen in rats of both sexes and in female mice. The study results indicated that rats are more sensitive than mice. The female rat appears to be slightly more sensitive than the male, although the study is not sensitive enough to definitively distinguish between the two. Cancer potency is based on mammary gland tumors in the female rat (see Table 2).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Because female rat survival was poor in this study, the potency was derived using a time-to-tumor analysis (Crump *et al*., 1991; Cal/EPA, 1992). The individual animal data for the time-to-tumor analysis were obtained from TOX_RISK (Crump *et al*., 1991). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

California Environmental Protection Agency (Cal/EPA) 1992. Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, Berkeley, CA.

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1,2-DIBROMO-3-CHLOROPROPANE

CAS No: 96-12-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	236.36
Boiling point	195.5°C
Melting point	5°C
Vapor pressure	0.8 mm Hg @ 21°C
Air concentration conversion	1 ppm = 9.67 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.9 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 7.0 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Two occupational epidemiological studies, Hearn *et al*. (1984) and Wong *et al*. (1984), were conducted using data from workers exposed during the formulation or manufacture of 1,2-dibromo-3-chloropropane (DBCP). The study by Hearn *et al*. (1984) examined a cohort of 550 chemical workers exposed to a variety of compounds, including DBCP. Twelve of the subjects in this cohort died from cancer (7.7 expected). In the study by Wong *et al*. (1984) 9 cases of respiratory cancer were reported in a cohort of 1034 workers exposed to DBCP (5.0 expected). Neither of these studies produced statistically significant ($p < 0.05$) associations between DBCP exposure and expected cancer incidence. In addition, it was not possible to account for all confounding chemical exposures in these studies. Therefore these studies were considered by IARC (1987) to be inadequate and were not used for the derivation of the cancer potency of DBCP.

An epidemiological study conducted by Jackson *et al.* (1982) found an association between DBCP in drinking water and increased incidence of stomach cancer and leukemia. In this study, patterns of DBCP contamination of well water in Fresno County, California were compared with deaths from selected cancers in the same area from 1970 to 1979. The cancers studied included stomach, esophageal, liver, kidney, and breast cancers in addition to lymphoid leukemia. Significant relationships between DBCP exposure level and cancer deaths were tested by Bartholomew's trend test. Exposed individuals were grouped into those with less than 0.05 ppb, those with 0.05 up to 1.0 ppb, and those with greater than 1.0 ppb DBCP in the drinking water. Mortality was age-adjusted using 20-year age groups. Significant trends for incidence of stomach cancer and lymphoid leukemia were found.

Results may have been confounded by smoking habits, ethnicity, and exposure to other carcinogens.

Additional analysis of these data by Environmental Health Associates (EHA, 1986) and sponsored by the Shell Oil Company did not show the above association. These data included corrections for ethnicity. This study used a different method for estimating DBCP concentrations. Although the associations between cancer incidence and DBCP exposure failed to reach significance at the $p < 0.05$ level in the EHA study, the magnitude of the associations in the high and low exposure groups were approximately the same as described in the Jackson *et al*. (1982) study. The trend for cancer risk and DBCP exposure is most closely related to the time of residence of the test subjects (Table 1).

Table 1. Relative risk of human gastric cancer in areas with high[1] concentrations of DBCP in the drinking water compared with areas of low[2] DBCP (Jackson *et al*., 1982).

Time of Residence	Relative Risk for Gastric Cancer
1 year at death	1.29
1 year prior to death	1.55
10 years prior to death	3.05

[1] DBCP concentrations greater than 1.0 ppb.
[2] DBCP concentrations less than 0.05 ppb.

Animal Studies

DBCP is a carcinogen in at least two laboratory rodent species by inhalation, ingestion, or dermal exposure. Tumors following DBCP exposure can arise not only at the site of application, but also at distal sites. Because of its carcinogenicity to multiple species, DBCP is assumed to represent a carcinogenic threat to humans (CDHS, 1985).

Three sets of long-term bioassays using mice and rats were conducted respectively by the National Cancer Institute (NCI, 1978), the National Toxicology Program (NTP, 1982) and Hazelton Laboratories (1977, 1978). In the NCI (1978) study, DBCP was administered by oral gavage to both sexes of rats and mice. Two major problems with this study, early mortality and nearly 100% forestomach carcinoma rate, precluded its usefulness in determining a cancer potency value. The inhalation study by NTP (1982) had much better survival rates than those observed in the gavage study, and carcinogenicity was observed for tissues at or near the site of the initial chemical contact.

In the NTP study, groups of 50 B6C3F1 mice or 50 F344 rats of either sex were exposed by inhalation to 0, 0.6 or 3.0 ppm DBCP for 6 hours/day, 5 days/week, for 76-103 weeks. Surviving high-dose rats were killed at week 84. High-dose female mice and low- and high-dose male mice were killed at week 76. Low-dose rats and female mice were killed at week 104. A significant increase in the combined incidence of nasal tumors was found in male and female rats at both concentrations (Table 2a, 2b). In mice, the combined

incidence of nasal tumors was significantly increased in females at both concentrations, and in males exposed to the high concentration. Proliferative lesions were observed at sites distal to the lung in the mice, including the kidney, forestomach, and spleen.

Table 2a. Incidence of combined nasal cancers from DBCP Inhalation exposure in rats and mice (NTP, 1982)

	Tumor Incidence DBCP Concentration (ppm)		
Species	0	0.6	3.0
F-344 Rats (males)	0/50	32/50	39/49
F-344 Rats (females)	1/50	21/50	32/50
B6C3F1 Mice (males)	0/45	1/42	21/48
B6C3F1 Mice (females)	0/50	11/50	38/50

Table 2b. Incidence of combined lung cancers from DBCP inhalation exposure in mice (NTP, 1982)

	Tumor Incidence DBCP Concentration (ppm)		
Species	0	0.6	3.0
B6C3F1 Mice (males)	0/41	3/40	11/45
B6C3F1 Mice (females)	4/50	12/50	18/50

In the studies conducted by the Hazelton Laboratories (1977, 1978), mice (50 males or females per group) or rats (60 males or females per group) were exposed to DBCP in the diet for 78 weeks. The intended daily doses were 0, 0.3, 1.0 and 3.0 mg/kg per day. Both species exhibited dose-dependent increases in forestomach squamous cell papillomas and carcinomas. The mouse study contained experimental errors in the diet preparation and food consumption measurements. Spillage of the food and evaporation in the mouse study may have resulted in an overestimate of the actual average daily exposure. For the rats, diets were prepared every two weeks, therefore loss of DBCP in the food due to evaporation was less significant than in the mouse study. The average amount of DBCP in the diet was estimated assuming first-order evaporation loss (Shell Oil Company, 1986). Using this model, the average daily doses of DBCP in the mouse study were 0, 0.3, 1.6 and 4.8 mg/kg per day. The study conducted by Hazelton Laboratories used lower doses than those in the NCI study, providing better information on the lower end of the dose-response curve. However, the times of death or times of tumor appearance were not reported. In addition, the study conducted by Hazelton Laboratories was terminated at 78 weeks in the case of the mice but lasted for 104 weeks in the case of the rats.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The Hazelton Laboratories (1977) study in female CD-1 mice was chosen as the critical study for the derivation of the cancer potency factor. In this study, female mice had a tumor incidence of 19/50 in the high dose group. No tumors were observed in the controls, and no histopathological examination was determined in the low and mid dose groups. The problem of food spillage and evaporation of the DBCP from the food bias the data toward an underestimation of the true cancer potency. Despite this fact, the data from this study gives a higher potency than that calculated from the rat data. The cancer potency for DBCP is based on the incidence of forestomach squamous cell carcinomas in the Hazelton Laboratory study, and is consistent with the incidence of stomach carcinomas in female mice in the NCI gavage study. In addition, the inhalation study conducted by NTP produced tumors at sites distal to the lung, including the forestomach. The cancer potency based on the NTP inhalation study is close to, but slightly lower than the potency derived from the Hazelton Laboratories study. The Hazelton Laboratory study was therefore taken to be the most appropriate animal data for the derivation of the cancer potency value.

Based on the calculated cancer potency derived from the animal studies, significant increases in cancer incidence would not be expected in the human occupational studies. The duration of exposure was too brief, the exposure too recent, and the number of subjects too small. In the ecological and case-control environmental studies by Jackson *et al*. (1982) and EHA (1986), a significant increase in the number of cancers would indicate that the true human cancer potency is an order of magnitude higher than that calculated from the animal studies.

Methodology

A linearized multistage procedure was used to estimate the cancer potency of DBCP from the Hazelton Laboratories (1977) data in female CD-1 mice (Crump *et al*., 1982). The actual daily doses received by the mice were estimated to be 0, 0.3, 1.6 and 4.8 mg/kg/day (Shell Oil Company, 1986). The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for DBCP.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 6.6 $(mg/kg \times day)^{-1}$ was derived (CDHS, 1988). An airborne unit risk factor was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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1,4-DICHLOROBENZENE

CAS No: 106-46-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	147.01
Boiling point	174°C
Melting point	53.1°C
Vapor pressure	10 mm Hg @ 25°C
Air concentration conversion	1 ppm = 6 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 4.0 E-2 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are several case reports of human leukemia associated with occupational exposure to chlorinated benzenes, including 1,4 - dichlorobenzene (1,4-DCB) (Girard *et al*., 1969). One case of chronic lymphocytic leukemia involved exposure to a solvent mixture of 80% ortho-, 2% meta-, and 15% para-dichlorobenzene. The association between leukemia and 1,4 - dichlorobenzene exposure was confounded by multiple chemical exposure.

Animal Studies

Loeser and Litchfield (1983) conducted a chronic inhalation carcinogenicity bioassay in male and female Alderly Park rats. In this study, groups of 76-79 rats were exposed to 0, 75, or 500 ppm p-DCB 5 hours/day, 5 days/week for 76 weeks. Control rats exhibited a high mortality rate and did not differ significantly from treated rats in overall tumor incidence (Table 1) or in the incidence of animals with multiple tumors and malignant tumors.

Table 1. Tumor incidence in rats exposed to 1,4-dichlorobenzene (DCB) in air for 76 weeks (Loeser and Litchfield, 1983)

Concentration of 1,4-DCB	Combined Tumors (males)	Combined Tumors (females)
0 ppm	39/60	55/61
75 ppm	31/60	54/61
500 ppm	35/60	53/58

A parallel experiment was conducted using groups of 75 Swiss mice of either sex (Loeser and Litchfield, 1983). In this experiment, female mice were exposed to 0, 75, or 500 ppm 1,4 – DCB for 5 hours/day, 5 days/week, for 57 weeks. A similar experiment in male mice was terminated due to high mortality due to fighting and respiratory infections. As with the rats, no significant increase in any tumor type was detected.

The National Toxicology Program (NTP, 1987) studied the carcinogenicity of 1,4 - DCB in male and female F344 rats and B6C3F1 mice via chronic (103 week) oral intubation. Male rats were given 0, 150, or 300 mg/kg 1,4 - DCB for 5 days/week for 103 weeks. Male and female mice, and female rats were given 0, 300, or 600 mg/kg for the same duration. Sentinel animals were killed periodically to test for infectious pathogenic agents. The survival of male rats given 300 mg/kg was significantly lower than controls after 97 weeks, but the survival of treated female rats was unchanged from controls. The time-weighted average doses in the study were 0, 214, and 428 mg/kg/day for the mice, and 0, 107, and 214 mg/kg/day for the rats. Male rats treated with 1,4-DCB displayed nephropathy and mineralization and hyperplasia of renal tubules. The incidence of renal tubular adenocarcinomas was also dose-dependently increased in the male rats (1/50, 3/50, or 7/50 for the 0, 107, or 214 mg/kg groups, respectively). A significant dose-dependent increase in the incidence of mononuclear cell leukemia (5/50, 7/50, or 11/50 for the 0, 107, or 214 mg/kg groups, respectively) was observed in the male rats. Additionally, an increasing trend in the incidence of mesothelioma was observed in the male rats (1/50, 0/50, 4/50, for the 0, 107, or 214 mg/kg groups, respectively).

Mice of both sexes exposed to 1,4 - DCB had significantly increased incidence of hepatocellular adenomas and carcinomas (NTP, 1987). In addition, four male mice exposed to 428 mg/kg were found to have hepatoblastomas, a rare hepatocellular carcinoma. The incidence of follicular thyroid cell adenomas was increased in female mice exposed to 428 mg/kg ($p < 0.038$). As with the male rats, male mice showed evidence of kidney tubule damage when treated with 1,4 - DCB. Females were not similarly affected.

NTP concluded from these data that 1,4 - DCB was carcinogenic to male rats, but not female rats. In addition, NTP concluded that the increased incidence of hepatocellular adenomas and carcinomas was evidence of carcinogenicity in male and female mice.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The study by NTP (1987) was chosen by CDHS (1988) as the key study for the development of a cancer potency value for 1,4-DCB. In the NTP (1987) study, mice and rats exhibited significant increases in several types of tumors. The mice were exposed for 5 days/week, resulting in average daily doses of 0, 214, and 428 mg/kg/day 1,4-DCB. Mice of either sex exhibited a significant increase in hepatocellular carcinomas or adenomas. The incidence of hepatocarcinomas or adenomas was 17/50, 22/49, and 40/50 in the control, 214, and 428 mg/kg/day groups, respectively. In addition, male rats showed a significant increase in kidney adenomas and mononuclear cell leukemia. The cancer

potency for 1,4-DCB was calculated from the male mouse hepatocarcinoma and adenoma data.

Methodology

A linearized multistage procedure was used to estimate the cancer potency of 1,4-DCB from the NTP (1987) data in male B6C3F1 mice (Crump *et al*., 1982). The concentrations of 1,4-DCB given in the feed were 0, 214, or 428 mg/kg/day. The premature mortality of animals without tumors was subtracted from the sample groups. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. In this case, the scaling factor was equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 0.04 $[mg/kg\text{-}day]^{-1}$ was calculated (CDHS, 1988). An airborne unit risk factor of 1.1E-5 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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3,3-DICHLOROBENZIDINE

CAS No: 91-94-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	253.1
Boiling point	402°C
Melting point	132-133°C
Vapor pressure	unknown
Air concentration conversion	1 ppm = 10.4 mg/m^3 (IARC, 1982)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.4 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.2 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

The body of literature addressing the carcinogenicity of 3,3'-dichlorobenzidine in humans is scant. Three retrospective epidemiological studies of occupational exposure have been conducted, focusing on the possibility that 3,3'-dichlorobenzidine is a bladder carcinogen like its parent compound, benzidine. None of the studies approximates exposure levels.

Gerarde and Gerarde (1974) conducted a study of 175 workers involved in the manufacture and use of dichlorobenzidine in a chemical manufacturing plant in the United States between 1938 and 1957. Workers were segregated from benzidine exposure. No bladder tumors were found among the exposed workers. General population incidence of bladder tumors predicts 0-2 cases in a cohort of this size.

Gadian (1975) conducted a study of 35 British workers exposed to dichlorobenzidine who had been segregated from exposure to benzidine in a chemical plant from 1953 to 1973. Cumulative hours of exposure were tabulated for all workers. No tumors were reported among the exposed workers at the end of the study (through 1973).

MacIntyre (1975) reports on bladder tumor incidence among 225 Scottish production and service workers, 119 of which had more than 5 years of exposure to dichlorobenzidine and 36 of which were exposed more than 16 years before the time of the study. No bladder tumors were reported among the study subjects.

Animal Studies

Stula *et al.* (1975) conducted a study on ChR-CD rats (50/sex/group), exposing animals to 1000 ppm 3,3'-dichlorobenzidine in feed for life (mean survival 51 weeks), with an interim exposed group of 6 rats/group sacrificed after 12 months. Control animals receiving no added compound were observed for up to two years (mean survival 81 weeks (males) and 90 weeks (females)). Male animals showed statistically significant increases in incidences of granulocytic leukemias (9/44 treated vs. 2/44 control; $p < 0.05$ by Fisher's exact test), mammary adenocarcinomas (7/44 treated vs. 0/44 control; $p < 0.01$), and Zymbal gland carcinomas (8/44 treated vs. 0/44 control; $p < 0.01$). Female animals only showed increased incidence of mammary adenocarcinomas (26/44 treated vs. 3/44 control; $p < 0.01$).

Stula *et al.* (1978) later conducted a study on six female beagle dogs, administering 100 mg 3,3'-dichlorobenzidine in gelatin capsules 3 times/week for 6 weeks followed by 100 mg, 5 times/week for up to 7.1 years, plus 6 untreated control animals sacrificed at 8-9 years of age. One animal which died during the course of the study (3.5 years) showed no sign of tumors, whereas another animal which died at 6.6 years showed both undifferentiated liver carcinoma and papillary transitional cell carcinoma of the bladder. Among the animals surviving to the end of the study there was an increased incidence of hepatocellular carcinoma (3/4 treated vs. 0/6 control; $p < 0.05$) and papillary transitional cell carcinoma of the bladder (4/4 treated vs. 0/6 control; $p < 0.01$). Control animals showed a high incidence of adenocarcinoma and carcinoma of the mammary gland (4/6).

Pliss (1959) reports on carcinogenesis in Rappolovskii white rats exposed to 3,3'-dichlorobenzidine in feed for 12 months. The addition of 10-20 mg added to feed in the form of a paste (50% with water) 6 days/week resulted in an estimated total dose of 4.5 g/animal. A group of 130 animals receiving injections of octadecylamine and methylstearylamine were termed a "historical control". Twenty-two of 29 animals were examined for tumors at the time of the first tumor's appearance. Findings included tumors of Zymbal gland (7/29), mammary gland (7/29), skin (3/29), bladder (3/29), hematopoietic system (3/29), adenocarcinoma of the ileum (2/29), connective tissue (2/29), salivary gland (2/29), liver (1/29), and thyroid (1/29). No tumors were reported among "control" animals. Pliss (1959, 1963) also conducted studies exposing rats to 3,3'-dichlorobenzidine by the subcutaneous route. In the first study (Pliss, 1959), animals (25 female, 36 male) received 120 mg 3,3'-dichlorobenzidine weekly for 10-11 months. The dose was reduced to 20 mg/rat after the sixth month due to toxicity. The same "control"animals were used as with the feeding study. The author notes the appearance of tumors of the Zymbal gland (10/35), mammary gland (6/35), skin (5/35), hematopoietic system (2/35), connective tissue (2/35), salivary gland (1/35), and local subcutaneous sarcomas (7/35) among animals surviving to the time of the appearance of the first tumors.

Griswold *et al.* (1968) dosed 20 female Sprague-Dawley rats with 300 mg 3,3'-dichlorobenzidine in sesame oil by gavage (10 doses at three day intervals) and observed the animals after 9 months for incidence of mammary tumors. Control groups included a

negative control (sesame oil only) and a positive control (7,12-dimethylbenz[a]anthracene). No tumors were observed in treated animals, but a 3% incidence was observed in the negative controls and 100% incidence in positive control animals. Osanai *et al.* (1976) treated 26 male ICR/JCL mice (plus 39 untreated control mice) with feed containing 0.1% 3,3'-dichlorobenzidine for 12 months with an interim sacrifice group at 6 months. Hepatomas were observed in all treated animals at 6 and 12 months ($p < 0.01$) and among control animals at an incidence of 0%, 9.5% (2/21) and 38.55% (5/13) at 6,12, and 18 months, respectively.

Tatematse *et al.* (1977) fed 22 male Wistar rats a diet containing 0.3% 3,3'-dichlorobenzidine alone or in sequence with o-N-butyl-N-(4-hydroxybutyl)nitrosamine (0.1% in drinking water), N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (0.15% in the diet) and N-fluorenylacetamide (0.025% in the drinking water) over a four week period. Twelve untreated animals served as controls. Animals were observed for a 40 week period. Only animals receiving combined exposures showed effects which included some bladder tumors and histological changes of the liver.

Saffiotti *et al.* (1967) and Sellakumar *et al.* (1969) report on a feeding study in which Syrian golden hamsters (30/sex/group) were exposed to 0.1% or 0.3% 3,3'-dichlorobenzidine in feed; an untreated control group (30/sex) was included. No significant carcinogenic effects were observed in the 0.1% 3,3'-dichlorobenzidine group. The 0.3% 3,3'-dichlorobenzidine group, however, showed increased incidence of transitional cell carcinomas of the bladder (4/30 treated, 0/30 control; $p = 0.056$ by Fisher's exact test). Other observations included some liver-cell and cholangiomatous tumors.

A single study suggests that 3,3'-dichlorobenzidine may act as a transplacental carcinogen (Golub *et al.*, 1974). Pregnant female BALB/c mice given 2 mg 3,3'-dichlorobenzidine (in 0.1 ml sesame oil) five times during the last week of pregnancy, showed increased incidence of lymphoid leukemia among the offspring of exposed animals (7/24 treated, 0/30 control; $p < 0.01$). This effect, however, could also have occurred by exposure via lactation.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

An IARC (1982) review of the human epidemiological studies deemed them inadequate for evaluating carcinogenicity due to the relatively small size of the cohorts, inadequate time since first exposure, and/or incomplete follow-up of exposed workers.

The only carcinogenesis studies amenable to the development of cancer potency values are those conducted by Stula *et al.* (1975, 1978) showing the induction of granulocytic leukemia, mammary adenocarcinoma, and Zymbal gland carcinoma in rats and papillary transitional cell carcinomas of the bladder and hepatocellular carcinomas in beagle dogs exposed to 3,3'-dichlorobenzidine. Limitations of the other available studies including

poor study design, inadequate scope of endpoints, and unclear interpretation of dose extrapolation, preclude the development of cancer potency values from these studies.

Methodology

The most sensitive experimentally determined endpoint for tumor development is mammary adenocarcinoma induction in female rats exposed to 3,3'-dichlorobenzidine (26/44 treated, 3/44 control) (Stula *et al*., 1975). A linearized multistage procedure (CDHS, 1985) applied to these data resulted in an estimation of the upper 95% confidence bound of cancer potency (q_1^*) of 0.023 $(mg/kg\text{-}day)^{-1}$. With a study duration of 49.9 weeks for females (T_e) and a natural lifespan assumption of 104 weeks (T), the cancer potency for animals (q_{animal}) was derived to be 0.21 $(mg/kg\text{-}day)^{-1}$ from the following relationship:

$$q_{animal} = q_1^* \times (T/T_e)^3$$

Human cancer potency (q_{human}) of 1.2 $(mg/kg\text{-}day)^{-1}$ based upon body weight assumptions of 0.35 kg for female rats (bw_a) and 70 kg for humans (bw_h) and the following relationship:

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

A unit risk value of 3.4 E-4 $(\mu g/m^3)^{-1}$ based upon air concentrations was derived by OEHHA/ATES assuming a human breathing rate of 20 m^3/day, a human body weight of 70 kg, and 100% fractional absorption after inhalation exposure.

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1, 1-DICHLOROETHANE

CAS No: 75-34-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	98.97
Boiling point	57.3°C (ATSDR, 1990)
Melting point	-96.7°C (ATSDR, 1990)
Vapor pressure	230 mm Hg at 25°C (ATSDR, 1990)
Air concentration conversion	1 ppm = 4.05 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 5.7 E-3 $(mg/kg\text{-}day)^{-1}$
[Female rat mammary gland adenocarcinoma tumor data (NCI, 1977), contained in Gold *et* al. database (1990), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 1,1-dichloroethane in humans are known to exist.

Animal Studies

Male and female Osborne-Mendel rats and $B6C3F_1$ mice were exposed to 1,1-dichloroethane dissolved in corn oil by gavage (NCI, 1977). The study design is summarized in Tables 1a and 1b. Dosing was performed once/day, 5 days/week. Dosing of the low- and high-dose mouse treatment groups was performed cyclically in the latter part of the experimental period; one exposure-free week was followed by 4 weeks of exposure.

Dose-related increases were noted in mammary adenocarcinomas and hemangiosarcomas in female rats. Statistically significant increases were observed in endometrial stromal polyps in high-dose female mice (4/46 compared to 0/79 for controls, $p = 0.017$) and in hepatocellular carcinomas in high-dose male mice (8/32 compared to 6/72 in pooled vehicle controls, $p = 0.027$). Female rat tumor incidence data is listed in Table 2.

Klaunig *et al*. (1986) exposed male $B6C3F_1$ mice to 1,1-dichloroethane in drinking water for 52 weeks. Exposure levels were 0, 835 and 2500 mg/l. Group sizes were 35 mice/group; 10 mice/group were killed after 24 weeks. Histology was only performed on kidney, liver and lung samples. No treatment-related increase in tumor incidence was

noted. However, histological examination was only performed on a limited number of tissues, and only male mice were used.

Table 1a. Study design for carcinogenicity bioassay of 1,1-dichloroethane (1,1-DCE): Osborne-Mendel rats (NCI, 1977)

Sex	Group	Group Size	1,1-DCE dose (mg/kg bw)	Observation period (weeks)		Time-weighted average dosage[1] (78 weeks)
				Treated	Untreated	
Male	Untreated control	20	0		109	0
	Vehicle control	20	0	78	33	0
	Low dose	50	350	8		382
			450	23		
			450[2]	37	10	
			0		33	
	High dose	50	700	8		764
			900	23		
			900[2]	37	10	
			0		33	
Female	Untreated control	20	0		105	0
	Vehicle control	20	0	78	33	0
	Low dose	50	750	8		475
			900	9		
			450	14		
			450[2]	37	10	
			0		33	
	High dose	50	1500	8		950
			1800	9		
			900	14		
			900[2]	37	10	
			0		33	

1. Time weighted average dosage = $\sum$ [(dosage × number of weeks) / 78 weeks]
2. Gavage doses were cyclically administered; one exposure-free week was followed by 4 weeks (5 days/week) of exposure at the exposure level indicated.

Table 1b. Study design for carcinogenicity bioassay of 1,1-dichloroethane (1,1-DCE): $B6C3F_1$ mice (NCI, 1977)

Sex	Group	Group Size	1,1-DCE dose (mg/kg bw)	Observation period (weeks)		Time-weighted average dosage[1] (78 weeks)
				Treated	Untreated	
Male	Untreated control	20	0		90	0
	Vehicle control	20	0	78	12	0
	Low dose	50	900	6		1442
			1200	3		
			1500	69		
			0		13	
	High dose	50	1800	6		2885
			2400	3		
			3000	69		
			0		13	
Female	Untreated control	20	0		91	0
	Vehicle control	20	0	78	12	0
	Low dose	50	900	6		1665
			1200	3		
			1500	11		
			1800	58		
			0		13	
	High dose	50	1800	6		3331
			2400	3		
			3000	11		
			3600	58		
			0		13	

1. Time weighted average dosage = $\sum$ [(dosage × number of weeks) / 78 weeks]

Table 2. Tumor induction in female Osborne-Mendel rats after gavage exposure to 1,2-dichloroethane (NCI, 1977)

Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
vehicle control	0	mammary adenocarcinomas hemangiosarcomas	0/20 0/40
low dose	238	mammary adenocarcinomas hemangiosarcomas	1/50 0/50
high dose	477	mammary adenocarcinomas hemangiosarcomas	5/50 4/50

1. Dose as reported by Gold *et al*., 1984. 2. Tumor incidence as reported by Gold *et al*., 1984

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al*. (1984) list the results of the NCI (1977) gavage studies in male and female $B6C3F_1$ mice and Osborne Mendel rats. Cancer potency for 1, 1-dichloroethane is based on mammary gland adenocarcinomas observed in female rats, the most sensitive of the species/sex combinations tested (see Table 2). Because female rat survival was poor in this study, the potency was derived using a time-to-tumor analysis (Crump *et al*., 1991; Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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DI-(2-ETHYLHEXYL)PHTHALATE

CAS No: 117-81-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	390.54
Boiling point	230°C @ 5 mm Hg
Melting point	-50°C
Vapor pressure	1.32 mm Hg @ 200°C
Air concentration conversion	1 ppm = 16.0 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.4 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 8.4 E-3 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency value derived for a Proposed Maximum Contaminant Level (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Thiess *et al.* (1978; reviewed by US EPA, 1994) report on a study of mortality among 221 workers involved in di-(2-ethylhexyl)phthalate (DEHP) production. Potential exposure periods range from 3 months to 24 years and the mean follow-up period was 11.5 years. Among workers exposed for more than 15 years, incidences of pancreatic carcinoma (1 case) and uremia (1 case with urethral and bladder papillomas) were elevated over incidence in the corresponding age group of the general population. No quantitation of exposure levels was reported.

Animal Studies

The National Toxicology Program (NTP, 1982; Kluwe *et al.,*1982) assayed the carcinogenic effects of di-(2-ethylhexyl)phthalate on rats and mice. Fischer F344 rats (50/sex/group) were treated with diet containing 0, 6000, or 12000 ppm DEHP for 103 weeks. $B6C3F_1$ mice (50/sex/group) were treated with diet containing 0, 3000, or 6000 ppm DEHP for 103 weeks. Survivors were sacrificed and examined histologically at 105 weeks. Survival of rats was not found to be significantly influenced by DEHP treatment. Increased incidence of hepatocellular carcinoma or hepatic neoplastic nodules was reported in male and female high-dose treated rats (see Table 1). The increase in incidence was found to be dose-related ($p < 0.01$). Among treated high-dose male and female mice, and

low-dose female mice, hepatocellular carcinoma incidence was increased. The increase in incidence was found to be dose-related ($p < 0.05$).

Table 1. Incidence of hepatocellular carcinoma in male and female $B6C3F_1$ mice and F344 rats fed diet containing DEHP (NTP, 1982).

species	treatment[1] (ppm in diet)	hepatocellular carcinoma incidence male	female
F344 rats	0	3/50	0/50
	6,000	6/49	2/49
	12,000	12/49[2]	8/50[3]
$B6C3F_1$ mice	0	9/50	0/50
	3,000	14/48	7/50[3]
	6,000	19/50[2]	17/50[4]

[1] Fischer F344 rats were treated with 0, 6000, or 12000 ppm DEHP in their diet for 103 weeks. $B6C3F_1$ mice were treated with 0, 3000, or 6000 ppm DEHP in their diet for 103 weeks. Survivors were sacrificed after 105 weeks.
[2] $p < 0.05$. [3] $p < 0.01$. [4] $p < 0.001$.

Carpenter *et al.* (1953) maintained 2 month old Sherman rats (32/sex/group) on a diet containing 0, 400, 1300, or 4000 ppm DEHP up to two years. Animals were sacrificed at one year with the exception of a subgroup of a maximum of 8 rats/sex/dose which were exposed for an additional year. A group of 80 F_1 generation rats, the progeny of females in the highest dose group exposed for more than 120 days, were exposed for one year to diet containing 4000 ppm DEHP. Survivors were sacrificed after one year. No malignant tumors were observed among treated animals. Three rats in the 4000 ppm DEHP dose group, four in the 1300 dose group, two in the 400 ppm dose group, and five in the control group were reported to have benign tumors. Two benign tumors in the treated F_1 rats (vs. one in the control group) had benign tumors. Mortality at two years was reported to be 70.3% among control animals and between 60 and 70% among the treated groups. Poor survival of animals precluded evaluation of carcinogenicity from this study.

Carpenter *et al.* (1953) also treated hybrid guinea pigs (~23/sex/dose) with diet containing 0, 1300, or 4000 ppm DEHP for 1 year, at which time animals were sacrificed. Survival among exposed animals was decreased. No carcinogenic effects were observed.

Carpenter *et al.* (1953) also treated 4 dogs with gelatin capsules containing a volume of 0.03 ml/kg body weight DEHP five days per week for 19 doses, then with 0.06 ml/kg body weight DEHP for 240 doses. Four control animals were also included in the study. No tumors were observed in treated or control animals.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The only data appropriate for the development of a cancer potency value come from the NTP (1982) study which showed a dose-related effect of DEHP on the incidence of hepatocellular carcinoma in Fischer 344 rats and $B6C3F_1$ mice. This study was conducted by standard protocols with an adequate number of animals and thorough reporting of results.

Methodology

For the purpose of developing a cancer potency in humans, US EPA (1986, 1987) converted the exposure levels of rats and mice in the NTP (1982) study to human equivalent doses (HEDs). Dosage levels were first converted from parts per million in the diet to mg/kg-day based upon reported food disappearance rates. The resulting daily low and high dose estimates were 322 and 674 mg/kg-day for male rats, 394 and 774 mg/kg-day for female rats, 672 and 1325 mg/kg-day for male mice, and 799 and 1821 mg/kg-day for female mice. HEDs were based on the following relationship, with D the applied dose level, bw_a the experimental animal body weight, bw_h the assumed human body weight, l_e the length of exposure, L_e the length of the study, and L the lifespan of the animal:

$$HED = D \times \frac{l_e}{L_e} \times \left(\frac{bw_a}{bw_h}\right)^{\frac{1}{3}} \times \left(\frac{L_e}{L}\right)^3$$

Using the derived HED values, US EPA (1987) applied the multistage procedure of Howe and Crump (Global 82; 1982) to the combined incidence data of hepatocellular carcinomas and neoplastic nodules reported by NTP (1982). The resulting upper 95% confidence bounds on the cancer potency (q_{human}) are presented in Table 2. The highest, and thus most sensitive, cancer potency value is derived from the incidence of hepatocellular carcinomas in male $B6C3F_1$ mice, with a q_{human} value of 8.4 E-3 $(mg/kg\text{-}day)^{-1}$. Selection of the cancer potency value for DEHP comes from the most sensitive site and species of tumor induction in experimental animals in the absence of human data appropriate for developing a potency value.

Table 2. Human cancer potency values derived by US EPA (1986, 1987) from the NTP (1982) study.

species	sex	q_{human} $[(mg/kg\text{-}day)^{-1}]$
F344 rats	male	2.95 E-3
	female	3.52 E-3
$B6C3F_1$ mice	male	8.36 E-3
	female	4.73 E-3

A unit risk value of 2.4 E-6 $(\mu g/m^3)^{-1}$ was derived by OEHHA/ATES assuming a 70 kg average human body weight, 20 m^3/day human breathing rate, and 100% fractional absorption.

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P-DIMETHYLAMINOAZOBENZENE

CAS No: 60-11-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	225.28
Boiling point	not available
Melting point	114-117 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 9.214 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 4.6 E+0 $(mg/kg\text{-}day)^{-1}$
[Female rat liver tumor data (Kirby and Peacock, 1947), contained in Gold *et al.* database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *p*-dimethylaminoazobenzene (DAB) in humans are known to exist.

Animal Studies

IARC (1974) reviewed a number of studies on the carcinogenic potential of DAB in animals. DAB was initially reported by Kinosita (1937) to induce liver tumors in rats after dietary exposure; tumors were produced after 50 or more days of treatment (smallest total dose, 176 mg DAB). Sherman, Wistar and Evans rats were found to be equally susceptible to the induction of liver tumors after exposure to diets containing 600 mg/kg DAB (Sugiura and Rhoads, 1941).

Kirby and Peacock (1947) exposed male and female Wistar-derived rats to a low-protein diet (12% casein) containing 0 or 600 mg/kg diet DAB. Group sizes were 8 animals/sex/group except for treated females, where the group consisted of 7 animals. Four male rats received treated diet for 28 weeks, followed by control diet; the other animals received treated diet for 33 weeks. At the end of the treatment period, all animals received control diet until sacrifice at 52 weeks. Both male and female rats developed hepatomas; Gold *et al*. (1984) list a tumor incidence of 0/8 and 5/7 for control and treated (average dose, 20.9 mg/kg-day) females, respectively.

Druckrey and Küpfmüller (1948; reviewed by IARC, 1975) exposed rats to 1, 3, 10, 20 or 30 mg DAB/day by gavage for the life of the animals. All doses induced the formation of liver tumors; the induction time was inversely proportional to the dose, ranging from 34 days (30 mg/day) to 700 days (1 mg/day). For exposure groups in the 3-30 mg/day range, the total carcinogenic dose was about 1000 mg. Daily exposures of 0.1 or 0.3 mg/rat did not induce tumors.

Druckrey (1967) exposed rats to 5 mg DAB/rat by gavage for 40, 60, 100, 140 or 200 days, then observed the animals for the remainder of their lifespan. Percent incidences of liver carcinomas were 20, 26, 49, 80 and 81, respectively.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The feeding study by Kirby and Peacock (1947) conducted in Wistar-derived albino rats is listed in Gold *et al*. (1984). Cancer potency is based on liver tumors in the female rats.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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2,4-DINITROTOLUENE

CAS No: 121-14-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	182.14
Boiling point	300°C
Melting point	71°C
Vapor pressure	0.00014 mm Hg @ 25°C
Air concentration conversion	1 ppm = 7.4 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 8.9 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 3.1 E-1 $(mg/kg\text{-}day)^{-1}$
[calculated from a potency factor derived by US EPA (1987) and adopted by CDHS (see Final Statement of Reasons)]

III. CARCINOGENIC EFFECTS

Human Studies

No data are available addressing the carcinogenicity of 2,4-dinitrotoluene (2,4-DNT) in humans.

Animal Studies

Lee *et al.* (1978) exposed male and female CD rats to practical grade 2,4-DNT in feed at concentrations of 0, 15, 100, and 700 ppm for 720 days. Animals were sacrificed at 750 days. Decreased weight gain and lifespan were observed among animals in the highest treatment group. Noncancer toxic effects observed included toxic anemia and aspermatogenesis. Tumors observed included fibromas of the connective tissue of male rats and fibroadenoma of the mammary gland of female rats. The incidence data for liver and mammary tumors in female rats are presented in Table 1. Significantly increased incidence was found in the highest dose group for liver tumors ($p = 4 \times 10^{-4}$; Fisher's exact test), mammary gland tumors ($p = 1.75 \times 10^{-4}$), and combined mammary gland and liver tumors ($p = 7 \times 10^{-5}$). Mammary tumor incidence among male rats was 1/37, 0/37, 0/29, and 17/23 in the 0, 15, 100, and 700 ppm 2,4-DNT dose groups, respectively. Only the highest dose group showed significantly increased tumor incidence ($p = 4 \times 10^{-9}$).

Table 1. Incidence of liver and mammary gland tumors among female CD rats exposed to practical grade 2,4-dinitrotoluene (2,4-DNT) in feed for 24 months (Lee *et al.*, 1978).

treatment level (ppm)	tumor incidence		
	liver[1]	mammary gland[2]	combined
0	0/31	11/31	11/31
15	3/43	12/43	13/43
100	3/35	18/35	18/35
700	30/42	34/43	35/43

[1] Tumor incidence includes neoplastic nodules and hepatocellular carcinoma of the liver.
[2] Tumor incidence includes adenoma, fibroadenoma, fibroma, or adenocarcinoma of the mammary gland.

The National Cancer Institute (NCI, 1978) conducted a study exposing Fischer rats and $B6C3F_1$ mice to practical-grade 2,4-DNT (>95% pure). Male and female Fischer rats (50/sex/group) were exposed to feed containing 0.02% or 0.008% 2,4-DNT (time-weighted concentrations). Control groups consisted of 25 rats/sex for the high-dose group and 50 rats/sex for the low-dose group. The treatment period was 78 weeks long and the observation period continued for 26 weeks. Among treated male rats in both high- and low-dose groups, the incidence of benign fibroma of the skin and subcutaneous tissue was increased over controls (high-dose: 13/49 treated vs. 0/25 control, $p = 0.003$; low-dose: 7/49 treated vs. 0/46 control, $p = 0.008$ by Fisher's exact test). Among treated female rats in the high-dose group, the incidence of fibroadenoma of the mammary gland was increased over control animals (23/50 treated vs. 4/23 control, $p = 0.016$).

In the same study (NCI, 1978), male and female $B6C3F_1$ mice (50/sex/group) were treated with diet containing 0.04% or 0.008% 2,4-DNT (time-weighted concentrations). Groups of 50 mice/sex served as controls for the high- and low-dose groups. The treatment period lasted 78 weeks and the animals were observed for an additional 13 weeks. No significant increase in tumor incidence was observed among treated animals.

Ellis *et al.* (1979) (also reported by Lee *et al.,*1985) exposed male and female CD (Sprague-Dawley) rats (38/sex/group) to 0, 15, 100, or 700 ppm 2,4-DNT in feed. At 12 months, 8 rats/group were sacrificed for necropsy; the remainder were sacrificed at 24 months. Cumulative deaths during the course of the study ranged from 55 to 100% in male rats and 60 to 97% in female rats, including control animals. Histopathological outcomes of animals that died during the course of the experiment (but after 52 weeks) were included in the final incidence data along with the incidence data among survivors. Tumors showing statistically significant increases ($p < 0.05$ by Fisher's exact test) were hepatocellular carcinomas and mammary gland tumors among female rats in the highest dose group. Hepatocellular carcinomas were reported in 18/34 treated high-dose female rats vs. 0/23 control rats ($p = 4.3 \times 10^{-6}$). Mammary gland tumors, including both benign and malignant tumors of epithelial or mesenchymal origin, were reported in 33/35 treated high-dose female rats vs. 11/23 control rats ($p < 0.0001$).

Ellis *et al.*(1979) (also reported by Hong *et al.,* 1985) exposed male and female CD-1 mice (38/sex/group) to 0, 100, 700, or 5000 ppm 2,4-DNT in feed as described in the rat study above. Since over 70% of the mice in the highest dose group died before 12 months, these animals were not included in the analysis. Mortality among the remaining dose groups and controls ranged from 70 to 85%. Tumor incidence data were drawn from animals surviving at least 12 months. A significantly increased incidence of renal tumors was found among male mice in the 700 ppm 2,4-DNT dose group (19/28 treated vs. 0/33 control; $p = 1.32 \times 10^{-9}$, Fisher's exact test). Renal tumor types included cystic papillary adenomas, solid renal cell carcinomas, and cystic papillary carcinomas. No significantly increased tumor incidence was reported among female mice.

Ellis *et al.* (1979, 1985) treated beagle dogs (6/sex/group) with 2,4-DNT in gelatin capsules daily for 2 years at dose rates of 0, 0.2, 1.5, or 10 mg/kg body weight. The highest dose was lethal to five of the 12 treated animals. Throrough examination of all animals upon sacrifice showed no evidence of carcinogenicity of 2,4-DNT.

The Chemical Industry Institute of Toxicology (CIIT, 1982) exposed male and female F344 rats (130/sex/dose) to technical grade DNT (76% 2,4-DNT and 19% 2,6-DNT) feed such that daily dosing was 0, 3.5, 10.0, and 35.0 mg/kg-day. The entire high-dose group was sacrificed at 55 weeks due to significantly reduced survival. Twenty rats (/sex) were examined histopathologically at this time. The animals in the remaining dose groups were sacrificed at the scheduled time of 104 weeks. The incidences of hepatocellular carcinoma and neoplastic nodules of the liver are reported in Table 1. Cholangiocarcinomas were also reported in 3/20 high-dose male rats (at 55 weeks) and 2/23 mid-dose male rats (at 104 weeks).

Table 1. Tumor incidence in male and female F344 rats exposed to technical grade dinitrotoluene (DNT) in feed (CIIT, 1982).

tumor type	males (mg/kg-day)				females (mg/kg-day)			
	0	3.5	10.0	35.0*	0	3.5	10.0	35.0*
hepatocellular carcinoma	1/61	9/70	22/23	20/20	0/57	0/61	40/68	11/20
neoplastic nodules	9/61	11/70	16/23	5/20	5/57	12/61	53/68	12/20

*All the high-dose group animals were sacrificed at 55 weeks due to significantly reduced survival. Histopathological examinations were performed on 20 rats/sex.

Leonard *et al.* (1987) exposed 20 male CDF(F344)/CrlBR rats to 2,4-DNT in the diet for 12 months such that daily dose rate was 27 mg/kg-day. No evidence of carcinogenicity was found, however, the study was short in duration and the number of animals was small.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The US EPA (1980) derived a cancer potency value based on the tumor incidence data in the study by Lee *et al.* (1978) showing the induction of liver and mammary tumors in female CD rats. This study was selected over the NCI (1978) study because of published reservations by NCI concerning the adequacy of the study for estimating cancer potency in humans.

Methodology

The US EPA (1980) calculated a "transformed" dose rate of 0, 0.71, 3.9, and 34.0 mg/kg-day for the animals in the study by Lee *et al.* (1978) exposed to 0, 15 100 and 700 ppm 2,4-DNT in their diet, respectively. A linearized multistage procedure was applied to the combined mammary gland and liver tumor incidence data presented in Table 1 in order to calculate an animal cancer potency value (q_{animal}). The calculated q_{animal} was 0.058 (mg/kg-day)$^{-1}$. The q_{animal} was converted to a human cancer potency (q_{humna}) based on the following relationship, where bw_{animal} is the assumed body weight for the test species (Lee *et al.*, 1978; bw_{animal} = 0.464 kg) and bw_{human} is the assumed human body weight (70 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting q_{human} is 0.31 (mg/kg-day)$^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 8.9 E-5 ($\mu g/m^3$)$^{-1}$.

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1,4-DIOXANE

CAS No: 123-91-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From ACGIH, 1994)

Molecular weight	88.1
Boiling point	101.1°C
Melting point	11.8°C
Vapor pressure	29 mm Hg @ 20°C
Air concentration conversion	1 ppm = 3.6 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: (7.7 E-6 µg/m^3)$^{-1}$
Slope Factor: 2.7 E-2 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1989)]

III. CARCINOGENIC EFFECTS

Human Studies

The two human epidemiological studies of the potential carcinogenicity of 1,4-dioxane (Thiess *et al*. (1976); Buffler *et al*. (1978)) did not show significant changes in the incidence of carcinogenicity. However, neither study had sufficient statistical power to detect moderate changes in cancer incidence due to the small size of the sample groups or the short duration of the studies.

In the study by Thiess *et al*. (1976), 74 German workers were exposed to various concentrations of 1,4-dioxane for an average of 24.9 years. Of the 74 workers, 24 were working at the end of the follow-up period (1964 - 1974), 23 were no longer working, 15 had retired, and 12 had died. Of the 12 deaths, two were attributed to neoplastic diseases (1 lamellar epithelial carcinoma and 1 myelofibrotic leukemia). The expected number of deaths during this period in the cohort was 14.5, based on Federal Republic of Germany mortality statistics. The overall death rate and the cancer death rate were not significantly increased over controls.

Buffler *et al*. (1978) studied the mortality of 165 workers exposed to 1,4-dioxane in a dioxane-manufacturing and processing facility in Texas. The employees were exposed to dioxane for at least 1-month up to 21 years (April, 1954 to June, 1975), and were divided into two cohorts. The cohort of manufacturing workers was composed of 100 individuals, and the processing workers numbered 65. The concentrations of dioxane in the workplaces were less than 25 ppm. Seven deaths occurred in the manufacturing cohort (4.9 expected), two from neoplasms (0.9 expected). Five deaths occurred in the processing cohort (4.9 expected), one from cancer (0.8 expected). These mortality and cancer rates were not

higher than the expected from Texas age- and sex-specific death rates for 1960-1969. Due to the small sample size and short exposure period of the study, the authors concluded that the negative results were not conclusive.

Animal Studies

Male Wistar rats (n = 26) were given drinking water containing 1% dioxane for 63 weeks (Argus *et al*., 1965). A group of 9 rats given untreated water were used as controls. Six hepatomas, one kidney tumor, and one case of leukemia were found in the treated animals. One lymphosarcoma was found in the control group. The increased incidence of cancer in the treated animals was not statistically significant ($p < 0.05$). However, due to the small size of the control group, this study was of very limited sensitivity, and therefore inconclusive.

Another drinking water study in male rats was conducted by Hoch-Ligeti *et al*. (1969) and further reported on by Argus *et al*. (1973). In this study, male Charles River rats (30 per group) were given 0, 0.75, 1.0, 1.4, or 1.8% dioxane in their drinking water from 2-3 months of age for 13 months. Animals were killed 16 months following treatment or earlier if tumors in the nasal cavity were observed. Survival data was not reported. Nasal histological examinations were only performed on animals with grossly visible tumors. The incidence of tumors found in this study are presented in Table 1.

Table 1. Tumor incidence in male Charles River rats exposed to 1,4-dioxane in drinking water (Hoch-Ligeti *et al*., 1969; Argus *et al*., 1973).

	Tumor Incidence				
1,4-Dioxane Concentration (%)	0	0.75	1.0	1.4	1.8
Hepatocarcinomas	0/30	0/30	0/30	2/30	2/30
Nasal tumors	0/30	1/30	1/30	2/30	2/30
Hepatic tumors (total)	NR	4/30	8/30	16/30	25/30

NR = Not reported

Kociba *et al*. (1974) studied the effects of dioxane in the drinking water of male and female Sherman rats. Rats (60/sex/group) were exposed to 0, 0.01, 0.1, or 1.0% dioxane for 2 years. Actual dosages of dioxane were estimated using drinking water consumption and body weight data. The dosages were 0, 9, 94, or 1015 mg/kg/day for the males, and 0, 14, 148, or 1599 mg/kg/day in females. Because the tumor incidence data are averaged for the combined male and female responses, the doses were also averaged. Mortality in the combined high dose group was 45% after 1 year of exposure, compared with 12% in the control group. The tumor incidence data is summarized in Table 2.

King *et al*. (1975) exposed male and female B6C3F1 mice (50/sex/group) to dioxane in the drinking water for 40-43 weeks. Concentrations of dioxane used were 0, 0.5, or 1.0 %. No tumors were observed in any group at the end of the treatment period. According to IARC

(1976), the duration of this study was insufficient to detect hepatocarcinoma, the tumor most commonly found in the National Cancer Institute (NCI, 1978) study.

Table 2. Tumor incidence in male and female Sherman rats exposed to dioxane in drinking water (Kociba *et al*., 1974).

	Tumor Incidence			
1,4-Dioxane Concentration (%)	0	0.01	0.1	1.0
Hepatocarcinomas	1/120	0/120	1/120	10/120
Nasal tumors	0/120	NR	NR	3/120

NR = Not reported

The NCI conducted a bioassay on male and female $B6C3F_1$ mice (50/sex/group) given 0, 0.5, or 1.0% dioxane in the drinking water from 5 weeks to 90 weeks (NCI, 1978). Mortality of the male rats was only 10% in the male mice after 91 weeks. Mortality in the female mice increased with increasing dose, up to 44% in the high dose group. Tumor incidence data from this study is presented in Table 3. The incidence of hepatocarcinomas was significantly increased in both the male and female mice exposed to the low and high concentrations of dioxane, compared with controls.

Table 3. Tumor incidence in male and female $B6C3F_1$ mice exposed to 1,4-dioxane in the drinking water (NCI, 1978).

	Tumor Incidence		
1,4-dioxane Concentration	0	0.5	1.0
Hepatocarcinomas (males)	2/49	18/50	24/47
Hepatocarcinomas (females)	0/50	12/48	29/37

In addition to the mouse study. the National Cancer Institute (1978) also exposed male and female Osborne-Mendel rats to 0, 0.1, or 1.0 % dioxane in their drinking water for 110 or 90 weeks, respectively. The incidences of nasal tumors in these groups were 0/33, 12/33, and 16/33 in the males, and 0/34, 10/35, and 8/35 in the females.

Male guinea pigs (20/group) were exposed to 0 or 0.5-2.0% dioxane in the drinking water for 23 months. After 28 months, the animals were killed and tumor incidence was recorded. Tumor incidences in the treated animals included 3 animals with hepatomas, 2 with gall bladder carcinomas, and one with adenoma of the kidney. Tumors were not found in the controls (n = 10). Although the cancer incidences were not significantly different from the controls, IARC (1976) concluded that dioxane caused liver and gall bladder tumors.

In an inhalation study, Torkelson *et al*. (1974) exposed groups of 288 male or female Wistar rats to 111 ppm 1,4-dioxane for 7 hours/day, 5 days/week, for 2 years. Control rats (192

male or female rats) were exposed to filtered room air. Weight gain among males and females was not affected by dioxane treatment compared with controls. Survival rates were not significantly different between control and treated rats. Similarly, the tumor incidence was not significantly different with dioxane treatment. The estimated equivalent dose rate from the inhalation study was 100 mg/kg/day, based on default values for rat body weight and breathing rate. This estimated dose is much lower than that used in the drinking water studies described above.

Male and female Swiss-Webster mice (30/sex/group) were exposed dermally to an unspecified concentration of dioxane in acetone 3 times/week (King *et al*., 1975). Dioxane was tested either as a complete carcinogen for 60 weeks, or as a promoter, following a single exposure to DMBA followed by 59-week exposure to dioxane. Control mice were treated with the acetone vehicle alone or with DMBA. Dioxane was a significant promoter of skin carcinomas compared to controls treated with DMBA only. However, no significant increase in skin papillomas or carcinomas was observed in the test for complete carcinogenicity.

The tumor-intitiating properties of dioxane were investigated using the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) in Sencar mice (40 females/group) (Bull *et al*., 1986). Mice were exposed to a single oral, topical, or subcutaneous dose of 1,000 mg/kg dioxane, followed by TPA in acetone 3 times per week for up to 52 weeks. No significant increase in skin tumor incidence was reported in the mice, however, tumor incidence was not reported and length of observation was not specified.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Five studies (Argus *et al*., 1965; Hoch-Ligeti *et al*., 1969; Argus *et al*., 1973; Kociba *et al*., 1974; and NCI, 1978) allow the estimation of cancer potency values for dioxane. Of these studies, only the Kociba *et al*. (1974) and NCI (1978) studies were considered for the determination of the cancer potency factor for dioxane.

In the Argus *et al*. (1965) study, 26 adult male Wistar rats were given drinking water containing 1% dioxane for 63 weeks. The estimated dose of dioxane by the authors was 300 mg/day. The incidence of liver hepatomas (6/26) in the treated animals was significantly higher than in untreated control animals (0/9) but not significantly different from historical control animals. The cancer incidence in the treated animals is considered biologically significant, but is not quantitatively suitable for use as the basis of a cancer potency factor for dioxane.

The Hoch-Ligeti *et al*. (1969) and Argus *et al*. (1973) study failed to demonstrate significant differences in tumor incidences between treated and control rats. The trend for increasing tumors was marginally signficant ($p < 0.07$). When analyzed, these data yield a human cancer potency factor of 2.0×10^3 to 5.8×10^3 $(mg/kg\text{-}day)^{-1}$.

In the Kociba *et al*. (1974) study, 60 male and female Sherman rats were exposed to concentrations of dioxane of 0, 0.01, 0.1, and 1.0 % for 716 days. The tumor incidence for the combined male and female data set was 1/120, 0/120, 1/120, and 10/120. Using the multistage procedure and an interspecies scaling factor, an estimate for human cancer potency of dioxane was 5.7×10^{-4} $(mg/kg/day)^{-1}$. This dataset was not used since tumor incidences for males and females were averaged.

The National Cancer Institute (1978) exposed male and female Osborne-Mendel rats to 0, 0.1, or 1.0 % dioxane in their drinking water for 110 or 90 weeks, respectively. The incidence of nasal tumors were 0/33, 12/33, and 16/33 in the males, and 0/34, 10/35, and 8/35 in the females. From measured water consumption and body weight data, the human cancer potency from a multistage polynomial fit of these data was 9.5×10^{-3} $(mg/kg/day)^{-1}$ from male rat data, and 4.9×10^{-3} $(mg/kg/day)^{-1}$ from female rat data. An adjustment for early mortality following the procedure of EPA (1988) yielded cancer potencies of 1.1×10^{-2} $(mg/kg/day)^{-1}$ and 6.0×10^{-3} $(mg/kg/day)^{-1}$ from male and female rat data, respectively. The NCI (1978) study using B6C3F1 mice was used as the basis for the cancer potency for dioxane. This study contained the best data on the most sensitive species and sex, and the most sensitive target tissue. In this study, 50 male or female mice were exposed to 0, 0.5, or 1.0% dioxane for 90 weeks. Average doses were determined from weekly measurements of water consumption. The estimated doses were 0, 720, and 830 mg/kg/day for the males and 0, 380, and 860 mg/kg/day for the females. The incidence of hepatocarcinomas were 2/49, 18/50, and 24/47 for males, and 0/50, 12/48, and 29/37 for the females. The incidence of hepatocarcinomas or adenomas were 8/49, 19/50, and 28/47 in males, and 0/50, 21/48, and 35/37 in females.

Methodology

A linearized multistage procedure (CDHS, 1985) was applied to the female mouse combined hepatocellular carcinoma and adenoma incidence from the NCI (1978) study. The animal cancer potencies were 8.3×10^{-4} and 1.4×10^{-3} $(mg/kg/day)^{-1}$, for the males and females, respectively. The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. The animal cancer potencies were therefore adjusted for the short duration of the experiment, using the factor $(104/90)^3$. A value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse). Body weights for interspecies scaling were assumed to be 0.04 and 0.035 kg for males and females, respectively. The combined incidence of hepatocarcinomas and adenomas in males and females gave human cancer potencies of 1.5×10^{-2}, and 2.7×10^{-2} $(mg/kg/day)^{-1}$, respectively. The combined incidence of hepatocarcinomas and adenomas in females was used to derive the human cancer potency for dioxane of 2.7×10^{-2} $(mg/kg/day)^{-1}$. The airborne unit risk factor for dioxane of 7.7 E-6 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES assuming a human body weight of 70 kg and an inhalation rate of 20 m^3/day.

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EPICHLOROHYDRIN

CAS No: 106-89-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	92.5
Boiling point	116.5°C
Melting point	-48°C
Vapor pressure	10 mm Hg at 16.6°C
Air concentration conversion	1 ppm = 3.79 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.3 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 8.0 E-2 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

A retrospective cohort mortality study of 533 white male Dow Chemical Company employees with potential epichlorohydrin (ECH) exposure for at least 1 month between October 1957 and November 1976 was performed by Shellenberger *et al*. (1979; reviewed by US EPA, 1984). Two cancer deaths were observed; this was less than the number expected (3.5) for the entire group. However, in a review of this study, US EPA (1984) pointed out that this study is inadequate for ECH carcinogenicity evaluation because of low exposures, short exposure duration, a short study period and the very young age of the cohort.

Enterline (1978, 1981; reviewed by US EPA, 1984) conducted a retrospective cohort mortality study of epichlorohydrin workers for Shell Oil Company. The cohort consisted of 864 workers at Shell plants in Louisiana and Texas; deaths were compared by cause with expected deaths in Louisiana and Texas, respectively. Study data were analyzed by vital status as of December 31, 1977 and as of December 31, 1979 (reported by Enterline in 1978 and 1981, respectively) for the cohort exposed to ECH for at least 3 months before January 1, 1966. Overall mortality in the ECH-exposed group was not increased compared to controls; a non-statistically significant increase in respiratory cancer and leukemias was reported (standardized mortality ratios (SMRs) of 146.2 and 224.7, respectively). Additionally, the data reported in 1978 indicated an apparent increase with increasing latent period since 11 of 12 of the respiratory cancer or leukemia deaths occurred in workers 15 or more years after first exposure. The possibility existed that increasing observation time would reveal more respiratory cancer/leukemia deaths. However, the 1981 report (Enterline, 1981) including the most recent data indicated that the SMRs for both

respiratory cancer and leukemia in the ECH-exposed group decreased, especially for those with greater than 15 years since first exposure. US EPA (1984) also noted that smoking was a potential confounder, exposure analysis failed to show a dose-response trend, and exposure to multiple chemicals was also a potential confounder. The SMR for respiratory cancer was much higher in workers exposed in the isopropyl alcohol manufacturing unit to other chemicals in addition to ECH than in the group exposed to ECH alone (SMRs = 214.8 and 63.3, respectively). US EPA (1984) concluded that the studies by Enterline (1978, 1981) provide only limited evidence for the human carcinogenicity of ECH.

Tassignon *et al*. (1983) studied the mortality of workers exposed to ECH in four European manufacturing plants which produced ECH, epoxy resins, glycerin and other ECH-derived specialty chemicals. Data was collected on 606 male workers with at least one year of exposure to ECH starting at least 10 years before December 31, 1978. No excess cancer mortality due to ECH exposure was observed; however, the authors noted that the small cohort size, short duration of the observation period and the limited number of deaths due to low average age (42 years) limited the power of the study.

Animal Studies

Female ICR/Ha Swiss mice were treated with ECH by dermal application, subcutaneous injection or intraperitoneal injection (Van Duuren *et al*., 1974). Dermal applications were performed 3 times/week; 2 mg ECH in 0.1 ml acetone was applied to 50 animals for 83 weeks. Untreated and vehicle control groups of 100 and 50 animals, respectively, were included. No increased incidence in skin tumors were noted in the treated animals. Intraperitoneal injections were performed weekly for 64 weeks; 1 mg ECH in 0.05 ml tricaprylin was injected into 30 animals. Untreated and vehicle control groups of 100 and 30 animals, respectively, were included. No treatment-related tumor induction was noted in the exposed animals. Subcutaneous injections were performed weekly for 83 weeks; 1 mg ECH dissolved in 0.05 ml tricaprylin was injected into 50 animals. Untreated and vehicle control groups of 100 and 50 animals, respectively, were included. An increased incidence of injection site tumors was noted (6/50 sarcomas, 1/50 adenocarcinomas) in the treated animals as compared to controls (no tumors in untreated controls, 1/50 sarcomas in vehicle controls).

Laskin *et al.* (1980) exposed male non-inbred Sprague-Dawley rats to 10, 30 or 100 ppm ECH by inhalation for the lifetime of the animals. Exposure durations were 6 hours/day, 5 days/week. Control groups consisted of 50 untreated animals and 100 air-treated animals. All groups demonstrated a high degree of early mortality, primarily due to respiratory disease (50% mortality by 64 weeks). Of a group of animals exposed to 100 ppm ECH for 6 weeks, 18/140 developed nasal cavity tumors, which were primarily squamous cell carcinomas. A group of 100 animals exposed for life (approximately 144 weeks) to 30 ppm developed 2 respiratory tract tumors; 1 larynx squamous papilloma and 1 nasal squamous cell carcinoma. The laryngeal tumor was misidentified in the original manuscript as a nasal tumor (US EPA, 1984). These tumor incidences were not significant when compared to those of the control group; however, they were significant when compared to the 1920 historical control animals from that laboratory, none of which had

developed nasal squamous carcinoma. No nasal or respiratory tract tumors were noted in a group of 100 animals exposed for life to 10 ppm. No equivalent nasal or respiratory tumors were noted in the control groups. CDHS (1988) noted that only 18%, 26% and approximately 50% of the animals in the 30 ppm, 10 ppm and 100 ppm dose groups, respectively, survived to mean time-to-tumor observed in the 100 ppm group (86 weeks).

Konishi *et al*. (1980) exposed male Wistar rats (18/group) to epichlorohydrin in drinking water at concentrations of 0, 375, 750 or 1500 ppm for up to 81 weeks; treatment was intermittently suspended between 60 and 81 weeks for all three epichlorohydrin treatment groups due to toxicity. Total dose for the 375, 750 and 1500 ppm treatment groups was 5.0, 8.9 and 15.1 g/animal, respectively. A dose-related increase in forestomach tumor (papillomas and squamous cell carcinomas) incidence was observed. Tumor incidence data is listed in Table 1.

Table 1: Incidence of forestomach tumors in male Wistar rats exposed to epichlorohydrin in drinking water (Konishi *et al*., 1980)

Concentration (ppm)	Calculated dose[1] (mg/kg-day)	Tumor incidence	
		papillomas	squamous cell carcinomas
0	0	0/10	0/10
375	15.1	0/9	0/9
750	31.9	1/10	1/10
1500	76.1	7/12	2/10

1. As listed in CDHS (1988).

Male and female ICR/HA Swiss mice (50/sex/group) were exposed to pure (99.9%) trichlorethylene (TCE), industrial grade (99.4%) TCE, or TCE containing 0.8% ECH, 0.8% 1,2-epoxybutane, or 0.8% ECH and 0.8% 1,2-epoxybutane by gavage for 104 weeks (Henschler *et al*., 1984). Corn oil vehicle control groups were included. Initial dosing provided TCE exposures of 2400 mg/kg/day^{-1} and 1800 mg/kg/day^{-1} for male and female mice, respectively. Because of toxicity, dosing was halted for all groups during weeks 35-40, 65 and 69-78. All doses were reduced by a factor of 2 at week 40. Mortality was significantly increased compared to controls in all male treatment groups, and in female treatment groups receiving pure TCE and TCE/ECH. Significant increases in the incidence of squamous cell carcinomas of the forestomach were observed in both male and female animals exposed to TCE/ECH. The tumor incidence in animals exposed to pure TCE was comparable to control values. Tumor incidence data is listed in Table 2.

Male and female Wistar rats (50/sex/group) were exposed to 0, 2 or 10 mg/kg body weight epichlorohydrin by gavage 5 times/week for 2 years (Wester *et al*., 1985). Intestinal obstruction by trichobezoars (hairballs) resulted in intercurrent mortality after 4 months. Cumulative incidences for control, low-dose and high-dose animals, respectively, were 8, 16 and 19 for females, and 1, 0 and 5 for males. The study diet formulation was changed at 4 months; this resulted in decreased mortality from this cause for the remainder of the

study. The percentage of surviving animals after 1 and 2 years of treatment is listed in Table 3.

Table 2. Epichlorohydrin-induced forestomach tumor incidence in male and female Swiss mice (Henschler *et al*., 1984)

Treatment group	Tumor incidence[1]	
	males	females
vehicle controls	1/50	1/50
pure trichloroethylene	1/50	0/50
pure trichloroethylene + 0.8% epichlorohydrin	8/50	12/50

1. Papilloma and squamous cell carcinoma incidences combined.

Table 3. Survival of male and female Wistar rats exposed to epichlorohydrin by gavage (Wester *et al*., 1985)

Dose level (mg/kg body weight)	% survival after 1 year of treatment		% survival after 2 years of treatment	
	males	females	males	females
0	98	80	76	62
2	94	62	62	40
10	90	62	58	44

Treatment-related increases in the incidence of forestomach tumors (papillomas and squamous cell carcinomas) were observed in both male and female animals. Tumor incidence data is listed in Table 4.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that a value derived from that data set would not be appropriate (CDHS, 1985). Several studies describe ECH-induced tumor incidence data which can be used to generate a cancer potency factor (male Wistar rat forestomach papilloma and squamous cell carcinoma data, Konishi *et al*. (1980); male Sprague-Dawley rat nasal tumor data, Laskin *et al.* (1980); male and female ICR/HA Swiss mouse forestomach squamous cell carcinoma data, Henschler *et al.* (1984); male and female Wistar rat papilloma and squamous cell carcinoma data, Wester *et al.* (1985). The data from the study by Konishi *et al*. (1980) was chosen by CDHS (1988) as the basis for a cancer potency factor for ECH. Data from the Laskin *et al*. (1980) study was considered to be less suitable for generating a cancer potency factor than data from the Konishi *et al.* (1980) study because of the poor survival of the study animals. The studies by Henschler *et al.* (1984) and Wester *et al.,* (1985) contained potential confounding factors. The ECH-exposed animals in the Henschler *et al.* (1984)

study were also exposed to trichloroethylene. The animals used in the Wester *et al*. (1985) study exhibited trichobezoar-induced intestinal obstructions early in the study due to the diet composition; CDHS (1988) noted that those obstructions could have been a contributing factor to the observed forestomach carcinogenesis.

Table 4. Epichlorohydrin-induced forestomach tumor incidence in male and female Wistar rats (Wester *et al*., 1985)

Sex	Dose level (mg/kg body weight)	Tumor type	Tumor incidence
male	0 2 10	papilloma	1/50 6/49 4/49
	0 2 10	squamous cell carcinoma	0/50 6/49 35/49
female	0 2 10	papilloma	2/47 3/44 0/39
	0 2 10	squamous cell carcinoma	0/47 2/44 24/39

Methodology

A linearized multistage procedure (CDHS, 1985) was applied to male Wistar rat forestomach papilloma and carcinoma incidence data (Konishi *et al*., 1980). US EPA (1984) lists the half-life of ECH in water as 0.69 days. Assuming first order decay due to hydrolysis, this corresponds to an average concentration throughout the day of 63% of the concentration of the freshly prepared solution. The control, low, mid and high dose groups were reported to have received cumulative doses of 0, 5.0, 8.9 and 15.1 grams (Konishi *et al*., 1980); however, these data do not compensate for hydrolysis loss of ECH. CDHS (1988) estimated the actual daily exposures after hydrolysis compensation for the low, mid and high dose groups to be 15.1, 31.9 and 76.1 mg/kg-day, respectively. This assumes a body weight of 400 grams for a control Wistar rat, and utilizes the body weight data supplied by Konishi *et al*. (1980) which indicated that the low, mid and high dose animals weighed 7.7, 22.4 and 44.9% less than the controls, respectively. Upper 95% confidence bounds on carcinogenic potency (q_1^*) were estimated using the incidences of forestomach tumors in animals surviving to the end of the study (81 weeks) and the above dose estimates. Estimates of lifetime potency values (q_{animal}) were calculated from the q_1^* derived from the 81 week study using the relationship $q_{animal} = q_1^* * (104/81)^3$. Estimates for q_{animal} of 0.015 and 0.011 $(mg/kg\text{-}day)^{-1}$ were obtained for the benign squamous cell papillomas and malignant squamous cell carcinomas, respectively. The fitted dose response functions associated with these potency estimates exhibited significant upward curvature (p = 0.03). Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors, using the relationship ($q_{human} = q_{animal}$ *

$(bw_h / bw_a)^{1/3}$), where q_{human} is the human potency, q_{animal} is the animal potency, and bw_h and bw_a are the human and animal body weights, respectively. Human carcinogenic potency values (q_{human}) of 0.08 and 0.06 mg/kg-day^{-1} were derived from the q_{animal} values for benign squamous cell papillomas and malignant squamous cell carcinomas, respectively. A unit risk factor was calculated by OEHHA/ATES from the benign squamous cell papilloma data-derived q_{human} value using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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ETHYLBENZENE

CAS No: 100-41-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 2003)

Molecular weight	106.2
Boiling point	136.2°C
Melting point	-94.9°C
Vapor pressure	9.6 mm Hg @ 25°C
Air concentration conversion	1 ppm = 4.35 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk:	2.5 x 10^{-6} (µg/m^3)$^{-1}$
Inhalation Cancer Potency:	0.0087 (mg/kg-day)$^{-1}$
Oral Cancer Potency:	0.011 (mg/kg-day)$^{-1}$

[Calculated from male rat renal tumor data (NTP, 1999), using the linearized multistage (LMS) methodology with lifetime weighted average (LTWA) doses (OEHHA, 2007).

III. METABOLISM and CARCINOGENIC EFFECTS

Metabolism

Ethylbenzene is rapidly and efficiently absorbed in humans via the inhalation route (ATSDR, 1999). Human volunteers exposed for 8 hours to 23-85 ppm retained 64% of inspired ethylbenzene vapor (Bardodej and Bardodejova, 1970). Gromiec and Piotrowski (1984) observed a lower mean uptake value of 49% with similar ethylbenzene exposures. There are no quantitative oral absorption data for ethylbenzene or benzene in humans but studies with [^{14}C]-benzene in rats and mice indicate gastrointestinal absorption in these species was greater than 97% over a wide range of doses (Sabourin *et al*., 1987).

Most of the metabolism of ethylbenzene is governed by the oxidation of the side chain (Fishbein, 1985). Engstrom (1984) studied the fate of ethylbenzene in rats exposed to 300 or 600 ppm (1305 or 2610 mg/m^3) ethylbenzene for six hours. Engstrom assumed 60 percent absorption of inhaled ethylbenzene and calculated that 83% of the 300 ppm dose was excreted in the urine within four hours of exposure. At the higher exposure of 600 ppm only 59 percent of the dose was recovered in the urine within 48 hr of exposure. Fourteen putative ethylbenzene metabolites were identified in the urine of exposed rats. The principal metabolites were 1-phenylethanol, mandelic acid, and benzoic acid. Metabolism proceeded mainly through oxidation of the ethyl moiety with ring oxidation appearing to play a minor role. Other metabolites included acetophenone, ω-hydroxyacetophenone, phenylglyoxal, and 1-phenyl-1, 2-ethandiol. Ring oxidation products include p-hydroxy- and m-hydroxyacetophenone, 2-ethyl- and 4-ethylphenol. With the exception of 4-hydroxyacetophenone all these other metabolites were seen only in trace amounts.

The metabolism of ethylbenzene was studied in humans (number unstated) exposed at 23 to 85 ppm (100 to 370 mg/m^3) in inhalation chambers for eight hours (Bardodej and Bardodejova, 1970). About 64 percent of the vapor was retained in the respiratory tract and only traces of ethylbenzene were found in expired air after termination of exposure. In 18 experiments with ethylbenzene, the principal metabolites observed in the urine were: mandelic acid, 64%; phenylglyoxylic acid, 25%; and 1-phenylethanol, 5%.

Engstrom *et al.* (1984) exposed four human male volunteers to 150 ppm ethylbenzene (653 mg/m^3) for four hours. Urine samples were obtained at two-hr intervals during exposure and periodically during the next day. For the 24-hr urine the metabolites were: mandelic acid, 71.5 ± 1.5%; phenylglyoxylic acid, 19.1 ± 2.0%; 1-phenylethanol, 4.0 ± 0.5%; 1-phenyl-1, 2-ethanediol, 0.53 ± 0.09%; acetophenone, 0.14 ± 0.04%; ω-hydroxyacetophenone, 0.15 ± 0.05%; m-hydroxyacetophenone, 1.6 ± 0.3%; and 4-ethylphenol, 0.28 ± 0.06%. A number of the hydroxy and keto metabolites were subject to conjugation. Differences were observed between the concentrations obtained with enzymatic and acid hydrolysis. For example, 50% of maximal yield of 4-ethylphenol was obtained with glucuronidase or acid hydrolysis and 100% with sulfatase indicating the presence of glucuronide and sulfate conjugates of this metabolite. Alternatively, acetophenone gave only 30-36% yield with enzymatic treatment but 100% with acid hydrolysis indicating the presence of other conjugates not susceptible to glucuronidase or sulfatase. The metabolic scheme proposed by Engstrom *et al.* (1984) is shown with modifications in Figure 1. The metabolism of ethylbenzene is similar in several respects to benzene in that benzene produces phenol, catechols and hydroquinone metabolites. As noted below these metabolites and their ethyl analogs participate in redox cycles generating the reactive oxygen species hydrogen peroxide, superoxide, and hydroxyl radical.

Gromiec and Piotrowski (1984) measured ethylbenzene uptake and excretion in six human volunteers exposed at concentrations of 18 to 200 mg/m^3 for eight hours. Average retention of ethylbenzene in the lungs was 49 ± 5% and total excreted mandelic acid accounted for 55 ± 2% of retained ethylbenzene.

Tardif *et al.* (1997) studied physiologically-based pharmacokinetic (PBPK) modeling of ternary mixtures of alkyl benzenes including ethylbenzene in rats and humans. As part of this investigation they determined Vmax and Km kinetic parameters for the rat by best fit of model simulations to the time-course data on the venous blood concentrations of ethylbenzene following single exposures. The maximal velocity (Vmax) was 7.3 mg/hr-kg body weight and the Michaelis-Menten affinity constant (Km) was 1.39 mg/L. For the human PBPK model the Vmax value from the rat was scaled on the basis of $(\text{body weight})^{0.75}$. All other chemical and metabolic parameters were unchanged.

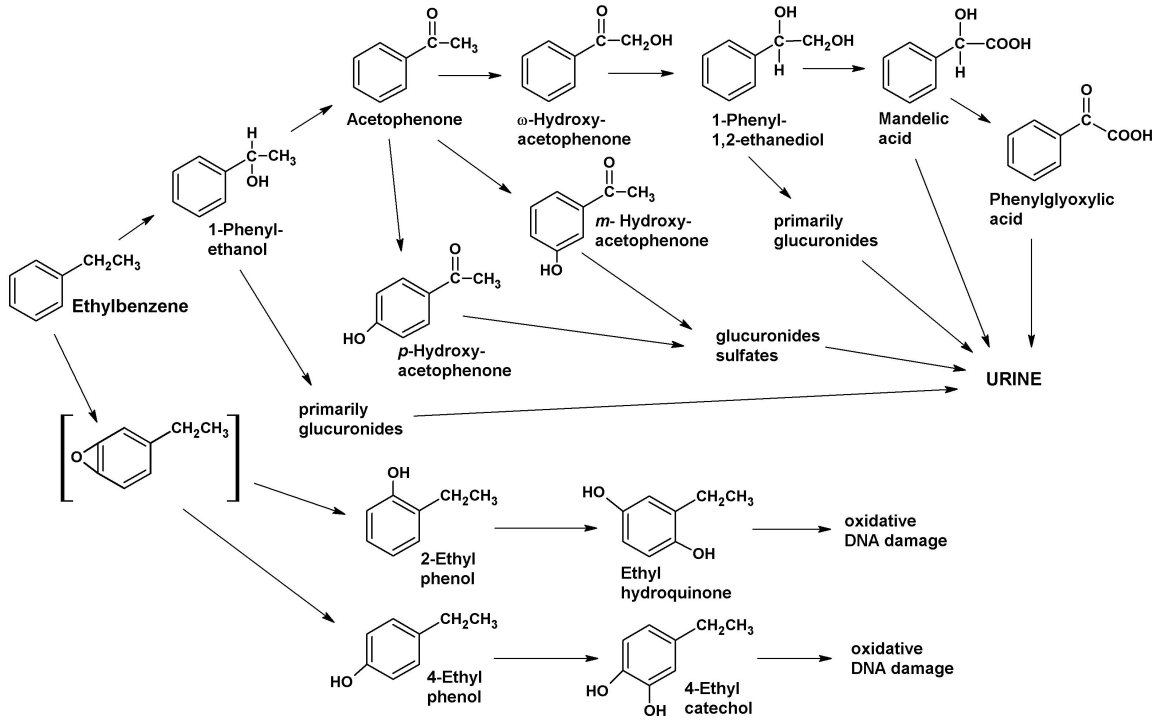

Figure 1. Ethylbenzene Metabolism (modified from Engstrom *et al.*, 1984).

The scaling of rodent metabolism of alkylbenzenes to humans was evaluated using kinetic data in an exposure study with human volunteers. Four adult male subjects (age, 22-47; body weight, 79-90 kg) were exposed to 33 ppm ethylbenzene for 7 hr/d in an exposure chamber. Urine samples were collected during (0-3 hr) and at the end (3-7 hr) of exposure and following exposure (7-24 hr). For the 0-24 hr collections mandelic acid amounted to 927 ± 281 μmol and phenylglyoxylic acid 472 ± 169 μmol. Venous blood (5.5 to 8 hr) and expired air (0.5 to 8 hr) were also measured in the subjects and exhibited good correspondence with PBPK model predictions. It is interesting that the metabolism of ethylbenzene in these human subjects was not significantly affected by simultaneous exposure to the other alkyl benzenes (toluene and xylene) studied. The metabolic parameters for ethylbenzene used by Haddad *et al.* (2001) and in the internal dosimetry modeling presented below were based on this study.

The oxidation of ethylbenzene to 1-phenylethanol by human liver microsomes and recombinant human cytochrome P450s was investigated by Sams *et al.* (2004). Human liver microsomes from seven subjects (four male, three female, age 37-74) and microsomes expressing recombinant human CYP1A2, 2A6, 2B6, 2C9*1(Arg144), 2C19, 2D6, 2E1, and 3A4 co-expressed with cytochrome P450 reductase/cytochrome b5 were both obtained from commercial sources. Kinetic experiments were conducted with microsomes and ethylbenzene over a 10-5000 μ*M* substrate concentration range. For chemical inhibition experiments, selective inhibitors of specific CYP isoforms were used to obtain maximum inhibition of the target CYP with minimum effect on other CYPs. Eadie-Hofstee plots (V vs. V/S) indicated that the reaction of ethylbenzene to 1-phenylethanol with human liver microsomes was biphasic with low and high affinity components. The Michaelis-Menten

equation was fit to the data and kinetic constants obtained by regression analysis. One microsome preparation was found to give a noticeably less curved Eadie-Hofstee plot and metabolized ethylbenzene at a much higher rate than the other preparations (Vmax = 2922 pmol/min/mg). It was excluded from the statistical analysis. For the high affinity reaction the mean Vmax was 689 ± 278 pmol/min/mg microsomal protein and the Km = 8.0 ± 2.9 μ*M* (n = 6). For the low affinity reaction the Vmax was 3039 ± 825 pmol/min/mg and Km = 391 ± 117 μ*M* (n = 6). The intrinsic clearance values of Vmax/Km were 85.4 ± 15.1 and 8.3 ± 3.0 for the high and low affinity reactions, respectively. The high affinity component of pooled human liver microsomes was inhibited 79%-95% by diethyldithiocarbamate, and recombinant CYP2E1 metabolized ethylbenzene with a low Km of 35 μ*M* and low Vmax of 7 pmol/min/pmol P450 indicating that the CYP2E1 isoform catalyzed this component. Recombinant CYP1A2 and CYP2B6 exhibited high Vmaxs (88 and 71 pmol/min/pmol P450, respectively) and Km's (502 and 219 μ*M*, respectively), indicating their role in the low affinity component. The mean Vmax and Km values above were used by OEHHA in addition to those from Haddad *et al.* (2001) in our human PBPK modeling of ethylbenzene.

Charest-Tardif *et al*. (2006) characterized the inhalation pharmacokinetics of ethylbenzene in male and female B6C3F1 mice. Initially groups of animals were exposed for four hr to 75, 200, 500 or 1000 ppm ethylbenzene. Subsequently groups of animals were exposed for six hr to 75 and 750 ppm for one or seven consecutive days. The maximum blood concentration (Cmax, mean (± SD), n = 4) observed after four hr exposure to 75, 200, 500 and 1000 ppm was 0.53 (0.18), 2.26 (0.38), 19.17 (2.74), and 82.36 (16.66) mg/L, respectively. The blood AUCs were 88.5, 414.0, 3612.2, and 19,104.1 (mg/L)-min, respectively, in female mice, and 116.7, 425.7, 3148.3, 16039.3 (mg/L)-min, respectively in male mice. The comparison of Cmax and kinetics of ethylbenzene in mice exposed to 75 ppm indicated similarity between 1 and 7-day exposures. However, at 750 ppm elimination of ethylbenzene appeared to be greater after repeated exposures. Overall, the single and repeated exposure PK data indicate that ethylbenzene kinetics is saturable at exposure concentrations above 500 ppm but is linear at lower concentrations.

Backes *et al*. (1993) demonstrated that alkylbenzenes with larger substituents (e.g., ethylbenzene, m-, p-xylene, n-propylbenzene) were effective inducers of microsomal enzymes compared to those with no or smaller substituents (benzene, toluene). Cytochrome P450 2B1 and 2B2 levels were induced with the magnitude of induction increasing with hydrocarbon size. P450 1A1 was also induced but less than 2B. A single intraperitoneal (i.p.) dose of 10 mmol/kg in rats was selected for optimum induction response with no overt toxic effects.

Bergeron *et al*. (1999) using the same daily dose of ethylbenzene for up to ten days observed changes in expression of CYP 2B1, 2B2, 2E1, and 2C11. While CYP 2C11 and 2E1 were attenuated by repeated dosing of ethylbenzene, CYP 2Bs were elevated after initial dosing despite the absence of detectable 2B1 or 2B2 mRNA. The authors interpreted this observation as the initial ethylbenzene dose leading to an increase in ethylbenzene clearance and an overall decrease in tissue ethylbenzene levels with repeated dosing and decreased induction effectiveness.

Serron *et al*. (2000) observed that treatment of rats with ethylbenzene (i.p., 10 mmol/kg) led to increased free radical production by liver microsomes compared to corn oil controls. Oxygen free radical generation was measured *in vitro* by conversion of 2', 7'-dichlorofluorescein diacetate (DCFH-DA) to its fluorescent product 2', 7'-dichlorofluorescein (DCF). A significant elevation (40%) of DCF was seen despite lack of effect on overall P450 levels. The DCF product formation was inhibited by catalase but not by superoxide dismutase suggesting a H_2O_2 intermediate. Anti-CYP2B antibodies inhibited DCF production indicating involvement of CYP2B. As noted above ethylbenzene treatment induces increased production of CYP2B.

While the doses in these studies were quite high at over 1000 mg/kg-d by the intraperitoneal route, earlier studies by Elovaara *et al*. (1985) showed P450 induction in livers of rats exposed to 50, 300 and 600 ppm (218, 1305 and 2610 mg/m^3) for 6 hours/day, 5 days/week for up to 16 weeks. So it is possible that the types of effects discussed above, notably the production of reactive oxygen species via induced CYP 2B, may have occurred during the cancer bioassays.

Genotoxicity

In vitro and *in vivo* animal studies

Ethylbenzene has been tested for genotoxicity in a variety of *in vitro* and *in vivo* genotoxicity assays. Those studies have been reviewed by ATSDR (1999). Ethylbenzene has not demonstrated genotoxicity in *Salmonella* reverse mutation assays. Those studies are listed in Table 1. All studies were performed in the presence and absence of metabolic activation (rat liver S9), and were negative. It has not been tested in strains sensitive to oxidative DNA damage.

Table 1. Ethylbenzene *Salmonella* reverse mutation studies

Test strains	**Reference**
TA98, TA100, TA1535, TA1537	Florin *et al*., 1980
TA98, TA100, TA1535, TA1537, TA1538	Nestmann *et al*., 1980
TA98, TA100, TA1535, TA1537, TA1538	Dean *et al*., 1985
TA97, TA98, TA100, TA1535	NTP, 1986
TA97, TA98, TA100, TA1535	NTP, 1999
TA98, TA100	Kubo *et al*., 2002

Ethylbenzene also did not induce mutations in the WP2 and WP2uvrA strains of *Escherichia coli* in the presence and absence of metabolic activation (Dean *et al*., 1985), or in *Saccharomyces cerevisiae* strains JDl (Dean *et al*., 1985), XVl85-14C, and D7 as measured by gene conversion assays (Nestmann and Lee, 1983).

Ethylbenzene has been observed to induce mutations in L5178Y mouse lymphoma cells at the highest nonlethal dose tested (80 µg/mL) (McGregor *et al*., 1988; NTP, 1999).

However, NTP noted significant cytotoxicity at this dose level (relative total growth was reduced to 34% and 13% of the control level in each of two trials).

Data on the ability of ethylbenzene to induce chromosomal damage in non-human mammalian cells are negative. Ethylbenzene did not cause chromosomal damage in rat liver epithelial-like (RL4) cells (Dean *et al*., 1985). Additionally, ethylbenzene did not induce an increase in either sister chromatid exchanges (SCE) or chromosomal aberrations in Chinese hamster ovary (CHO) cells in the presence or absence of metabolic activation (NTP 1986, 1999).

The frequency of micronucleated erythrocytes in bone marrow from male NMRI mice exposed to ethylbenzene by intraperitoneal injection was not significantly increased compared to controls (Mohtashamipur *et al*., 1985). Additionally, ethylbenzene did not increase the frequency of micronucleated erythrocytes in peripheral blood from male and female $B6C3F_1$ mice treated for 13 weeks with ethylbenzene (NTP, 1999).

Midorikawa *et al* (2004) reported oxidative DNA damage induced by the metabolites of ethylbenzene, namely ethylhydroquinone and 4-ethylcatechol. Ethylbenzene was metabolized to 1-phenylethanol, acetophenone, 2-ethylphenol, and 4-ethylphenol by rat liver microsomes *in vitro*. 2-Ethylphenol and 4-ethylphenol were ring-dihydroxylated to ethylhydroquinone (EHQ) and 4-ethylcatechol (EC). These dihydroxylated metabolites induced DNA damage in ^{32}P-labeled DNA fragments from the human p53 tumor suppressor gene and induced the formation of 8-oxo-7, 8-dihydro-2'-deoxyguanosine in calf thymus DNA in the presence of Cu2+. Addition of exogenous NADH enhanced EC-induced oxidative DNA damage but had little effect on EHQ action. The authors suggest that Cu+ and H_2O_2 produced via oxidation of EHQ and EC were involved in oxidative DNA damage. NADH enhancement was attributed to reactive species generated from the redox cycle of EC → 4-ethyl-1, 2-benzoquinone → EC. The NADH-mediated conversion of 4-Ethyl-1, 2-benzoquinone appears to be the result of a two electron reduction which accelerates the redox reaction, resulting in enhanced DNA damage (Figure 2).

Similar effects of NADH were observed with benzene metabolites benzoquinone (BQ) and catechol (Hirakawa *et al*. 2002). In the presence of Cu^{2+} and endogenous NADH, catechol (1,2-BQH_2) induced more DNA damage than 1,4-BQH_2. In the absence of NADH the DNA damaging activities were reversed. In both cases, DNA damage resulted from base modification at guanine and thymine residues in addition to DNA strand breaks by Cu^+ and H_2O_2 generated during the oxidation of 1,2-BQH_2 and 1,4- BQH_2 to 1,2_BQ and 1,4-BQ, respectively (Hirakawa *et al*., 2002). The authors noted that NADH consumption in the presence of 1,2-BQH_2/1,2-BQ was faster than that in the 1,4-BQH_2/1,4-BQ system. The results suggest that the structure of 1,2-BQ may facilitate the two-electron reduction by NADH better than 1,4-BQ. Thus, the reduction of 1,2-BQ accelerates the turnover rate of the redox cycle in 1,2-BQH_2/1,2-BQ greater than in 1,4-BQH_2/1,4-BQ. The authors conclude that "…the NADH-dependent redox cycle may

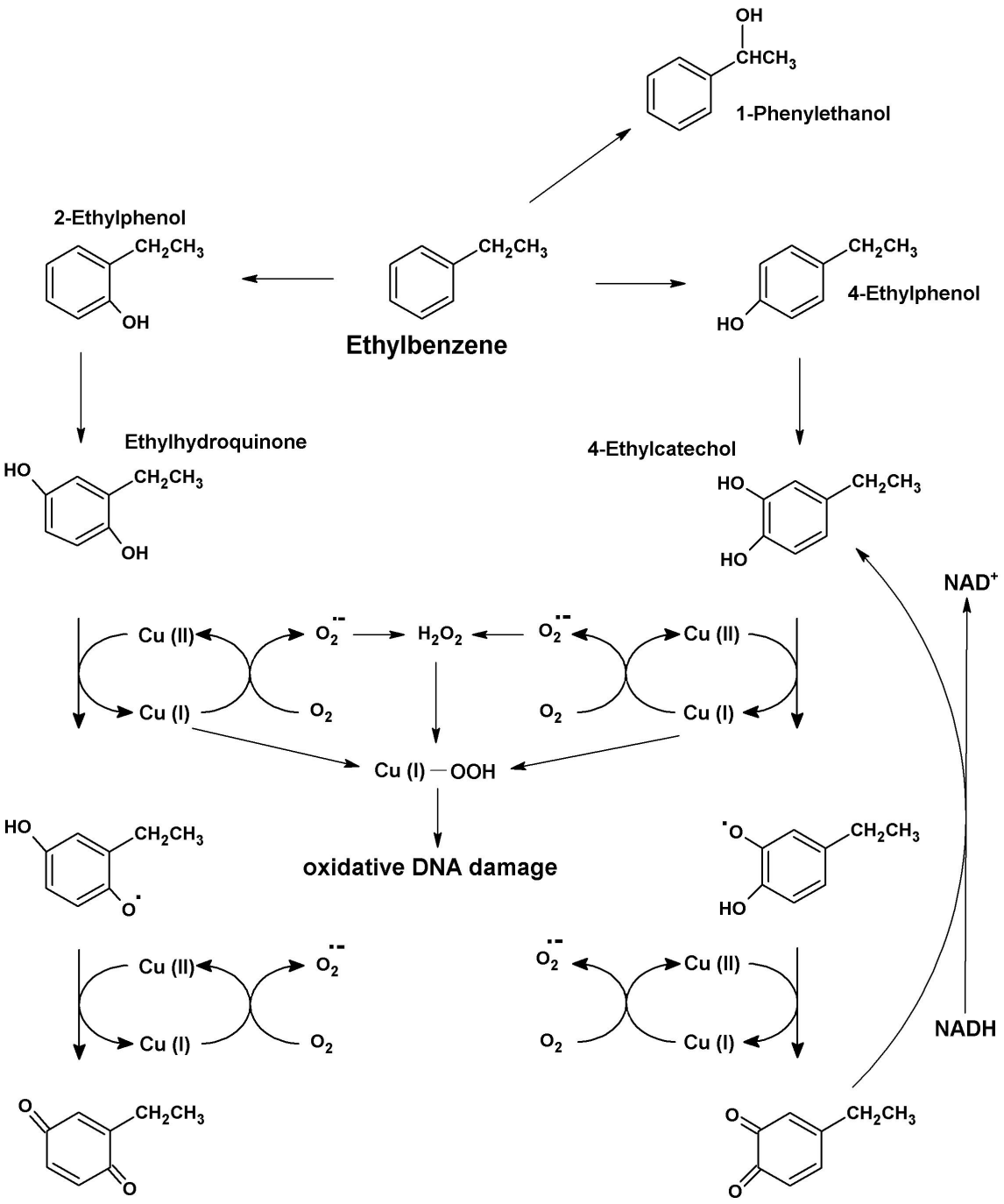

Figure 2. Possible mechanism of oxidative DNA damage induced by EHQ and EC. (Adapted from Midorikawa *et al*., 2004)

continuously generate reactive oxygen species, resulting in the enhancement of oxidative DNA damage. NADH, a reductant existing at high concentrations (100- 200 μM) in certain tissues, could facilitate the NADH-mediated DNA damage observed in this study under physiological conditions."(Hirakawa *et al*., 2002).

Similar reactions were also observed with methylcatechols, toluene metabolites that participated in Cu^{2+}-mediated DNA damage, which was enhanced by NADH compared with methylhydroquinone (Nakai *et al*., 2003; Murata *et al*., 1999).

In vitro and *in vivo* human studies

Norppa and Vainio (1983) exposed human peripheral blood lymphocytes to ethylbenzene in the absence of metabolic activation. The authors reported that ethylbenzene induced a marginal increase in SCEs at the highest dose tested, and that the increase demonstrated a dose-response.

Holz *et al*. (1995) studied genotoxic effects in workers exposed to volatile aromatic hydrocarbons (styrene, benzene, ethylbenzene, toluene and xylenes) in a styrene production plant. Peripheral blood monocytes were assayed for DNA adducts using a nuclease P1-enhanced ^{32}P-postlabeling assay, and DNA single strand breaks, SCEs and micronuclei frequencies in peripheral blood lymphocytes were determined in workers and controls. No significant increases in DNA adducts, DNA single strand breaks, SCEs or total micronuclei were noted in exposed workers. Significantly increased kinetochore-positive micronuclei (suggestive of aneuploidy-induction) were noted in total exposed workers, exposed smokers, and exposed non-smokers. However, the mixed exposures made it impossible to ascribe the kinetochore-positive micronuclei increase in exposed workers solely to ethylbenzene exposure.

The effects of benzene and ethylbenzene exposure on chromosomal damage in exposed workers were examined by Sram *et al*. (2004). Peripheral blood lymphocytes from exposed workers and controls were analyzed for chromosomal aberrations. Exposure to ethylbenzene resulted in a significant increase in chromosomal aberrations. A reduction in ethylbenzene concentration due to improved workplace emissions controls resulted in a reduction in chromosomal damage in exposed workers. However, these workers were also exposed to benzene, making it impossible to determine if the chromosomal damage was due to ethylbenzene alone.

Ethylbenzene sunlight-irradiation products

Toda *et al*. (2003) found that sunlight irradiation of ethylbenzene resulted in the formation of ethylbenzene hydroperoxide (EBH). EBH induced oxidative DNA damage in the presence of Cu^{2+} as measured by the formation of 8-hydroxy-deoxyguanosine (8-OH-dG) adducts in calf thymus DNA. The Cu^{2+}-specific chelator bathocuproine strongly inhibited EBH-induced oxidative DNA damage. Superoxide dismutase (catalyzes superoxide decomposition) partly inhibited 8-OH-dG adduct formation, and catalase (catalyzes hydrogen peroxide decomposition) slightly inhibited 8-OH-dG adduct formation.

Summary of ethylbenzene genotoxicity

The above data indicate that ethylbenzene generally has not been demonstrated to induce gene mutations or chromosomal damage in bacteria, yeast or non-human mammalian cells, with the exception of positive results in the L5178Y mouse lymphoma cell mutation assay at concentrations producing significant cytotoxicity (McGregor *et al*., 1988; NTP, 1999). Data on the genotoxicity of ethylbenzene in humans is mixed (Norppa and Vainio, 1983; Holz *et al*., 1995; Sram *et al*., 2004), and interpretation of the epidemiological studies is made difficult because of confounding due to coexposures to other chemicals, including benzene. Ethylbenzene has been demonstrated to generate reactive oxygen species in liver microsomes from exposed rats (Serron *et al*., 2000), and ethylbenzene hydroperoxide (a sunlight-irradiation product) has been demonstrated to induce oxidative DNA damage in calf thymus DNA *in vitro* (Toda *et al*., 2003). The ethylbenzene metabolites EHQ and EC have demonstrated the ability to induce oxidative DNA damage in human DNA *in vitro* (Midorikawa *et al*., 2004).

Animal Cancer Bioassays

Maltoni *et al.* (originally reported in 1985; additional information published in 1997) studied the carcinogenicity of ethylbenzene in male and female Sprague-Dawley rats exposed via gavage. The authors reported an increase in the percentage of animals with malignant tumors associated with exposure to ethylbenzene. In animals exposed to 800 mg/kg bw ethylbenzene, Maltoni *et al.* (1997) reported an increase in nasal cavity tumors, type not specified (2% in exposed females versus 0% in controls), neuroesthesioepitheliomas (2% in exposed females versus 0% in controls; 6% in exposed males versus 0% in controls), and oral cavity tumors (6% in exposed females versus 2% in controls; 2% in exposed males versus 0% in controls). These studies were limited by inadequate reporting and were considered inconclusive by NTP (1999) and IARC (2000).

The National Toxicology Program (NTP, 1999; Chan *et al*., 1998) conducted inhalation cancer studies of ethylbenzene using male and female F344/N rats and B6C3F$_1$ mice. Groups of 50 animals were exposed via inhalation to 0, 75, 250 or 750 ppm ethylbenzene for 6.25 hours per day, 5 days per week for 104 (rats) or 103 (mice) weeks.

Survival probabilities were calculated by NTP (1999) using the Kaplan-Meier product-limit procedure. For male rats in the 75 ppm and 250 ppm exposure groups, survival probabilities at the end of the study were comparable to that of controls but significantly less for male rats in the 750 ppm exposure group (30% for controls and 28%, 26% and 4% for the 75 ppm, 250 ppm and 750 ppm exposure groups, respectively). NTP (1999) stated that the mean body weights of the two highest exposure groups (250 and 750 ppm) were "generally less than those of the chamber controls from week 20 until the end of the study." Expressed as percent of controls, the mean body weights for male rats ranged from 97 to 101% for the 75 ppm group, 90 to 98% for the 250 ppm group, and 81 to 98% for the 750 ppm group.

In female rats, survival probabilities were comparable in all groups (62% for controls and 62%, 68% and 72% for the 75 ppm, 250 ppm and 750 ppm exposure groups, respectively). NTP (1999) reported that the mean body weights of exposed female rats were "generally less than those of chamber controls during the second year of the study." Expressed as percent of controls, the mean body weights for female rats ranged from 92 to 99% for the 75 ppm group, 93 to 100% for the 250 ppm group, and 92 to 99% for the 750 ppm group.

The incidences of renal tumors (adenoma and carcinoma in males; adenoma only in females) were significantly increased among rats of both sexes in the high-dose group (males: 3/50, 5/50, 8/50, 21/50; females: 0/50, 0/50, 1/50, 8/49 in control, 75 ppm, 250 ppm and 750 ppm groups respectively [standard and extended evaluations of kidneys combined]). The incidence of testicular adenomas (interstitial and bilateral) was significantly elevated among high-dose male rats (36/50, 33/50, 40/50, 44/50 in control, 75 ppm, 250 ppm and 750 ppm groups respectively). NTP noted that this is a common neoplasm, which is likely to develop in all male F344/N rats that complete a natural life span; exposure to ethylbenzene "appeared to enhance its development." NTP concluded that there was clear evidence of carcinogenicity in male rats and some evidence in female rats, based on the renal tumorigenicity findings.

The survival probabilities at the end of the study for exposed male mice were comparable to that of controls (57% for controls and 72%, 64% and 61% for the 75 ppm, 250 ppm and 750 ppm exposure groups, respectively). The same was true for exposed female mice (survival probabilities at end of study: 71% for controls and 76%, 82% and 74% for the 75 ppm, 250 ppm and 750 ppm exposure groups, respectively). Mean body weights in exposed male mice were comparable to those of controls. NTP (1999) reported that the mean body weights in exposed female mice were greater in the 75 ppm group compared to controls after week 72, and generally lower in the 750 ppm group compared to controls from week 24 through week 68. Expressed as percent of controls, the ranges of mean body weights in exposed female mice were 96 to 110% in the 75 ppm group, 93 to 108% in the 250 ppm group, and 92 to 101% in the 750 ppm group.

Increased incidences of alveolar/bronchiolar adenoma and adenoma or carcinoma (combined) were observed in male mice in the high-dose group (7/50, 10/50, 15/50, 19/50 in control, 75 ppm, 250 ppm and 750 ppm groups respectively). Among female mice in the high-dose group, the incidences of combined hepatocellular adenoma or carcinoma and hepatocellular adenoma alone were significantly increased over control animals (for adenomas and carcinomas the tumor incidences were 13/50, 12/50, 15/50, 25/50 in control, 75 ppm, 250 ppm and 750 ppm groups, respectively). NTP (1999) concluded that these findings provided some evidence of carcinogenicity in male and female mice.

Human Studies of Carcinogenic Effects

Studies on the effects of workplace exposures to ethylbenzene have been complicated by concurrent exposures to other chemicals, such as xylenes and benzene. IARC (2000) concluded that there was inadequate evidence in humans for the carcinogenicity of ethylbenzene.

Mode of Action for Ethylbenzene carcinogenesis

A mode of action (MOA) is a clear explanation of the critical events in an agent's influence on the development of tumors. An MOA analysis includes physical, chemical, and biological information and the entire range of information developed in the assessment contributes to a reasoned judgement concerning the plausibility of potential MOAs (U.S.EPA, 1996). An agent may work by more than one MOA at different sites and at the same tumor site. Inputs into an MOA analysis include tumor data in humans, animals, and in structural analogs, genetic toxicity and other key data e.g. on metabolites, DNA or protein adducts, oncogene activation and shape of the dose response. In any event conflicting data and data gaps often require careful evaluation before reaching any conclusions with respect to a prospective MOA (U.S.EPA, 1996).

OEHHA has not determined a convincing mode of action (MOA) for any of the tumor sites evaluated in this report. Various MOAs have been suggested for the tumors induced by ethylbenzene in rodent species. For instance it has been hypothesized that rat kidney tumor incidence increases are the result of ethylbenzene or its metabolites increasing the incidence and/or severity of chronic progressive nephropathy (CPN), a common process in aged control rats (Hard, 2002). However, OEHHA and others (Seely *et al*., 2002) have found no basis to support a conclusion that the sole or primary cause of the kidney tumors is exacerbation of CPN. Similarly, it has been suggested that an increase in eosinophilic foci in the liver, possibly associated with induction of cytochrome P450 enzymes, is involved in the mechanism of production of the liver tumors. In fact, the data from which a correlation between liver eosinophilic foci and liver tumors was inferred are not consistent or convincing in this respect. Moreover, such MOAs have not been adequately elucidated with respect to their quantitative dose-response relations, or how significant they are with respect to other MOAs, possibly involving genotoxicity, which may also be operating.

A proposed MOA for ethylbenzene-induced tumors, especially those in the mouse lung, involves the generation of quinone metabolites. This is analogous to the actions of styrene and naphthalene, which are also carcinogenic. OEHHA recognizes the plausibility of quinone metabolites participating in a potential MOA for ethylbenzene-induced lung cancer in mice (see *Genotoxicity* above). However, a suggestion that the role of these metabolites is confined to cytotoxicity (resulting in promotion of spontaneous tumors) is not convincing. The observation of oxidative DNA damage *in vitro* (Midorikawa *et al*., 2004) supports a role for quinone metabolites in carcinogenic initiation, following the analogy with benzene (a well-known genotoxic carcinogen targeting multiple sites in various species including humans). The observation of chromosomal damage in peripheral blood lymphocytes of workers exposed to ethylbenzene and benzene (Sram *et al*., 2004) may be indicative of quinone metabolite induced DNA damage. Thus, the involvement of quinone metabolites is plausible and supported by at least some data. Although this does not of itself establish the quantitative nature of the dose-response relationship, a mechanism involving oxidative DNA damage might display low-dose linearity. Since ring oxidation may produce a genotoxic epoxide metabolite it is possible that more than one metabolic

process which generates genotoxic intermediates may be operating. In our view the genotoxicity of ethylbenzene, particularly with respect to oxidative DNA effects, merits further investigation.

OEHHA therefore concludes that the limited data do not conclusively establish any particular MOA for ethylbenzene carcinogenesis. However, one or more genotoxic processes appear at least plausible and may well contribute to the overall process of tumor induction. Because of this, the default linear approach has been used for extrapolating the dose-response curve to low doses.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Unit risk values for ethylbenzene were calculated based on data in male and female rats and mice from the studies of NTP (1999) utilizing both linearized multistage and benchmark dose methods. The incidence data used to calculate unit risk values are listed below in Tables 2 thru 6. The methodologies for calculating average concentration, lifetime weighted average (LTWA) dose and PBPK adjusted internal dose are discussed below. An internal dose metric representing the amount of ethylbenzene metabolized per kg body weight per day (metabolized dose) was used in the dose response analysis with published PBPK modeling parameters. In addition, for the mouse, recent pharmacokinetic data simulating mouse bioassay conditions were used to improve PBPK model predictions (Tables 5 and 6).

The metabolized dose metric is considered the most appropriate metric for assessment of carcinogenic risks when the parent compound undergoes systemic metabolism to a variety of oxidative metabolites which may participate in one or more mechanisms of carcinogenic action, and the parent compound is considered unlikely to be active. In this case the dose response relation is likely to be more closely related to the internal dose of metabolites than of the parent compound. Other metrics commonly investigated using PBPK methods are the area under the concentration-time curve (AUC), and the maximum concentration (Cmax) for parent or metabolites in blood and target tissues. The PBPK metabolized dose metric was used in the ethylbenzene dose-response analysis.

Table 2. Incidence of renal tubule adenoma or carcinoma in male rats exposed to ethylbenzene via inhalation and relevant dose metrics (from NTP, 1999).

Chamber concentration (ppm)	Average concentration[a] (mg/m^3)	LTWA dose[b] (mg/kg-day)	PBPK metabolized dose[c] (mg/kg-d)	Tumor incidence[d]		Statistical significance[e]	
				Quantal Response	%	Fisher Exact Test	TrendTest
0	0	0	0	3/42	7.1		
75	60.7	35.6	19.09	5/42	11.9	$p = 0.356$	$p < 0.001$
250	202	119	58.78	8/42	19.0	$p = 0.0972$	
750	607	356	124.26	21/36	58.3	$p < 0.001$	

a. Average concentration during exposure period calculated by multiplying chamber concentration by 6.25 hours/24 hours, 5 days/7 days, and 4.35 $mg/m^3/ppm$.
b. Lifetime weighted average doses determined by multiplying the lifetime average concentrations during the dosing period by the male rat breathing rate (0.264 m^3/day) divided by the male rat body weight (0.450 kg). The duration of exposure was 104 weeks, so no correction for less than lifetime exposure was required.
c. Rodent PBPK models were used to estimate internal doses under bioassay conditions; methods are described in detail below.
d. Effective rate. Animals that died before the first occurrence of tumor (day 572) were removed from the denominator. Total number of tumors/number of survivors.
e. The *p*-value listed next to each dose group is the result of pair wise comparison with controls using the Fisher exact test. The *p*-value listed for the trend test is the result obtained by the National Toxicology Program (NTP, 1999) using the life table, logistic regression and Cochran-Armitage methods, with all methods producing the same result.

Table 3. Incidence of testicular adenoma in male rats exposed to ethylbenzene via inhalation and relevant dose metrics (from NTP, 1999).

Chamber concentration (ppm)	Average concentration[a] (mg/m^3)	LTWA dose[b] (mg/kg-day)	PBPK metabolized dose[c] (mg/kg-d)	Tumor incidence[d]		Statistical significance	
				Quantal Response	%	Fisher Exact Test[e]	Trend Test
0	0	0	0	36/48	75.0		
75	60.7	35.6	19.09	33/46	71.7	$p = 0.450$N	$p < 0.001$[f]
250	202	119	58.78	40/49	81.6	$p = 0.293$	$p = 0.010$[g]
750	607	356	124.26	44/47	93.6	$p < 0.05$	

a. Average concentration during exposure period calculated by multiplying chamber concentration by 6.25 hours/24 hours, 5 days/7 days, and 4.35 mg/m^3/ppm.
b. Lifetime weighted average doses determined by multiplying the lifetime average concentrations during the dosing period by the male rat breathing rate (0.264 m^3/day) divided by the male rat body weight (0.450 kg). The duration of exposure was 104 weeks, so no correction for less than lifetime exposure was required.
c. Rodent PBPK models were used to estimate internal doses under bioassay conditions; methods are described in detail below.
d. Effective rate. Animals that died before the first occurrence of tumor (day 420) were removed from the denominator. Total number of tumors/number of survivors
e. The *p*-value listed next to each dose group is the result of pair wise comparison with controls using the Fisher exact test. An "N" after the *p*-value signifies that the incidence in the dose group is lower than that in the control group.
f. Results of trend tests conducted by NTP (1999) using the life table and logistic regression tests.
g. Result of Cochran-Armitage trend test conducted by NTP (1999).

Table 4. Incidence of renal tubule adenoma in female rats exposed to ethylbenzene via inhalation and relevant dose metrics (from NTP, 1999).

Chamber concentration (ppm)	Average concentration[a] (mg/m^3)	LTWA dose[b] (mg/kg-day)	PBPK metabolized dose[c] (mg/kg-d)	Tumor incidence[d]		Statistical significance[e]	
				Quantal Response	%	Fisher Exact Test	Trend Test
0	0	0	0	0/32	0		
75	60.7	41.6	21.60	0/35	0	--	$p < 0.001$
250	202	139	67.04	1/34	2.9	$p = 0.515$	
750	607	416	144.62	8/37	21.6	$p < 0.01$	

a. Average concentration during exposure period calculated by multiplying chamber concentration by 6.25 hours/24 hours, 5 days/7 days, and 4.35 mg/m3/ppm.
b. Lifetime weighted average doses were determined by multiplying the lifetime average concentrations during the dosing period by the female rat-breathing rate (0.193 m3/day) divided by the female rat body weight (0.282 kg). The duration of exposure was 104 weeks, so no correction for less than lifetime exposure was required.
c. Rodent PBPK models were used to estimate internal doses under bioassay conditions; methods are described in detail below.
d. Effective rate. Animals that died before the first occurrence of tumor (day 722) were removed from the denominator. Total number of tumors/number of survivors
e. The p-value listed next to each dose group is the result of pair wise comparison with controls using the Fisher exact test. The *p*-value listed for the trend test is the result obtained by the National Toxicology Program (NTP, 1999) using the life table, logistic regression and Cochran-Armitage methods, with all methods producing the same result.

Table 5. Incidence of lung alveolar/bronchiolar carcinoma or adenoma in male mice exposed to ethylbenzene via inhalation and relevant dose metrics (from NTP, 1999).

Chamber concentration (ppm)	Average concentration[a] (mg/m^3)	LTWA dose[b] (mg/kg-day)	PBPK metabolized dose[c] (mg/kg-d)	PBPK metabolized dose: Charest-Tardif[d] (mg/kg-d)	Tumor incidence[e]		Statistical significance[f]	
					Quantal Response	%	Fisher Exact Test	Trend Test
0	0	0	0	0	7/46	15.2		
75	60.7	69.3	40.40	46.60	10/48	20.8	$p = 0.331$	$p = 0.004$
250	202	231	89.38	152.8	15/50	30.0	$p = 0.0688$	
750	607	693	134.77	340.2	19/48	40.0	$p < 0.01$	

a. Average concentration during exposure period calculated by multiplying chamber concentration by 6.25 hours/24 hours, 5 days/7 days, and 4.35 mg/m^3/ppm.
b. Lifetime weighted average doses were determined by multiplying the average concentrations during the dosing period by the male mouse breathing rate (0.0494 m^3/day) divided by the male mouse body weight (0.0429 kg) and by 103 weeks/104 weeks to correct for less than lifetime exposure.
c. Rodent PBPK models were used to estimate internal doses under bioassay conditions; methods are described in detail below.
d. PBPK metabolized dose based on published parameters from Charest-Tardif *et al*. (2006).
e. Effective rate. Animals that died before the first occurrence of tumor (day 418) were removed from the denominator. Total number of tumors/number of survivors.
f. The *p*-value listed next to each dose group is the result of pair wise comparison with controls using the Fisher exact test. The *p*-value listed for the trend test is the result obtained by the National Toxicology Program (NTP, 1999) using the life table, logistic regression and Cochran-Armitage methods, with all methods producing the same result.

Table 6. Incidence of liver hepatocellular carcinoma or adenoma in female mice exposed to ethylbenzene via inhalation and relevant dose metrics (from NTP, 1999).

Chamber concentration (ppm)	Average concentration[a] (mg/m^3)	LTWA dose[b] (mg/kg-day)	PBPK metabolized dose[c] (mg/kg-d)	PBPK metabolized dose: Charest-Tardif[d] (mg/kg-d)	Tumor incidence[e]		Statistical significance	
					Quantal Response	%	Fisher Exact Test[f]	Trend Test
0	0	0	0	0	13/47	27.7		
75	60.7	71.6	41.53	47.98	12/48	25.0	$p = 0.479$N	$p = 0$[g]
250	202	239	91.22	157.3	15/47	31.9	$p = 0.411$	$p = 0.002$[h]
750	607	716	136.68	348.1	25/48	52.1	$p < 0.05$	

a. Average concentration during exposure period calculated by multiplying chamber concentration by 6.25 hours/24 hours, 5 days/7 days, and 4.35 mg/m^3/ppm.
b. Lifetime weighted average doses were determined by multiplying the average concentrations during the dosing period by the female mouse breathing rate (0.0463 m^3/day) divided by the female mouse body weight (0.0389 kg) and by 103 weeks/104 weeks to correct for less than lifetime exposure.
c. Rodent PBPK models were used to estimate internal doses under bioassay conditions; methods are described in detail below.
d. PBPK metabolized dose based on published parameters from Charest-Tardif *et al*. (2006).
e. Effective rate. Animals that died before the first occurrence of tumor (day 562) were removed from the denominator. Total number of tumors/number of survivors.
f. The *p*-value listed next to each dose group is the result of pair wise comparison with controls using the Fisher exact test. An "N" after the *p*-value signifies that the incidence in the dose group is lower than that in the control group.
g. Result of trend test conducted by NTP (1999) using the life table method.
h. Results of trend tests conducted by NTP (1999) using the logistic regression and Cochran-Armitage trend tests.

Methodology

Linearized Multistage Approach

The default approach, as originally delineated by CDHS (1985), is based on a linearized form of the multistage model of carcinogenesis (Armitage and Doll, 1954). Cancer potency is estimated from the upper 95% confidence limit, q_1^*, on the linear coefficient q_1 in a model relating lifetime probability of cancer (p) to dose (d):

$$p = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \cdots + q_j d^j)] \qquad (1)$$

with constraints, $q_i \geq 0$ for all i. The default number of parameters used in the model is n, where n is the number of dose groups in the experiment, with a corresponding polynomial degree of n-1.

The parameter q_1^* is estimated by fitting the above model to dose response data using MSTAGE (Crouch, 1992). For a given chemical, the model is fit to one or more data sets. The default approach is to select the data for the most sensitive species and sex.

To estimate animal potency, q_{animal}, when the experimental exposure is less than lifetime the parameter q_1* is adjusted by assuming that the lifetime incidence of cancer increases with the third power of age. The durations of the NTP experiments were at least as long as the standard assumed lifetime for rodents of 104 weeks, so no correction for short duration was required.

Benchmark Dose Methodology

U.S. EPA (2005) and others (*e.g.* Gaylor *et al.*, 1994) have more recently advocated a benchmark dose method for estimating cancer risk. This involves fitting a mathematical model to the dose-response data. A linear or multistage procedure is often used, although others may be chosen in particular cases, especially where mechanistic information is available which indicates that some other type of dose-response relationship is expected, or where another mathematical model form provides a better fit to the data. A point of departure on the fitted curve is defined: for animal carcinogenesis bioassays this is usually chosen as the lower 95% confidence limit on the dose predicted to cause a 10% increase in tumor incidence (LED_{10}). Linear extrapolation from the point of departure to zero dose is used to estimate risk at low doses either when mutagenicity or other data imply that this is appropriate, or in the default case where no data on mechanism are available. The slope factor thus determined from the experimental data is corrected for experimental duration in the same way as the q_1^* adjustments described for the linearized multistage procedure. In the exceptional cases where data suggesting that some other form of low-dose extrapolation is appropriate, a reference dose method with uncertainty factors as required may be used instead.

The quantal tumor incidence data sets were analyzed using the BMDS software (version 1.3.2) of U.S.EPA (2000). In general the program models were fit to the data with the X^2 fit criterion ≥ 0.1. In those cases when more than one model gave adequate fit the model that gave the best fit in the low dose region (visually and by X^2 residual) was chosen for the LED_{10} estimation.

Implementation of LMS and BMD Methodology

The linearized multistage approach and the benchmark dose methodology were both applied to the tumor incidence data for ethylbenzene in the NTP (1999) studies. No nonlinear mode of carcinogenic action has been established for ethylbenzene. Hard (2002) suggested that "chemically induced exacerbation of CPN [chronic progressive nephropathy] was the mode of action underlying the development of renal neoplasia" in the NTP ethylbenzene studies. In a retrospective evaluation of NTP chronic studies, Seely *et al.* (2002) found that renal tubule cell neoplasms (RTCNs) "tend to occur in animals with a slightly higher severity of CPN than animals without RTCNs. However, the differential is minimal and clearly there are many male F344 rats with severe CPN without RTCNs." Seely *et al.* (2002) go on to say that "the data from these retrospective reviews suggest that an increased severity of CPN may contribute to the overall tumor response. However, any contribution appears to be marginal, and additional factors are likely involved."

Stott *et al.* (2003) reported accumulation of the male rat specific protein α2u-globulin in 1-week and 4-week inhalation studies of ethylbenzene in groups of six (1-week study) or eight (4-week study) male rats; the accumulation measured as an increase in hyaline droplets in proximal convoluted tubules was statistically significant only in the 1-week study. In the 13-week and 2-year inhalation studies of ethylbenzene, NTP (1992; 1999) found no evidence of an increase in hyaline droplets in treated rats. NTP (1999) therefore dismissed any involvement of α2u-globulin accumulation in renal tumor development in rats. The fact that the lesion appears in both male and female rats further argues against the involvement of α2u-globulin in the development of kidney toxicity. This mechanism was discounted by Hard (2002) as well. Stott *et al.* (2003) also postulated mechanisms of tumorigenic action involving cell proliferation and/or altered cell population dynamics in female mouse liver and male mouse lung. Stott et al. (2003) propose various hypothetical mechanisms which might involve nonlinear dose responses but the metabolism data clearly show the formation of epoxides and related oxidative metabolites, which could potentially be involved in a genotoxic mechanism of carcinogenic action possibly similar to benzene. Midorikawa *et al*. (2004) reported that the oxidative metabolism of ethylbenzene metabolites ethylhydroquinone and 4-ethylcatechol resulted in oxidative DNA damage *in vitro*. In view of the variety of metabolites and possible modes of action a low-dose linearity assumption is considered appropriate when extrapolating from the point of departure to obtain an estimate of the cancer risk at low doses with the BMD methodology as is use of the LMS approach.

Calculation of Lifetime Weighted Average Dose

Male and female rats (NTP, 1999) were exposed to ethylbenzene for 6.25 hours/day, five days/week for 104 weeks. Male and female mice (NTP, 1999) were exposed to ethylbenzene for 6.25 hours/day, five days/week for 103 weeks. Average concentrations, expressed in mg/m^3, during the exposure period were calculated by multiplying the reported chamber concentrations by 6.25 hours/24 hours, five days/seven days and 4.35 mg/m^3/ppm.

The average body weights of male and female rats were calculated to be 0.450 kg and 0.282 kg, respectively, based on data for controls reported by NTP (1999). The average body weights of male and female mice were estimated to be approximately 0.0429 kg and 0.0389 kg, respectively,

based on data for controls reported by NTP (1999). Inhalation rates (I) in m^3/day for rats and mice were calculated based on Anderson *et al.* (1983):

$$I_{rats} = 0.105 \times (bw_{rats}/0.113)^{2/3} \quad (3)$$

$$I_{mice} = 0.0345 \times (bw_{mice}/0.025)^{2/3} \quad (4)$$

Breathing rates were calculated to be 0.264 m^3/day for male rats, 0.193 m^3/day for female rats, 0.0494 m^3/day for male mice, and 0.0463 m^3/day for female mice. Lifetime weighted average (LTWA) doses were determined by multiplying the average concentrations during the dosing period by the appropriate animal breathing rate divided by the corresponding animal body weight. For mice, the exposure period (103 weeks) was less than the standard rodent lifespan (104 weeks), so an additional factor of 103 weeks/104 weeks was applied to determine lifetime average doses.

Physiologically Based Pharmacokinetic (PBPK) Modeling

The carcinogenic potency of ethylbenzene was calculated using rodent PBPK models to estimate internal doses under bioassay conditions. Extrapolations to human potencies were done using interspecies scaling. For comparison, a human PBPK model was used to estimate risk-specific doses for occupational and ambient environmental exposure scenarios. The PBPK models were comprised of compartments for liver, fat, vessel poor tissues (e.g., muscle), vessel rich tissues, and lung. Typical model parameters are given in Table 7 for flow-limited PBPK models and a model diagram is shown in Figure 2. Chemical and metabolic parameters for mouse and human models were taken from Haddad *et al.* (2001) and additionally from Sams *et al.* (2004) for human metabolism. The rat PBPK model was based on Dennison *et al*. (2003). Simulations were conducted using Berkeley Madonna (v.8.3.9) software (e.g., 6.25 hr exposure/day x 5 days/wk for one week simulations of bioassay exposure levels, see sample model equations in Appendix A). The chemical partition coefficients used in the Haddad et al. model were: blood:air, 28.0; fat:blood, 55.57; liver:blood, 2.99; muscle:blood, 0.93; and vessel rich:blood, 2.15 (Haddad *et al.*, 2001). For the Dennison et al. rat model the chemical partition coefficients were: blood:air, 42.7; fat:blood, 36.4; liver:blood, 1.96; muscle:blood, 0.609; and vessel rich:blood, 1.96. The metabolic parameters from Haddad *et al.* (2001) were: VmaxC = 6.39 mg/hr/kg body weight scaled to the ¾ power of body weight; Km = 1.04 mg/L. For the rat model the metabolic parameters were: VmaxC = 7.60 mg/kg-d scaled to the 0.74 power of body weight and Km = 0.1 mg/L. A second set of human metabolic parameters from Sams *et al.* (2004) was also used. In this case constants for low and high affinity saturable pathways were incorporated into the models: high affinity Vmax = 689 pmol/min/mg microsomal protein, Km = 8.0 μM; low affinity Vmax = 3039 pmol/min/mg protein, Km = 391 μM. A value of 28 mg/mL liver for microsomal protein concentration was assumed. Published values we reviewed ranged from 11 to 35 mg/g tissue. The value we used was similar to that of Kohn and Melnick (2000) (30 mg/g liver) and Medinsky *et al*. (1994) (35 mg/g liver). All model units were converted to moles, liters, or hours for simulation. A molecular weight of 106.16 g/mol for ethylbenzene was used throughout. In addition to PBPK modeling based on published parameters the recent pharmacokinetic data of Charest-Tardif *et al*. (2006) was used in the mouse PBPK modeling for comparison purposes. During the final revisions of this document we obtained the recently published paper of Nong *et al*. (2007), which describes a mouse PBPK model for ethylbenzene inhalation based on the pharmacokinetic data of Charest-Tardif *et al*.

(2006) and other parameter measurements. This model differs from that of Haddad *et al*. (2001) in having gender- and dose-specific chemical and metabolic parameters. The model also includes metabolism by lung and vessel-rich tissues in addition to liver. We employed the Nong *et al*. model in simulations of bioassay conditions identical to the Haddad *et al.* (2001) and Charest-Tardif *et al*. (2006) based models run previously, except that only the BMD dose response analysis was performed with the resulting total metabolized dose.

Although no systematic evaluation of PBPK model parameter uncertainty was conducted, the fact that we essentially used two rat models (Haddad *et al*., 2001 in the first draft and Dennison *et al*., 2004 in the revised draft) and two mouse models (Haddad *et al*. 2001, and Nong *et al*. 2007) and three key metabolic parameters (Charest-Tardif *et al*., 2006) for the mouse addresses this concern to some extent. The potency estimates in all cases were similar indicating a relative insensitivity to the PBPK parameters varied.

Johansen and Filser (1992) studied a series of volatile organic chemicals including ethylbenzene and developed theoretical values for clearance of uptake (CLupt) defined as the product of the rate constant for transfer of chemical from air to body and the volume of air in a closed chamber. The CLupt values were based on alveolar ventilation (Qalv), cardiac output (Qtot), and blood:air partition coefficients (Pbi). For most chemicals the experimentally determined values for inhalation uptake in rats and mice were about 60% of the theoretical values. The values determined for ethylbenzene in the rat of 70 mL/min for CLupt and 73 mL/min for alveolar ventilation are about 50% the value given in Table 7 (i.e., 4.38 L/hr vs. 8.58 L/hr). In the work described below selected simulations were run with lower alveolar ventilation rates for comparison with the main analysis.

The primary model prediction was the amount of ethylbenzene metabolized over the course of the simulation. The AUCs, the areas under the concentration x time curves for mixed venous concentration and liver concentration of ethylbenzene, were also recorded. The values for one week simulations of the amount metabolized (mmoles) were divided by 7d/week and body weight in kg to give daily values and multiplied by the molecular weight to give the PBPK metabolized dose in mg/kg-d. These values were then used in the dose response assessment of individual tumor site incidences using the benchmark dose software of U.S. EPA (BMDS v. 1.3.2) to obtain ED_{10}s, LED_{10}s and curve fit statistics.

Table 7. Parameters for Ethylbenzene PBPK Models.

Parameter	Mouse	Rat	Human
Alveolar ventilation rate Qalv, L/hr	$15*BW^{0.7}$	$12*BW^{0.74}$	$36*BW^{0.7}$ occ $15*BW^{0.7}$ env
Cardiac output Qtot, L/hr	$15*BW^{0.7}$	$15*BW^{0.74}$	$18*BW^{0.7}$ occ $15*BW^{0.7}$ env
Blood flows (fraction of cardiac output)			
Fat, Qf	0.09	0.07	0.05
Liver, Ql	0.25	0.183	0.26
Muscle, Qm	0.15	0.237	0.25
Vessel Rich Group, Qvrg	0.51	0.51	0.44
Tissue volumes, L (fraction of body weight unless otherwise indicated)			
Fat, Vf	0.06	0.035*BW + 0.0209	0.20, 0.40
Liver, Vl	0.04	0.037	0.026
Muscle, Vm	0.76	0.91*BW - (Vf + Vl + Vvrg + Vlu)	0.61, 0.41
Vessel Rich Group, Vvrg	0.05	0.054	0.036
Lung, Vlu	0.014	0.002	0.014
Body weight, BW kg	0.043 male 0.039 female	0.45 male 0.28 female	70
Metabolism VmaxC	6.39[a] 25.56[b]*	7.60 [c]	6.39[a]
Km mg/L	1.04[a]	0.10[c]	1.04[a]
Metabolism High/Low Affinity Vmax mg/hr/L_{liver} High/Low Affinity Km mg/L			 122.8/542.0 [d] 0.85/41.5[d]

Note: occ = occupational scenario values; env = environmental exposure scenario; [a]Haddad *et al*. (2001) mg/hr-$kg^{3/4}$; [b]this value provided better fit to the kinetic data of Charest-Tardif *et al*. (2006); [c]Dennison *et al*. (2003) mg/hr-$kg^{0.74}$; [d]Sams *et al*. (2004).

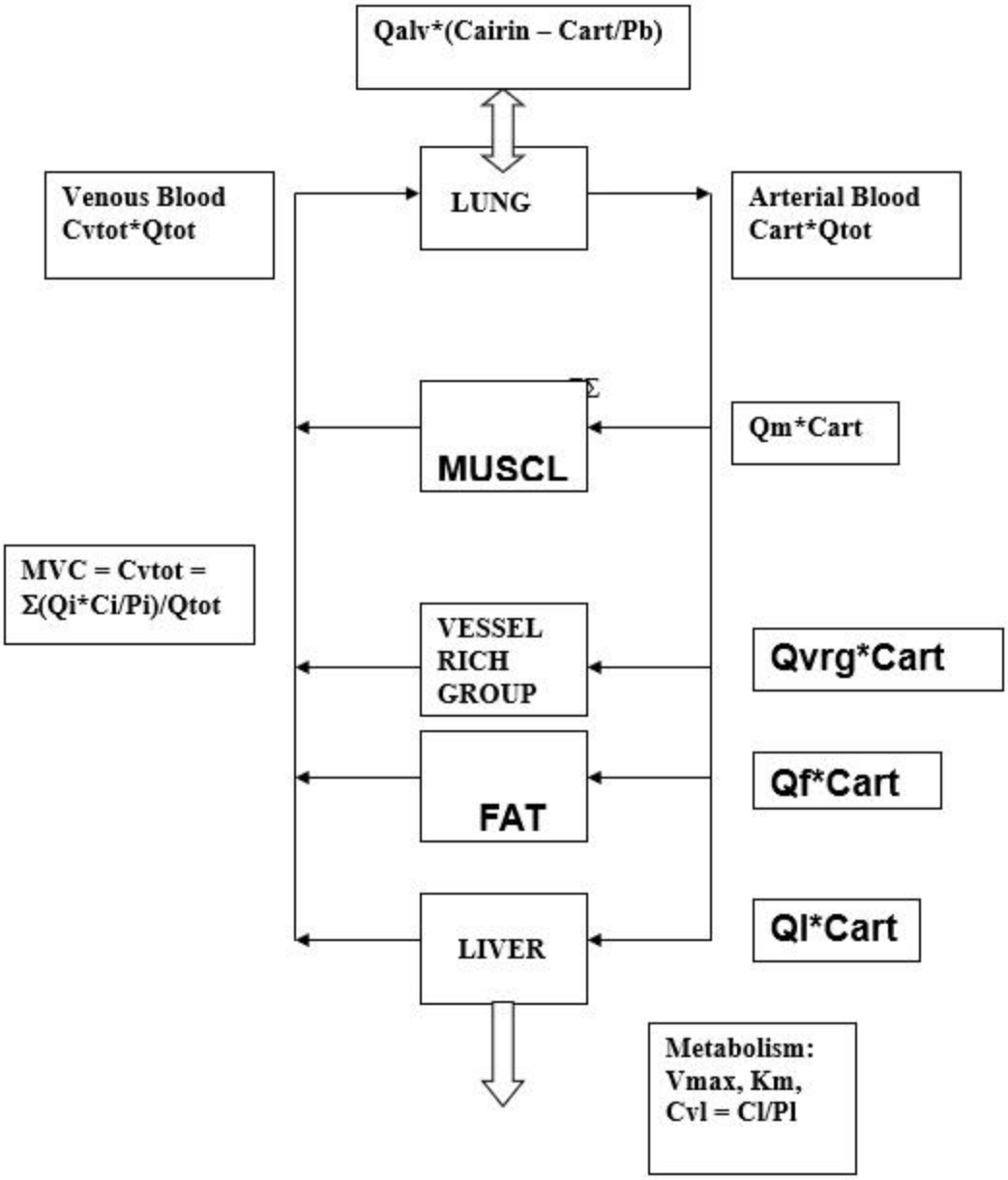

Figure 2. General Scheme for Ethylbenzene PBPK Model:

Qtot = Cardiac Output; Qalv = Alveolar Ventilation Rate ; Pb = Blood/Air Partition Coefficient; Pi = Tissue/Blood Partition Coefficients; Qi = Tissue Fractional Blood Flows ;Cart = Arterial Blood Concentration; Cvtot = Mixed Venous Blood Concentration; Cairin = Inhaled Concentration (e.g. ppm Ethylbenzene); Cexhaled = Cart/Pb(Concentration of Ethylbenzene Exhaled); Ci = Ai/Vi = Mass/Volume.

Internal to External Dose Conversion

In order to estimate external equivalent air concentrations associated with internal doses, the PBPK models were used. Simulation of 10 ppb ethylbenzene for 8 hours in the human PBPK model with the Haddad *et al*. (2001) parameters resulted in the predicted uptake of 3.04 µmoles in tissues and blood compared to 3.96 µmoles inhaled, or an uptake of 77%. Practically all of the 3.04 µmoles represents metabolized ethylbenzene. Based on these results, OEHHA assumed that all absorbed ethylbenzene is metabolized at low dose. Thus, for the inhalation route, the internal metabolized dose is converted to an external dose by applying an uptake factor of 77%. As noted above, uptake values of 49 to 65% have been observed in studies with human subjects exposed via inhalation to ethylbenzene. OEHHA has occasionally used a default value of 50% for inhalation uptake of similar volatile organic compounds.

For the oral route at low dose, OEHHA assumed that ethylbenzene is 100% metabolized and that uptake of ethylbenzene is also 100%. Thus, at low dose, the internal metabolized dose of ethylbenzene would be equivalent to an external applied dose by the oral route. No conversion factor for internal to external dose is necessary in this case.

Interspecies Extrapolation

Interspecies extrapolation from experimental animals to humans is normally based on the following relationship, where bw_h and bw_a are human and animal body weights, respectively, and potency (*e.g.*, q_{animal}) is expressed on a per dose per body weight basis (e.g., $(mg/kg\text{-}d)^{-1}$ see Watanabe *et al*. (1992):

$$q_{human} = q_{animal} \times \left(\frac{bw_h}{bw_a} \right)^{1/4} \qquad (2)$$

This is equivalent to an adjustment based on $(\text{human body weight})^{3/4}$ relative to the animal body weight or $BWh^{3/4}/BWa^{4/4} = (BWh/BWa)^{4/4-3/4} = (BWh/BWa)^{1/4}$. This is the default relationship currently recommended by OEHHA and by U.S. EPA (2005)

Alternatively, when performing calculations based on applied dose in terms of air concentrations, the assumption has sometimes been made that air concentration values are equivalent between species (CDHS, 1985). However, using the interspecies scaling factor shown above is preferred because it is assumed to account not only for pharmacokinetic differences (*e.g.*, breathing rate, metabolism), but also for pharmacodynamic considerations i.e. tissue responses to chemical exposure.

When extrapolating from an animal potency in terms of PBPK adjusted internal dose, only a pharmacodynamic scaling factor is required. Since an equal contribution of pharmacokinetic and pharmacodynamic considerations is assumed, animal potency values already adjusted for pharmacokinetic considerations require a scaling factor of only $(bw_h/bw_a)^{1/8}$:

$$q_{human} = q_{animal} \times \left(\frac{bw_h}{bw_a} \right)^{1/8} \qquad (3)$$

Derivation of the Human Inhalation Unit Risk Value

To derive the human inhalation unit risk value, the human internal potency value based on PBPK metabolized dose is multiplied by the human breathing rate (assumed to be 20 m^3/day), divided by the human body weight (assumed to be 70 kg) and multiplied by the estimated inhalation uptake factor in humans (0.77 for ethylbenzene). This yields a human inhalation unit risk value in terms of external air concentration.

For the case of LTWA doses, the human inhalation unit risk value is derived by multiplying the human inhalation cancer potency value by the human breathing rate (assumed to be 20 m^3/day), divided by the human body weight (assumed to be 70 kg). Because the LTWA doses represent external applied dose from an inhalation study, no uptake factor is necessary in deriving the unit risk value.

Inhalation and Oral Cancer Potency Values

The cancer potency derived based on internal doses (i.e., PBPK metabolized dose) is equivalent to the oral cancer potency, because of the assumption of 100% oral uptake and 100% metabolism of ethylbenzene at low doses. To derive the inhalation cancer potency, the human inhalation unit risk value is multiplied by the human body weight (assumed to be 70 kg) and divided by the human breathing rate (assumed to be 20 m^3/day).

For the case of LTWA doses, the human cancer potency derived based on these external applied doses from the inhalation study is equivalent to the inhalation cancer potency. To determine the oral cancer potency, the inhalation cancer potency is multiplied by the ratio of the oral to inhalation uptake factors (i.e., 1/0.77).

Example Calculations – BMD Approach

In this section, example calculations of the human cancer potency values (oral and inhalation) and the human unit risk value based on the LED_{10} for the male rat kidney tumor data and either the PBPK metabolized doses or the LTWA doses are provided. The same logic would apply to the derivation using the LMS methodology, with the only difference being that the animal potency is taken directly from the MSTAGE program under the LMS approach instead of being calculated from the LED_{10} in the BMD approach. To distinguish the results obtained under the two approaches, the terms P_{animal}, P_{human}, and U_{human} were used for the values derived using the BMD methodology.

Calculations based on BMD methodology and PBPK metabolized doses

Under the BMD methodology, the ED_{10}s and LED_{10}s are obtained from the BMDS program, with the animal potency value being simply $0.1/LED_{10}$ (i.e., 10% risk (0.1) divided by the 95% lower confidence limit on the dose that induced 10% risk or LED_{10}; this is the definition of a slope). To obtain the animal potency based on internal dose ($P_{animal\_internal}$), 0.1 is divided by the LED_{10} derived for the male rat kidney tumor data and the PBPK metabolized doses:

$$P_{animal\_internal} = 0.1/LED_{10} = 0.1/25.38 = 0.00394\ (mg/kg\text{-}d)^{-1}$$

The human potency value based on internal dose ($P_{human\_internal}$) is calculated from the animal potency as follows:

$$P_{human\_internal} = 0.00394\ (mg/kg\text{-}day)^{-1} \times (70\ kg/0.450\ kg)^{1/8}$$
$$= 0.0074\ (mg/kg\text{-}day)^{-1}$$

$P_{human\_internal}$ is equivalent to the oral human potency, because of the assumptions of 100% oral uptake and 100% metabolism of ethylbenzene at low dose.

The human unit risk value (U_{human}) is derived from the internal human cancer potency as follows:

$$U_{human} = 0.0074\ (mg/kg\text{-}day)^{-1} \times (20\ m^3/day/70\ kg) \times 0.77$$
$$= 1.64 \times 10^{-3}\ (mg/m^3)^{-1}$$
$$= 1.64 \times 10^{-6}\ (\mu g/m^3)^{-1}$$

As noted above the value of 0.77 was based on the prediction of the human ethylbenzene PBPK model, assuming exposure to low levels of ethylbenzene, and is similar to values obtained in studies with human subjects. By applying this uptake factor and assuming that the metabolism of ethylbenzene is 100% at low dose, the resulting unit risk value is expressed in terms of external concentration.

The inhalation cancer potency is derived from the unit risk value as follows:

$$P_{human\_inhalation} = 1.64 \times 10^{-3}\ (mg/m^3)^{-1} \times (70\ kg/20\ m^3/day)$$
$$= 0.0057\ (mg/kg\text{-}day)^{-1}$$

<u>Calculations based on BMD methodology and LTWA doses</u>

The LED_{10} based on the male rat kidney data and the LTWA doses is determined using the BMDS software. The animal potency, which in this case is the inhalation animal potency (P_{animal_inh}), is determined by dividing the LED_{10} into 0.1:

$$P_{animal\_inh} = 0.1/LED_{10} = 0.1/42.62 = 0.002346\ (mg/kg\text{-}d)^{-1}$$

The human inhalation cancer potency (P_{human_inh}) is derived from the animal potency using the interspecies scaling factor:

$$P_{human\_inh} = 0.002346\ (mg/kg\text{-}day)^{-1} \times (70\ kg/0.450\ kg)^{1/4}$$
$$= 0.0083\ (mg/kg\text{-}day)^{-1}$$

The unit risk factor is derived from the human inhalation cancer potency as follows:

$$U_{human} = 0.0083\ (mg/kg\text{-}day)^{-1} \times (20\ m^3/day/70\ kg)$$

$= 2.4 \times 10^{-3}$ $(mg/m^3)^{-1}$
$= 2.4 \times 10^{-6}$ $(\mu g/m^3)^{-1}$

For the calculation based on LTWA doses, the oral cancer potency is derived from the inhalation cancer potency by multiplying by the ratio of uptake factors (1/0.77):

$P_{human\_oral} = 0.0083$ $(mg/kg\text{-}day)^{-1} \times (1/0.77)$
$= 0.011$ $(mg/kg\text{-}day)^{-1}$

Results and Discussion

Linearized multistage approach

Tables 8a and 8c list the q_{animal}, q_{human} and unit risk values based on the linearized multistage approach. The cancer potencies and unit risk values were derived using the applied LTWA doses and PBPK adjusted internal doses, as described above. The most sensitive tumor sites are the male rat testicular interstitial cell adenoma and the male rat kidney adenoma and carcinoma, when the LTWA doses are used. If PBPK doses are used, the most sensitive sites are the male rat testicular interstitial cell adenoma and the male mouse lung. Regardless of whether LTWA or PBPK doses are used, the results based on the male mouse lung tumor data, the female mouse liver tumor data, and the male rat renal tumor data are comparable, producing unit risk values of approximately 0.002 $(mg/m^3)^{-1}$. Further, the results using either the LTWA doses or the PBPK metabolized doses are quite similar indicating that the PBPK modeling does not markedly improve the estimates. Some of the inherent uncertainty associated with PBPK modeling is demonstrated by the fact that the results based on the PBPK modeling using the Charest-Tardif parameters differ by roughly a factor of two for the mice compared to the results derived based on the other equally valid PBPK modeling approach.

The testicular interstitial cell adenoma site gives the highest values. However, the very high background incidences of this tumor make it less reliable and suitable for dose-response analysis than the male rat kidney site.

Thus, the unit risk value of 0.0025 $(mg/m^3)^{-1}$ derived based on the LMS approach from the male rat kidney tumor data using the LTWA doses is selected as the representative value for ethylbenzene. It is very similar to the estimate derived using the PBPK approach (0.0026 $(mg/m^3)^{-1}$), and does not require the many assumptions made in applying the more complex PBPK approach.

Table 8a. Cancer potency and unit risk values for ethylbenzene derived using the linearized multistage procedure (LMS) with applied LTWA doses based on data from NTP (1999).

Sex, species	**Site, tumor type**	**q_{animal_inh}** **(mg/kg-day)$^{-1}$**	**q_{human_inh}[a]** **(mg/kg-day)$^{-1}$**	**Human unit risk value[b]** **(mg/m^3)$^{-1}$**	**Goodness-of-fit test[c]**
Male rats	Renal tubule carcinoma or adenoma	0.002472	0.0087	**0.0025**	$p = 0.81$
	Testicular interstitial cell adenoma	0.006547	0.023	0.0066	$p = 0.52$
Female rats	Renal tubule adenoma	0.0005528	0.0022	0.00063	$p = 0.95$
Male mice	Lung alveolar/ bronchiolar carcinoma or adenoma	0.0008494	0.0054	0.0015	$p = 0.75$
Female mice	Liver hepatocellular carcinoma or adenoma	0.0009421	0.0061	0.0017	$p = 0.68$

a. The interspecies extrapolation was applied to q_{animal_inh} in (mg/kg-d)$^{-1}$ to determine q_{human_inh} (mg/kg-day)$^{-1}$, as described above.

b Unit risk was determined by multiplying the human cancer potency in (mg/kg-day)$^{-1}$ by the human breathing rate (20 m^3/day) divided by human body weight (70 kg), as described above.

c. A *p*-value of greater than 0.05 for the chi-square goodness-of-fit test indicates an adequate fit with the LMS procedure.

Table 8b. Cancer potency and unit risk values for ethylbenzene derived using the BMD procedure with applied LTWA doses based on data from NTP (1999).

Sex, species	Site, tumor type	P_{animal_inh} (mg/kg-day)$^{-1}$	P_{human_inh}[a] (mg/kg-day)$^{-1}$	Human unit risk value[b] (mg/m^3)$^{-1}$	Model Goodness-of-fit test[c]
Male rats	Renal tubule carcinoma or adenoma	0.002589	0.0091	0.0026	Quantal Linear $p = 0.49$
	Testicular interstitial cell adenoma	0.006333	0.022	0.0063	Quantal Linear $p = 0.73$
Female rats	Renal tubule adenoma	0.0004704	0.0019	0.00054	Quantal Quadratic $p = 0.99$
Male mice	Lung alveolar/ bronchiolar carcinoma or adenoma	0.0008062	0.0051	0.0015	Quantal Linear $p = 0.75$
Female mice	Liver hepatocellular carcinoma or adenoma	0.0009256	0.0060	0.0017	Quantal Linear $p = 0.74$

a. The interspecies extrapolation of $(BW_h/BW_a)^{1/4}$ was applied to P_{animal_inh} in (mg/kg-d)$^{-1}$ to determine P_{human_inh} (mg/kg-day)$^{-1}$, as described above.

b Unit risk was determined by multiplying the human cancer potency in (mg/kg-day)$^{-1}$ by the human breathing rate (20 m^3/day) divided by human body weight (70 kg).

c. A p-value ≥ 0.1 for the chi-square goodness-of-fit test indicates an adequate fit with the BMD procedure.

Table 8c. Cancer potency and unit risk values for ethylbenzene derived using the linearized multistage procedure with PBPK metabolized doses and bioassay data from NTP (1999).

Sex, species	Site, tumor type	$q_{animal\_internal}$ (mg/kg-day)$^{-1}$	$q_{human\_internal}$[a] (mg/kg-day)$^{-1}$	Human unit risk value[b] (mg/m^3)$^{-1}$	Goodness-of-fit test[c]
Male rats	Renal tubule carcinoma or adenoma	0.00473	0.0089	0.0020	$p = 0.68$
	Testicular interstitial cell adenoma	0.0154	0.029	0.0064	$p = 0.89$
Female rats	Renal tubule adenoma	0.00101	0.0020	0.00044	$p = 0.97$
Male mice	Lung alveolar/ bronchiolar carcinoma or adenoma	0.003747 0.001680[d]	0.0094 0.0042[d]	0.0021 0.00092[d]	$p = 0.99$ $p = 0.93$[d]
Female mice	Liver hepatocellular carcinoma or adenoma	0.002702 0.001705[d]	0.0069 0.0044[d]	0.0015 0.00097[d]	$p = 0.86$ $p = 0.73$[d]

a. The interspecies extrapolation of $(bw_h/bw_a)^{1/8}$ was applied to $q_{animal\_internal}$ in $(mg/kg\text{-}d)^{-1}$ to determine $q_{human\_internal}$ in $(mg/kg\text{-}day)^{-1}$, as described above.

b. Unit risk was determined by multiplying the human internal cancer potency in $(mg/kg\text{-}day)^{-1}$ by the human breathing rate (20 m^3/day) divided by human body weight (70 kg) and by an uptake factor of 0.77, as described above.

c. A *p*-value of greater than 0.05 for the chi-square goodness-of-fit test indicates an adequate fit with the LMS procedure.

d. These values obtained with PBPK model adjusted to approximate the PK data of Charest-Tardif *et al.* (2006).

Table 8d. Cancer potency and unit risk values for ethylbenzene derived using the BMD procedure with PBPK metabolized doses and bioassay data from NTP (1999).

Sex, species	Site, tumor type	$P_{animal\_internal}$ $(mg/kg\text{-}day)^{-1}$	$P_{human\_internal}$[a] $(mg/kg\text{-}day)^{-1}$	Human unit risk value[b] $(mg/m^3)^{-1}$	Model Goodness-of-fit test[c]
Male rats	Renal tubule carcinoma or adenoma	0.00394	0.0089	0.00164	Multistage (order = 3) $p = 0.57$
	Testicular interstitial cell adenoma	0.01460	0.027	0.00594	Quantal Quadratic $p = 0.87$
Female rats	Renal tubule adenoma	0.00126	0.0025	0.00055	Multistage (order = 3) $p = 0.98$
Male mice	Lung alveolar/ bronchiolar carcinoma or adenoma	0.003557	0.0090	0.0020	Multistage (order = 3) $p = 0.99$
		0.001595[d]	0.0040[d]	0.00088[d]	Quantal Linear $p = 0.93$
		0.000908[e]	0.00229[e]	0.00050[e]	$p = 0.74$
Female mice	Liver hepatocellular carcinoma or adenoma	0.002604	0.0066	0.0015	Multistage (order = 3) $p = 0.86$
		0.0007523[d]	0.0019[d]	0.00042[d]	Quantal Quadratic $p = 0.94$[d]
		0.00104[e]	0.00265[e]	0.00058[e]	Multistage (order = 3) $p = 0.67$

a. The interspecies extrapolation of $(BWh/BWa)^{1/8}$ was applied to $P_{animal\_intneral}$ in $(mg/kg\text{-}d)^{-1}$ to determine $P_{human\_internal}$ $(mg/kg\text{-}day)^{-1}$, as described above.

b. Unit risk was determined by multiplying the human internal cancer potency in $(mg/kg\text{-}day)^{-1}$ by the human breathing rate (20 m^3/day) divided by human body weight (70 kg) and by an uptake factor of 0.77, as described above.

c. A *p*-value of 0.1 or greater for the chi-square goodness-of-fit test indicates an adequate fit with the BMD procedure.

d. These values obtained with PBPK model adjusted to approximate the mouse pharmacokinetic data of Charest-Tardif *et al*. (2006).

e. These values obtained with the PBPK model of Nong *et al*. (2007). Cardiac output = 24BW^0.75; Alveolar ventilation = 0.68*Cardiac output.

Benchmark Dose Approach

Tables 8b and 8d list the P_{animal}, P_{human}, and human unit risk values based on the BMD approach. The cancer potencies and unit risk values were derived using the applied LTWA doses and PBPK adjusted internal doses, as described above. As expected the results from the BMD approach are quite similar to those just described using the LMS approach. Unit risk values ranged from 0.00054 to 0.0063 $(mg/m^3)^{-1}$. When LTWA doses are used, the most sensitive sites are the male rat testicular interstitial cell adenoma and the male rat kidney adenoma and carcinoma. When PBPK doses are used, the most sensitive sites are the male rat testicular interstitial cell adenomas and the male mice lung tumors. Regardless of whether LTWA or PBPK doses are used, the unit risk values based on male rat kidney, male mouse lung, and female mouse liver are comparable at approximately 0.002 $(mg/m^3)^{-1}$. The results based on the Charest-Tardif PBPK parameters are about a factor of two to four less than those based on the PBPK parameters from Haddad. The results obtained with the Nong *et al*. (2007) PBPK model were similar to the Charest-Tardif *et al*. (2006) adjusted mouse model. This is not surprising since they are largely based on the same kinetic data (Table 8d). The various estimates indicate some of the uncertainty in the PBPK approach.

As discussed above, the male rat testicular tumors are not considered appropriate for unit risk and potency estimation because of the high background rate. The preferred unit risk value of 0.0025 $(mg/m^3)^{-1}$, is derived from the male rat kidney data based on LTWA doses with the LMS method. The value derived using the BMD approach based on LTWA doses is not significantly different (0.0026 $(mg/m^3)^{-1}$).

Human PBPK Models

Initial predictions of risk-specific exposure concentrations from a human PBPK model used metabolic parameters from Haddad *et al.* (2001), two exposure scenarios, and two methods of risk estimation. The exposure scenarios utilized were an occupational-like time of exposure (8.0 hr exposure/day x 5 d/week; 7 days simulation) and a continuous environmental time of exposure (24 hr/d x 7d/week; 10 days simulation). Two methods of risk estimation were used. In method I a human potency value, P_{human}, was used to estimate an internal dose equivalent to 1 x 10^{-6} lifetime theoretical risk (e.g., 10^{-6} risk/0.0087 $(mg/kg`-d)^{-1}$ = 1.15 x 10^{-4} mg/kg-d.) The human PBPK model with differing exposure scenarios was then used to estimate the external ethylbenzene concentrations resulting in that internal dose. In method II the animal LED_{10} was divided by 10^5 to obtain the 10^{-6} risk specific dose and the equivalent external concentration was adjusted for possible pharmacodynamic (PD) differences between rats and humans (i.e., $(70/0.45)^{1/8}$). For the tumor site of male rat kidney the 1 x 10^{-6} values from the human models vary by 2-fold (0.48 to 0.79 ppb; Table 9). The same analysis was repeated with the human metabolic parameters from Sams *et al*. (2004) and the range was similar (0.33 to 0.74 ppb). PBPK models with higher body weight of 90 kg and 40% body fat gave only slightly higher ppb predictions. According to the discussion above, the preferred value for the unit risk of ethylbenzene is 2.5 x 10^{-6} $(\mu g/m^3)^{-1}$, based on the data for male rat kidney tumors. With the human model unit risk estimates ranged from 1.27 x 10^{-6} to 3.06 x 10^{-6} ppb^{-1} (2.9 x 10^{-7} to 7.0 x 10^{-7} $[\mu g/m^3]^{-1}$ at 4.35 $\mu g/m^3$/ppb) or somewhat lower than the animal PBPK based values. These unit risk estimates from the human PBPK models were not used as final values due to issues of tumor site concordance and human variability and

parameter uncertainty. The information is provided here for comparative purposes and methodology development.

Table 9. Estimates of Virtually Safe Exposure Levels (ppb) based on Human PBPK Modeling[a]

Method/Model	Occupational Scenario	Environmental Scenario
I . Human Potency based		
70 kg human 20% fat Haddad	0.70	0.50
20% fat Sams	0.66	0.33
90 kg human 40% fat Haddad	0.79	0.56
40% fat Sams	0.74	0.34
II. Animal LED_{10} based		
70 kg human 20% fat Haddad	0.68	0.48
20% fat Sams	0.64	0.32
90 kg human 40% fat Haddad	0.74	0.53
40% fat Sams	0.69	0.34

[a] Note: Values are calculated for 1 x 10^{-6} theoretical lifetime cancer risk. Occupational scenario was 8.0 hr/d x 5 days/week, for one-week simulations; environmental scenario was continuous exposure for one week. Method I used the human potency (Ph) in $(mg/kg\text{-}d)^{-1}$ to calculate a 10^{-6} risk internal dose in metrics of ethylbenzene metabolized by the liver (AMET, μmol/d). Method II uses the animal LED_{10} to calculate a 10^{-6} risk dose. The human models were the 70 kg default with 20% fat and a 90 kg variant with 40% fat (and comparatively less muscle). The Ph was based on the male rat kidney tumors of 0.0087 $(mg/kg\text{-}d)^{-1}$. Inhalation was 20 m^3/d. The models were run with metabolic parameters from Haddad *et al*. (2001) and Sams *et al*. (2004).

Conclusion

The male rat was the most sensitive sex and species tested by NTP (1999) in the inhalation carcinogenesis studies of ethylbenzene. While the highest potency and unit risk values were obtained for rat testicular adenomas, the high background rate of this common tumor made interpretation difficult. NTP considered the increased incidences of renal tubule carcinoma or adenoma to provide clear evidence of the carcinogenic activity of ethylbenzene, and this site was considered to be the more reliable basis for estimating human cancer potency.

OEHHA has examined various proposals for the mode of action of ethylbenzene in causing the observed increases in tumor incidence in rodent lung, kidney and liver. Some of these involve cytotoxicity or exacerbation of existing degenerative processes, which might be considered capable of increasing tumor incidence by a non-genotoxic mechanism, although the precise implications of these proposals for dose-response relationships have not been fully explored.

Moreover, it appears likely that metabolism of ethylbenzene involves generation of reactive metabolites. These metabolites include quinone/hydroquinone species capable of causing oxidative DNA damage and carcinogenesis, analogous to the processes established for benzene and some similar carcinogens. OEHHA concludes that overall, the limited data do not conclusively establish any particular mode of action for ethylbenzene carcinogenesis, and indeed several of the proposed processes may be influential. However, one or more genotoxic processes appear at least plausible and may well contribute to the overall process of tumor induction. Because of this, the default linear approach has been used for extrapolating the dose-response curve to low doses.

Using either the LMS or BMD methodology with different dose metrics, the 95% upper confidence bound on the unit risk value for purposes of calculating cancer risks associated with exposure to ethylbenzene is in the range 5.5×10^{-4} to 6.6×10^{-3} $(mg/m^3)^{-1}$, based on the incidence data from the NTP (1999) studies (Table 10). The unit risk value of 2.5×10^{-3} $(mg/m^3)^{-1}$, or 2.5×10^{-6} $(\mu g/m^3)^{-1}$, based on the renal tubule carcinoma or adenoma incidence data in male rats and using the LMS methodology applied to LTWA doses, is considered the most appropriate for purposes of calculating cancer risks associated with exposure to low levels of ethylbenzene. As noted above and summarized in Table 10 below, unit risks based on the PBPK internal doses were not markedly different than those based on the LTWA doses, and involved a number of assumptions. Because the PBPK modeling is uncertain and the results were relatively insensitive to the approach used, the LMS results based on the LTWA doses were selected as most appropriate. The inhalation cancer potency, from which the unit risk value was derived, is 0.0087 $(mg/kg\text{-}d)^{-1}$. The oral cancer potency value of 0.011 $(mg/kg\text{-}d)^{-1}$ is derived from the inhalation potency value by multiplying by the ratio of the uptake values (i.e., 1/0.77). The inhalation and oral cancer potency values are considered applicable to low dose ethylbenzene exposures.

Table 10. Comparison of unit risk values for ethylbenzene

Species/sex/tumor site	**Unit Risk value $(mg/m^3)^{-1}$**			
	LTWA doses, LMS approach	**LTWA doses, BMD approach**	**PBPK doses, LMS approach**	**PBPK doses, BMD approach**
Male rat kidney	0.0025	0.0026	0.0020	0.0016
Male rat testicular	0.0066	0.0063	0.0064	0.0059
Female rat kidney	0.00063	0.00054	0.00044	0.00055
Male mouse lung	0.0015	0.0015	0.0021	0.0020
Female mouse liver	0.0017	0.0017	0.0015	0.0015

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Appendix A

Berkeley Madonna Model Code Example (Male Rat 75 ppm x 6.25 hr/d x 5days/week, 1 week simulation. If cut and pasted into BM demo program available online this model will run)

```
METHOD Stiff

STARTTIME = 0
STOPTIME= 168
DT = 0.001

{ethylbenzene moles}
init Af = 0
Limit Af >= 0
init Al = 0
Limit Al >= 0
init Am = 0
Limit Am >= 0
init Avrg = 0
Limit Avrg >= 0
init Alu = 0
Limit Alu >= 0

{moles, metabolized}
init Ametl = 0
init Ametlg = 0

{tissue flows L/hr}
Qtot = 15*BW^0.74
Qalv = 12*BW^0.74
Qf = 0.07*Qtot
Qvrg = 0.51*Qtot
Ql = 0.183*Qtot
Qm = Qtot - (Ql + Qf + Qvrg)
Qlu = Qtot

{tissue volumes L}
Vf = 0.035*BW + 0.0205
Vl = 0.037*BW
Vm = 0.91*BW - (Vf + Vl + Vvrg + Vlu)
Vvrg = 0.054*BW
Vlu = 0.014*BW
BW = 0.45

{blood/air and tissue/blood partition coefficients}
Pb = 42.7
Pl = 1.96
Pf = 36.4
Pm = 0.609
Pvrg = 1.96
Plu = 1.96

{ethylbenzene metabolic parameters, CLh, Vmax mol/hr, Km, M}
VmaxC = 7.6
Vmax = VmaxC*BW^0.74/(1000*106.16)
Km = 0.1/(1000*106.16)
```

```
{exposure in ppm converted to moles/L}
Cair = IF TIME <= 6.25 THEN 75*(1E-6/25.45) ELSE IF (24<TIME) AND (TIME <=
30.25) THEN 75*(1E-6/25.45) ELSE IF (48<TIME) AND (TIME <= 54.25) THEN 75*(1E-
6/25.45) ELSE IF (72<TIME) AND (TIME <= 78.25) THEN 75*(1E-6/25.45) ELSE IF
(96<TIME) AND (TIME <= 102.25) THEN 75*(1E-6/25.45) ELSE 0

{calculated concentrations of ethylbenzene}
Cart = Pb*(Qalv*Cair + Qtot*Cvtot)/(Pb*Qtot + Qalv)
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvm = Am/(Vm*Pm)
Cvlu = Alu/(Vlu*Plu)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qtot
Cexh = Cart/Pb

{differential equations for ethylbenzene uptake and metabolism}
d/dt(Alu) = Qtot*(Cvtot - Cvlu)
d/dt(Al) = Ql*(Cart - Cvl)  - Vmax*Cvl/(Km + Cvl)
d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
d/dt(Am) = Qm*(Cart - Cvm)

{amount of ethylbenzene metabolized}
d/dt(Ametl)  = Vmax*Cvl/(Km + Cvl)
d/dt(Ametlg) = (Vmax*Cvl/(Km + Cvl))/BW
init AUCvtot = 0
init AUCvl = 0
d/dt(AUCvtot) = Cvtot
d/dt(AUCvl) =  Cvl
```

ETHYLENE DIBROMIDE

CAS No.: 106-93-4

I. PHYSICAL AND CHEMICAL PROPERTIES SUMMARY (HSDB, 1998)

Molecular weight	187.88
Boiling Point	131-132° C
Melting Point	9.8° C
Vapor pressure	0.11 mm Hg at 20° C
Air concentration conversion	1 ppm = 7.81 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 7.1 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 2.5 E-1 $(mg/kg\text{-}day)^{-1}$
[Male rat nasal tumor incidence (NTP, 1982), cancer risk range calculated using the Weibull-multistage procedure CDHS (1985); unit risk "best value" selected by CDHS (1988) for Proposition 65 purposes.]

III. CARCINOGENIC EFFECTS

Human Studies

Quantitative and qualitative information on the carcinogenicity of ethylene dibromide (EDB) in humans is limited. The epidemiological studies to date have either been suggestive but inconclusive or have lacked the statistical power to detect an effect.

Carcinogenic effects were not observed in men exposed to EDB for four years or more at two Associated Octel manufacturing facilities in the United Kingdom (Turner and Barry, 1979). Excess cancers would not have been expected, however, given the duration and magnitude of exposure, the carcinogenic potency of EDB in laboratory animals, the number of workers studied and the length of time elapsing since first exposure.

Ott *et al.* (1980) reported on the cancer mortality among workers exposed while employed at EDB manufacturing facilities in Texas and Michigan. Among workers at the Texas facility, there were no statistically significant increases in cancer above those expected. Among workers at either facility with more than six years of exposure, four died from malignant cancers, compared to an expected 1.6 deaths from cancer (p = 0.08). At the Michigan facility, five of the EDB-exposed workers died from malignant tumors, whereas 2.2 deaths were expected (p = 0.07). Excluded from this analysis were five individuals from the Michigan facility who had worked with arsenicals in addition to EDB. Two of the five died of respiratory cancer at ages 46 and 58, respectively. One had been exposed to arsenical compounds for only 1 1/2 months, in contrast to 102 months of exposure to EDB; the other had been exposed to arsenicals for 20 months and to EDB for 111 months. Had these been included in either the analysis of those exposed for more than six years

to EDB or the analysis of the Michigan facility mortalities, the results would have been found to be statistically significant ($p < 0.05$).

Animal Studies

The carcinogenic activity of EDB has been demonstrated in a number of studies using mice and rats by dermal, oral, inhalation and intraperitoneal routes of administration. Tumors occurred in both test species at sites local to, and distant from, the site of first chemical contact.

The National Toxicology Program (NTP) conducted an inhalation carcinogenesis bioassay for EDB in male and female Fischer 344 rats and $B6C3F_1$ mice (50 animals/sex/group) (NTP, 1982). The durations of exposure were 90 weeks at 40 ppm, 103 weeks at 10 ppm and 104 weeks for controls. NTP concluded that EDB was carcinogenic to rats, causing increased incidences of carcinomas, adenocarcinomas, and adenomas of the nasal cavity, hemangiosarcomas of the circulatory system (spleen), mesotheliomas of the tunica vaginalis (males only), adenomatous polyps of the nasal cavity (males only), fibroadenomas of the mammary gland (females only) and alveolar/bronchiolar adenomas and carcinomas (females only). EDB was also carcinogenic for mice, causing increased incidences of alveolar/bronchiolar adenomas and carcinomas, hemangiosarcomas of the circulatory system (females only), fibrosarcomas in the subcutaneous tissue (females only), carcinomas of the nasal cavity (females only), and adenocarcinomas of the mammary gland (females only). The tumor incidence by site for rats and mice are shown in Tables 1 and 2, respectively.

Table 1: Results of the NTP (1982) inhalation bioassay of EDB in Fischer-344 rats.

Tumor		Sex	Control	10 ppm	40 ppm
Nasal cavity:	Adenocarcinoma	M	0/50	20/50 [a]	28/50 [a]
		F	0/50	20/50 [a]	29/50 [a]
	Carcinoma	M	0/50	0/50	21/50 [a]
		F	0/50	0/50	25/50 [a]
	Adenomatous polyps	M	0/50	18/50 [a]	5/50 [e]
		F	0/50	5/50 [e]	5/50 [e]
	Adenomas	M	0/50	11/50 [a]	0/50
		F	0/50	11/50 [a]	3/50
	Squamous cell carcinoma	M	0/50	3/50	3/50
		F	1/50	10/50	5/50
Lung alveolar/bronchiolar carcinomas or adenomas		F	0/50	0/48	5/47
Tunica vaginalis mesotheliomas		M	1/50	8/50 [c]	25/50 [a]
Mammary fibroadenomas		F	4/50	29/50 [a]	24/50 [a]
Circulatory system hemangiosarcomas		M	0/50	1/50	15/50 [a]
		F	0/50	0/50	5/50 [e]
Pituitary adenomas		M	0/45	7/48 [b]	2/47
		F	1/50	18/49 [a]	4/45

[a] $p = 0.001$; [b] $p = 0.008$; [c] $p = 0.015$; [e] $p = 0.028$

Table 2: Results of the NTP (1982) inhalation bioassay of EDB in $B6C3F_1$ mice.

Tumor	Sex	Control	10 ppm	40 ppm
Lung:				
Alveolar/bronchiolar carcinomas or adenomas	M	0/41	3/48	23/46 [a]
Alveolar/bronchiolar carcinomas or adenomas	F	4/49	11/49	41/50 [a]
Circulatory system:				
Hemangioma or hemangiosarcoma	M	0/45	0/50	4/50
	F	0/50	12/50 [a]	27/50 [a]
Subcutaneous tissue fibrosarcoma	F	0/50	5/50 [c]	11/50 [a]
Mammary gland adenocarcinoma	F	2/50	14/50 [a]	8/50 [e]
Nasal cavity carcinoma or adenoma	F	0/50	0/50	8/50 [b]

[a] $p = 0.001$; [b] $p = 0.003$; [c] $p = 0.028$; [e] $p = 0.046$

A chronic inhalation bioassay was conducted by NIOSH to evaluate the effect of disulfiram on carcinogenic and other toxic effects of EDB. The findings have been reported in several publications (Plotnick, 1978; Wong *et al.*, 1982). The study exposed four groups of 48 male and four groups of 48 female Sprague-Dawley rats to room air or 20 ppm EDB for 7 hours/day for 5 days/week over an 18-month period. Diets which contained 0.05% disulfiram were given to one set of controls and EDB exposed rats.

Male rats receiving EDB exposure had significantly higher tumor incidences in spleen, adrenals, and subcutaneous tissues than either the control or disulfiram tested rats. Also a significant finding was the high incidence of hemangiosarcoma in the spleen of male rats exposed to EDB. Tumors were also found in the liver, kidneys, and lungs in these animals. Female rats exposed to EDB also showed significantly high tumor incidences in the spleen (hemangiosarcoma), adrenals, and mammary glands. Tumors were also found in the liver. The number of rats with tumors were 15/96, controls on normal diet; 13/96 controls, on disulfiram diet; 54/96, EDB-exposed on normal diet; and 90/96, EDB-exposed on disulfiram diet. The tumor incidence by site was not available.

Osborne-Mendel rats and $B6C3F_1$ mice were administered various levels of EDB in corn oil by stomach tube 5 days/week (NCI, 1978). Time-weighted averages for the high and the low dose groups were 41 and 38 mg/kg/day for male rats, 39 and 37 mg/kg/day for female rats, and 107 and 62 mg/kg/day for male and female mice, respectively (50 animals/sex/group). The responses were compared with two control groups (20 animals/group), of which one received corn oil and the other had no treatment. In rats, squamous cell carcinomas of the forestomach were observed in 45/50, 33/50, 40/50, and 29/50 of the low-dose males, high-dose males, low-dose females, and high-dose females, respectively (all statistically significant). None were observed in controls. The female rats also had statistically significant increases in hepatocellular carcinomas (5/25, time-adjusted, high dose). Hemangiosarcomas were found in male and female rats and the incidences were statistically significant in the males (11/50, low dose). Squamous cell carcinomas of the stomach were found in 45/50, 29/49, 46/49, and 28/50 of the low-dose males, high-dose males, low-dose females, and high-dose females, respectively (all statistically significant, $p < 0.001$). None were observed in controls. Male and female mice had statistically significant incidences of alveolar/bronchiolar adenomas (10/47, high-dose males; 10/43, low-dose females).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Epidemiologic studies of EDB carcinogenicity in humans have been suggestive but inconclusive, or of insufficient power to detect an effect. In animals, however, EDB is a potent carcinogen causing tumors in rats and mice of both sexes at multiple sites via various routes of exposure. CDHS (1985) based their risk assessment on the inhalation bioassays in rats and mice reported by NTP (1982). CDHS (1988) also based an oral EDB cancer potency on the NCI (1978) gavage male and female rat and mouse forestomach squamous cell carcinoma incidence data.

Methodology

CDHS (1985) fitted the Weibull-multistage, multistage, and probit models to data from the NTP inhalation study (NTP, 1982) which describes tumor incidence at two sites: tumors at the site of first chemical contact (nasal malignancies in male rats), and tumors at a remote site (hemangiosarcomas in female mice). For continuous lifetime exposures to 10 parts per trillion (ppt) in air, CDHS estimated essentially zero risk under the probit model, and for the Weibull-multistage and multistage models, risks of 1.0 to 5.5 excess cancers per million exposed. These estimates correspond to potencies of 0.05 - 0.25 $(mg/kg\text{-}day)^{-1}$ [$1.4 - 7 \times 10^{-5}$ $(\mu g/m^3)^{-1}$]. Particular estimates depended upon the model used, the tumor selected (rat nasal malignancies or mice hemangiosarcomas), and whether the upper 95% confidence limit or maximum likelihood estimate of potency was used. Potency estimates derived from distant site (hemangiosarcomas) and local site (nasal malignancies) did not differ substantially.

CDHS (1988), under Proposition 65, recommended that a "best value" cancer potency factor of 0.25 $(mg/kg\text{-}day)^{-1}$ be used for EDB inhalation. This potency was obtained using the NTP (1982) male rat nasal tumor data (Weibull-multistage, 95% upper confidence limit). This potency corresponds to a unit risk of 7.1×10^{-5} $(\mu g/m^3)^{-1}$.

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ETHYLENE DICHLORIDE

CAS No: 107-06-2

I. PHYSICAL AND CHEMICAL PROPERTIES (from HSDB, 1998)

Molecular weight	98.97
Boiling point	83.5º C
Melting point	-35.3º C
Vapor pressure	64 mm Hg @ 20º C
Air concentration conversion	1 ppm = 4.05 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor	2.1 E-5 $(\mu g/m^3)^{-1}$
Slope Factor	7.2 E-2 $(mg/kg\text{-}day)^{-1}$

[Calculated from the incidence of hemangiosarcomas in male rats (NCI, 1978) using a time-corrected (Weibull) multistage procedure (CDHS, 1985).]

III. CARCINOGENC EFFECTS

Human Studies

CDHS (1985), U.S. EPA (1985), and IARC (1985) reported that there was no data on the carcinogenicity of ethylene dichloride (EDC) in humans.

Animal Studies

A number of studies have investigated the carcinogenicity of EDC. The National Cancer Institute (NCI, 1978) conducted a carcinogenesis bioassay of EDC in corn oil by oral gavage in male and female Osborne-Mendel rats and $B6C3F_1$ mice. There were four groups for each sex of both species, including an untreated control, a vehicle (corn oil) control, a low dose group and a high dose (the maximum tolerated dose) group. Time-weighted average low and high dose levels were 47 and 95 mg/kg for both male and female rats, 97 and 195 mg/kg for male mice, and 149 and 299 mg/kg for female mice, respectively. The animals were dosed five days/week for 78 weeks and observed for an additional 12-32 weeks. Mortality was early and severe in dosed animals, especially for high dose rats. A statistically significant ($p \leq 0.025$) increase in the incidence of squamous cell carcinomas of the forestomach, hemangiosarcomas of the circulatory system, and fibromas of the subcutaneous tissue occurred in male rats. Female rats exhibited a statistically significant increase in the incidence of adenocarcinomas of the mammary gland and hemangiosarcomas of the circulatory systems. Male $B6C3F_1$ mice demonstrated a statistically significant increase in incidences of hepatocellular carcinomas and alveolar/bronchiolar adenomas, while female mice exhibited an increased incidence for alveolar/bronchiolar adenomas, mammary gland adenocarcinomas and endometrial stromal sarcomas (NCI, 1978).

Table 1: Tumor incidence data in rats and mice exposed to ethylene dichloride (NCI, 1978).

Tumor Type	Exposure Concentration (mg/kg-day)		
	0	47	95
Male rats			
Squamous cell carcinoma (forestomach)	0/60	3/50	9/50*
Hemangiosarcoma	1/60	9/50*	7/50*
Female rats			
Hemangiosarcoma	0/59	4/50*	4/50*
Mammary adenomas	1/59	1/50	18/50*
	Exposure Concentration (mg/kg-day)		
	0	97	195
Male mice			
Hepatocellular carcinomas	4/59	6/47	12/48*
Alveolar/bronchiolar adenomas	0/59	1/47	15/48*
	Exposure Concentration (mg/kg-day)		
	0	149	299
Female mice			
Alveolar/bronchiolar adenomas	2/60	7/50*	15/48*
Mammary adenocarcinoma	0/60	9/50*	7/48*
Endometrial polyp or stromal sarcomas	0/60	5/49*	5/47*

*Significantly increased incidence in treated animals compared with pooled vehicle controls; significance calculated using Fisher Exact Test (one-tailed); $p \leq 0.05$.

Maltoni *et al.* (1980) conducted extensive inhalation carcinogenicity studies in Sprague-Dawley rats and Swiss mice. Four groups, each consisting of 180 rats or mice of both sexes, were exposed to EDC concentrations of 5, 10, 50, or 150-250 ppm, respectively, seven hours/day, five days/week, for 78 weeks. Two groups of 180 rats per sex, or one group of 249 mice, served as controls. Although all animals received a lifetime exposure and extensive histopathology was performed on each animal, no significant increased in tumor incidences were seen (Maltoni *et al.*, 1980).

Several factors have been suggested to account for the difference in carcinogenicity between the gavage and inhalation studies, including the strains of animal used, the differences in the actual dose received by the animal, and the pharmacokinetic differences in rates of formation and/or retention of reactive metabolites in target organs for different routes of administration (US EPA, 1985; CDHS, 1985; Hooper *et al.*, 1980).

Theiss *et al.* (1977) conducted a pulmonary tumor bioassay in mice with EDC. Groups of twenty mice received intraperitoneal (ip) injections of either 0, 20, 40 or 100 mg/kg EDC three times weekly for a total of 24 injections per mouse. The mice were sacrificed 24 weeks after the first injection. The lungs were subsequently examined for surface adenomas. Although the incidence of lung tumors increased with dose, none of the groups had a significantly greater number of pulmonary adenomas than did vehicle-treated control mice (Theiss *et al.*, 1977).

Van Duuren *et al.* (1979) conducted a bioassay of EDC and one of its suspected metabolite, chloroacetaldehyde, using the two-stage mouse skin test on female Swiss mice. The results of this study indicated that neither EDC nor chloroacetaldehyde induced a statistically significant increase of papillomas or carcinomas of the skin, although dermal application of EDC was associated with a significant increase in the number of mice with benign lung papillomas (Van Duuren *et al.*, 1979).

In summary, EDC has been demonstrated to increase the incidence of tumors in rats and mice, both local to, and distant from, the initial site of chemical contact.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

EDC has caused statistically significant increases in tumor incidences in both rats and mice in several different laboratories by different routes of exposure. The State of California Scientific Advisory Panel for Proposition 65 has identified EDC as a compound known to the State to cause cancer. EDC has been classified by the US EPA and IARC as a B2 and 2B carcinogen, respectively. CDHS (1985) used the tumor incidence data from the NCI (1978) carcinogenesis bioassay for developing a quantitative risk assessment.

Methodology

DHS staff performed several different analyses to generate estimates of cancer potency of EDC in humans using the NCI tumor data. The Crump polynomial model was applied to data which summarizes the tumor incidence observed, time-dependent analyses were performed to take into account early death of treated animals, crude adjustments were made to take into account the saturable pharmacokinetics of EDC, and a physiologically-based pharmacokinetics model (PBPK) was applied to correct for the differing effects of species, routes, and dose levels on the pharmacokinetics of EDC. Due to the lack of data on the metabolism and disposition of EDC in humans and the inherent assumptions required for estimation of metabolic dose in the absence of such data, CDHS decided that animal/human scaling was insufficiently accurate to permit

reliance on PBPK-derived estimated doses to calculate "risk-specific intake levels" (CDHS, 1985).

CDHS (1985) fit the multistage Weibull-in-time model to time to tumor data. The data set for the most sensitive species and tumor type, male rat hemangiosarcomas, was used to calculate a cancer potency factor. The cancer potency values which are normalized for surface area were approximated by assuming that the ratio of animal to human surface areas is equivalent to the ratio of body weights (BW) taken to the two-thirds power. CDHS (1985) estimated the cancer potency from the hemangiosarcoma data to be 0.072 $(mg/kg\text{-}day)^{-1}$. CDHS recommended that a cancer potency of 0.072 $(mg/kg\text{-}day)^{-1}$ be used for estimating risks from exposure to EDC. A unit risk value of 2.1×10^{-5} $(\mu g/m^3)^{-1}$ was derived assuming a human breathing rate of 20 m^3/day, a human body weight of 70 kg, and 100% fractional absorption after inhalation exposure.

V. REFERENCES

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ETHYLENE OXIDE

CAS No: 75-21-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1998) except as noted.)

Molecular weight	44.06
Boiling point	10.7 ºC at 760 mm Hg
Melting point	-111 ºC
Vapor pressure	1314 mm Hg at 25 ºC
Air concentration conversion	1 ppm = 1.83 mg/m^3 (NIOSH, 1994)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 8.8 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 3.1 E-1 $(mg/kg\text{-}day)^{-1}$
[Female rat mononuclear cell leukemia data (Snellings et al., 1984), analyzed by US EPA (1985) using a linearized multistage procedure (GLOBAL82), reevaluated by CDHS (1987).]

III. CARCINOGENIC EFFECTS

Human Studies

Epidemiologic evidence for the carcinogenic effects of ethylene oxide at the time the Toxic Air Contaminant (TAC) document (CDHS, 1987) was written was based on five longitudinal studies of occupational cohorts in Sweden, the United States and West Germany. Together the studies demonstrate an association between exposure to ethylene oxide and cancer. Two additional studies, which were cross-sectional in design, evaluated leukemia incidence as part of a health evaluation of two separate occupational cohorts (Joyner 1964; Ehrenberg and Hallstrom, 1967). Neither of these studies was adequate to evaluate the carcinogenic effect of ethylene oxide since they were not designed to study this outcome.

The five longitudinal studies examined cancer outcomes for all sites and site-specific cancers, with leukemia as a focus for all studies. Four studies reported excesses in leukemia, while one study found no cases of leukemia. A discussion of these studies follows.

Hogstedt *et al*. (1979a) reported that three cases of leukemia had occurred between 1972 and 1977 among 230 Swedish workers exposed to 50% ethylene and 50% methyl formate at a factory that sterilized hospital equipment. Exposure at the plant began in 1968 and measurements taken in 1977 indicated concentrations of ethylene oxide of approximately 20 ± 10 ppm (time-weighted average); exposure levels prior to 1977 were not known. The expected number of leukemia cases at this factory for 1968-1977 was 0.2 cases, based on national rates. Three cases were observed, including two myelogenous leukemias (4 and 8 years exposure) and one primary macroglobulinemia (6 years exposure).

In order to replicate these findings, Hogstedt *et al*. (1979b) conducted a cancer mortality study of the cohort of ethylene oxide production workers originally studied by Ehrenberg and Hallstrom (1967). The findings were similar, demonstrating elevated rates of leukemia and other cancers (Table 1). The cohort was, however, exposed to other carcinogens, such as ethylene dichloride and bis(2-chloroethyl)ether. Exposure to ethylene oxide was between 5.5 and 27.5 ppm (10 to 50 mg/m^3) in the 1960s and 0.55 to 5.5 ppm (2 to 10 mg/m^3) in the 1970s. Exposed workers developed 9 tumors (including leukemias) where 3.4 would have been expected (SMR = 265)($p < 0.01$).

Table 1: Leukemia cases observed and expected in the studies of Hogstedt *et al*. (adapted from Table 5 of Hogstedt *et al*., 1986)

		Time interval					
		1960's*-1977		1978-1981		1960's*-1981	
Plant	Workers Studied	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
1	203	2**	0.09	1	0.05	3	0.14
2	175	3	0.38	1	0.14	4	0.52
3	355	1	0.09	0	0.07	1	0.16
Total	733	6	0.56	2	0.27	8	0.83

* The initial year was 1968 for plant 1, 1961 for plant 2, and 1964 for plant 3.

** One of the original cases (macroglobulinemia) was later reclassified as a non-Hodgkin's lymphoma.

Hogstedt *et al*. (1986) published findings from follow-up studies of the two cohorts described above and a group of production workers from a third plant that had not been studied previously. This last group included workers exposed only to ethylene oxide, exposed to ethylene oxide and propylene oxide, or exposed to a mixture of chemicals. All workers from this third plant had been exposed for at least one year. One leukemia was detected where 0.16 was expected. Leukemia cases from the three plants are shown in Table 4.7. An excess of leukemia cases was reported in Plants 1 and 2 during the 1978-1981 follow-up study, but not in Plant 3. Eight cases of leukemia were observed among 733 workers in the three plants where 0.83 were expected (SMR = 964)(Table 1).

In addition to excess leukemia among the three groups of workers, six stomach cancers were reported among Plant 2 workers where 0.65 were expected. Neither the leukemia nor stomach cancer cases follow a dose-response pattern when analyzed by years of employment. However, years of employment can be a poor surrogate for exposure if, for example, highly exposed workers tended to shift to jobs with lower exposure or terminate their employment early.

It should be noted that although these three studies (Hogstedt 1979a, 1979b, 1986) include many of the ethylene oxide-exposed workers in Sweden, the number of workers involved in the above calculations are relatively small, resulting in large variability in the estimates of the ratios of observed to expected cases. On the other hand, the SMRs obtained are quite large. A second consideration in the finding of an association between ethylene oxide exposure and leukemia is that the leukemias were not limited to any one particular type. However, a single agent can induce

a spectrum of cytogenetic aberrations in hematopoietic tissues resulting in the pattern of leukemias reported by Hogstedt *et al.* In addition, ethylene oxide induces cellular proliferation, including tumors in several rat tissues. Third, in these studies all production workers experienced exposure to other chemicals, including carcinogens, in addition to ethylene oxide; however, the chemical common to all was ethylene oxide.

Two other epidemiologic studies have been conducted. Morgan *et al*. (1981) conducted a cohort study of ethylene oxide production workers at a Texas plant which had been in continuous operation since 1948. To be included in the study cohort, workers had to have been employed for at least five years. Unlike the previous studies, most of the employees worked outdoors. Although Morgan *et al*. did not report specific levels, ethylene oxide exposure levels were generally below 0.2 ppm, the limit of detection of the analytical instrument used, since the authors state that in most areas sampled in a 1977 industrial hygiene survey, virtually no ethylene oxide was detected. A modified lifetable program was used to compare the mortality experience of 767 workers with the pattern expected on the basis of U.S. vital statistics. A reduced overall mortality (SMR = 58) was reported. Morgan and his colleagues observed an excess of pancreas, bladder, and brain cancers and of Hodgkin's disease, but these excesses were not statistically significant. No leukemia cases were seen; however, the cohort size was sufficient to detect only very large increases, i.e., a 10.5-fold increase in leukemia, with 80% power. A 10.5-fold excess would not be expected, given the low levels of ethylene oxide exposure, when compared to Hogstedt's series. Also, this study, by excluding workers employed at the plant for less than five years, could have excluded a significant fraction of exposed workers, since entry level jobs are often associated with higher exposure to chemicals. In a published letter (Divine and Amanollahi, 1986), one of the authors of this study has attempted to use the above data to refute the studies of Hogstedt. The reasons that the study is inadequate for such a refutation are pointed out above.

Thiess *et al.* (1982) reported on the mortality experience of 602 production workers exposed to alkylene (ethylene plus propylene) oxide and other chemicals in nine West German plants. Ninety-two percent of workers employed between 1928 and 1980 were followed. Overall observed mortality and cancer deaths for the total cohort and for those with a minimum of 10 years of observation were lower than expected, based on mortality for either the local area or for West Germany. This indicates a strong healthy worker effect. A second comparison was made using a cohort of 1662 styrene workers at the same plant in order to eliminate the healthy worker effect. However, the choice of styrene-exposed workers as a comparison group may have been inappropriate, since styrene monomer has been shown to be carcinogenic in animals (IARC 1979) and has been associated with an excess in lymphocytic leukemia among styrene-exposed workers (Ott *et al*., 1980). Nevertheless, in older workers, age 65 to 75, the relative risk of malignant tumors was 2.78 in ethylene oxide workers compared to styrene workers ($p < 0.05$). The increased relative risks in younger age groups in the cohort were not statistically significant.

CDHS noted that the evidence supporting an association between working with ethylene oxide and leukemia came from 4 out of 5 occupationally exposed cohorts. The overall evidence could not be considered conclusive due to the small numbers of workers involved and to the possibility that other workplace carcinogens may have been confounders. Nevertheless, the high estimates of risk were striking; standardized incidence and mortality ratios for leukemia ranged from 6 to 21. Furthermore, the replication of the early findings in other plants and in the follow-up of those

same cohorts reduces the probability that the observed excesses of leukemia were chance findings. Since worker recall was not used to determine exposure, bias about exposure from that source is not present. The magnitude of the effect argues against the findings being due to confounding, particularly since the other carcinogens were different for the different plants. Though not conclusive, these studies provide substantial evidence of ethylene oxide's carcinogenicity in humans.

Animal Studies

Rats

A dose-related increase in local tumors, mainly squamous cell carcinomas of the forestomach, was observed in female Sprague-Dawley rats given doses of 7.5 or 30 mg/kg body weight of 99.7% pure ethylene oxide twice a week by gastric intubation for 107 weeks (average total dose of 1186 and 5112 mg/kg body weight, respectively)(Dunkelberg 1982, US EPA 1985). Rats treated with the high dose of ethylene oxide showed increased tumor-related mortality as well as decreased tumor latency compared to the low dose or the control groups. The incidence of local tumors was 0/50 in both control groups, 8/50 in the low-dose group, and 31/50 in the high-dose group. The frequency of tumors at other sites was not increased by ethylene oxide treatment (Dunkelberg, 1982; US EPA 1985).

In a two-year inhalation study in rats, Snellings *et al*. (1984) found that ethylene oxide increased the incidence of mononuclear cell leukemia in animals of both sexes, and peritoneal mesotheliomas in males. Tumor frequency among female rats was greater in all exposed groups than in controls. In addition, brain gliomas were observed in male and female exposed rats. Since this tumor has an historically rare background occurrence in Fischer 344 (F344) rats, it was considered to be a tumor type appropriate for use in risk evaluation.

Eight-week-old F344 rats were exposed in inhalation chambers to 10, 33, or 100 ppm of 99.9% pure ethylene oxide 6 hours/day, 5 days/week, for two years. Initially, 120 males and 120 females were exposed per dose. Two control groups (C1 and C2) of 120 rats per sex were exposed in inhalation chambers to room air.

Planned terminations of 10 rats per sex per dose were performed at 6 and 12 months of exposure and of 20 rats per sex per dose at 18 months. The remainder of the females were sacrificed at 24 months and the males at 25 months. Postmortem examinations were performed on all rats. Histopathologic examinations of about 50 tissues were performed on rats from the 100 ppm and two control groups that were killed at the 6 month and final intervals and on rats in any group that died or were killed in a moribund state. About 15 major organs and tissues from rats in the 100 ppm and both control groups were examined microscopically at 12 and 18 months. At 6, 12, and 18 months, only tissues with gross lesions were examined from the 10 and 33 ppm groups. At the end of the study about 20 major organs and tissues from the rats in the 10 and 33 ppm groups were examined. During the 15th month of exposure, rats in all groups became infected with sialodacryoadenitis virus. This resulted in a loss in body weight in all groups and increased mortality in the females exposed to 100 ppm compared with the other groups. Exposure to ethylene oxide was stopped for 2 weeks after which time body weights, clinical signs, and

mortality rates returned to preinfection status. The authors concluded that this outbreak was unlikely to have affected the results of the study. Cumulative percentage mortality did not increase significantly in the 10 or 33 ppm dose groups, but did increase in the 100 ppm dose groups, after 22 months exposure for males and after 21 months for females.

Table 2: Tumor incidence in F344 rats exposed to ethylene oxide by inhalation for 24 months (adapted from Snellings *et al*., 1984).

		ppm ethylene oxide				
		C1	C2	10	33	100
Sex		# animals examined grossly				
male		48	49	51	39	30
female		60	56	54	48	26
Sex	Tumor type	# animals with tumors				
male	spleen mononuclear cell leukemia	5	8	9	12	9
female		5	6	11	14	15*
male	peritoneal mesothelioma	1	1	2	4	4
male	pituitary adenoma	16	13	15	13	12

C1, C2 control groups

* significantly greater than appropriate control incidence ($p < 0.001$)

Tumor incidence was not significantly increased at 18 months of exposure; however, increased incidences of several types of tumors were observed in groups sacrificed at 24 and 25 months, the end of the study for female and male rats, respectively (Table 2).

The incidence of mononuclear cell leukemia (MNCL) was increased for both sexes in all dose groups, but was statistically significant only for females treated with 100 ppm ethylene oxide. A positive dose-related increase in MNCL incidence in females was observed ($p < 0.01$). A statistically significant trend was not observed for males. When the incidence of MNCL in rats killed at the end of the study is combined with the incidence in the rats dying spontaneously or euthanized when moribund, a statistically significant increase also occurs in females exposed to 33 ppm ($p < 0.01$) and 100 ppm ($p < 0.001$) (Table 3). A significant increase was not observed in males. A mortality-adjusted trend analysis revealed a significant positive trend for females ($p < 0.005$) and males ($p < 0.05$). The time to first tumor was not significantly decreased for MNCL in the exposed rats, but trend analysis indicated earlier tumor development.

Table 3: Tumor incidences in F344 rats exposed to ethylene oxide which died spontaneously, were killed when moribund, or were killed after 24 months of exposure (adapted from Snellings *et al*., 1981 and cited in US EPA, 1985).

Sex, Tumor type	ppm ethylene oxide				
	C1	C2	10	33	100
spleen mononuclear cell leukemia					
males	20/80 (25%)	18/80 (23%)	21/80 (26%)	23/80 (29%)	25/80 (31%)
females	9/80 (11%)	13/76 (17%)	14/80 (18%)	24/80[a] (30%)	27/80[b] (34%)
peritoneal mesothelioma					
males	2/80 (3%)	1/80 (1%)	3/80 (4%)	6/80[c] (8%)	21/80[d] (26%)

C1, C2 control groups
a $p < 0.01$ compared to C1 and combined controls, $p < 0.05$ compared to C2
b $p < 0.001$ compared to C1 and combined controls, $p < 0.05$ compared to C2
c $p < 0.001$ compared to C1, C2 and combined controls
d not significant compared to C1 or C2; $p < 0.05$ compared to combined controls

Note: These data are from US EPA (1985); US EPA questioned whether microscopic examination of all tissues or only tissues with gross lesions was performed on animals that died spontaneously or were killed when moribund. Information from Snelling *et al*. (1984) indicates that histopathology was performed on all tissues from these animals.

The increased incidence of peritoneal mesotheliomas observed in males treated with ethylene oxide for 24 months (Table 2) was not statistically significant; however, when the rats that died spontaneously or were euthanized when moribund are included, a statistically significant increase ($p < 0.001$) for the high-dose group compared with controls was observed (Table 3, data from US EPA, 1985). A mortality-adjusted trend analysis showed a highly significant relationship ($p < 0.005$) between ethylene oxide exposure and induction of peritoneal mesotheliomas. Snellings *et al*. state that this observation indicates that exposure to ethylene oxide was associated with this earlier occurrence of mesotheliomas. Although the incidence of pituitary adenomas was not significantly increased in either sex, exposure to ethylene oxide significantly decreased the time to tumor in males ($p < 0.01$) and females ($p < 0.0001$).

From the time of the 18-month sacrifice until the end of the study, the incidence of brain tumors, including gliomas (twelve astrocytomas, one oligodendroglioma, two mixed gliomas), granular cell tumors, and malignant reticulosis was increased in both sexes. The classification of brain tumors was based on light microscopic cytomorphologic features and on patterns of growth and infiltration. Immunohistochemical staining was not done; thus, the cellular origin of these tumors remained unresolved.

Data on tumors for rats killed at 18 or 24 months and those who died spontaneously or were sacrificed due to morbidity were further evaluated by Garman *et al*. (1985, 1986). The first brain tumors were noted in animals killed at 18 months. The combined incidence of all three tumor types is shown in Table 4. The incidence in the 100 ppm and 33 ppm groups was significantly increased (p = 0.004 and p = 0.027, respectively) compared with the controls. In females a statistically non-significant, dose-related increase was noted in the combined incidence of these three tumor types (Table 4). The IARC working group (1985) noted that combining the three different histological types of tumors precluded a proper evaluation of the effects of ethylene oxide on the brain. (The IARC working group did not have the 1985 paper by Garman *et al*. available and based their results on Snellings *et al*. 1984a). However, even when only the gliomas are considered, a dose-related increase in tumor frequency is also observed (Table 4).

Table 4: Statistical analyses on adjusted ratios of primary brain tumor frequencies in F344 rats exposed to ethylene oxide for two years (Adapted from Garman *et al*., 1985)

Tumor type	Sex	ppm ethylene oxide			
		0*	10	33	100
Gliomas	males	1/181 (0.6%)	0/92 (0%)	3/85 (3.5%)	6/87 (6.9%)
	females	0/187 (0%)	1/94 (1.1%)	2/90 (2.2%)	2/78 (2.6%)
Gliomas,malignant reticulosis and granular cell tumors					
	males	1/181 (0.6%)	1/92 (1.1%)	5/85 (5.9%)	7/87 (8.0%)
	females	1/188 (0.5%)	1/94 (1.1%)	3/92 (3.3%)	4/80 (5.0%)

(a) p = 0.011; (b) p = 0.195; (c) p = 0.172; (d) p = 0.004; (e) p = 0.027; (f) p = 0.058
* control groups C1 and C2

When the data are adjusted for early deaths, the Cox test statistic for adjusted trends in males is significant ($p < 0.001$) for gliomas or the combination of the three tumor types. In females, p = 0.023 for gliomas only and p = 0.001 for the three tumor types combined. Comparison of the controls with historical controls indicates that the concurrent group and the 10 ppm groups had the expected incidence of primary brain tumors.

The frequency of multiple primary (benign plus malignant) neoplasms was significantly greater than the controls in the 100 ppm-exposed male rats. For females all three exposed groups had significantly more multiple primary neoplasms than controls ($p < 0.05$).

Lynch *et al*. (1984) reported the results of a study in male Fischer 344 rats which confirmed the findings of Snellings *et al*. (1984a). Groups of 80 weanling rats were exposed to 0 (filtered air), 50 or 100 ppm 99.7% pure ethylene oxide, 7 hours/day, 5 days/week, for two years. Histopathology was performed on standard sets of 34 tissues plus all gross lesions for all rats that died or were sacrificed. At approximately 8, 16, and 20 months into the study, rats were treated for 2 to 3 weeks with tetracycline for pulmonary infections. *Mycoplasma pulmonis* was confirmed

by serology during the 16th month outbreak. Exposure to ethylene oxide was stopped only for 14 days during the 16th month.

The median survival time and body weight gain were decreased in animals exposed to both concentrations of ethylene oxide compared with controls, and survival time in the high-dose group was significantly decreased ($p < 0.01$). The authors concluded that mortality was affected by ethylene oxide treatment as well as by the *M. pulmonis* infection. Rats exposed to 50 or 100 ppm had a higher incidence than controls of inflammatory lesions of the lungs, nasal cavities, trachea and internal ear as well as an increased incidence of bronchiectasis and bronchial epithelial hyperplasia. These findings are consistent with the manifestations seen in chronic respiratory disease complex in rodents.

The incidence of MNCL in animals dying during the study plus the terminal sacrifices was significantly greater ($p = 0.03$) in the 50 ppm group, but not the 100 ppm group, than in the controls (Table 5). Survival in the 100 ppm group was 19% compared to 49% in controls. If the incidence of MNCL of only the terminally sacrificed rats is compared, a statistically significant increased incidence of MNCL ($p < 0.01$) is observed for the 100 ppm group.

Peritoneal mesotheliomas were significantly increased in the 100 ppm group ($p = 0.002$), but not the 50 ppm group, compared with controls, even in the presence of excess mortality. Use of the Armitage test for trend suggested a proportional increase in the incidence of mesotheliomas with increased exposure.

The incidence of brain gliomas was increased in the 100 ppm dose group ($p < 0.05$) compared with controls (Table 5). Trend analysis suggested a significant increase in gliomas with increased exposure to ethylene oxide. Two additional rats exposed to 50 ppm and four additional rats exposed to 100 ppm had increased numbers of glial cells, termed "gliosis." The authors suggested that these cases of gliosis represent incipient gliomas.

Table 5: Selected tumor incidence in male F344 rats exposed to ethylene oxide for 2 years (adapted from Lynch *et al*., 1984)

Organ	ppm ethylene oxide		
	100	50	Control
Spleen Mononuclear Cell Leukemia	30/76[a] (39%)	38/79[b] (48%)	24/77 (31%)
Peritoneal Mesothelioma	21/79[c] (27%)	9/79 (11%)	3/78 (4%)
Brain			
Glioma (Mixed cell)	5/79[b] (6%)	2/77 (3%)	0/76 (0%)
Astrocytoma	0/79	0/77	0/76

[a] Groups consisted of 80 male rats at beginning of study. Denominators less than 80 reflect tissues accidentally lost on that could not be examined histologically due to autolysis.
[b,c] Statistically significant difference versus controls: $p < 0.05$, $p < 0.01$, respectively.

Mice

The National Toxicology Program performed a two-year inhalation study of ethylene oxide at concentrations of 0, 50, and 100 ppm in male and female B6C3F$_1$ mice (NTP 1986). Statistically significant, increased incidences of both benign and malignant lung tumors and of Harderian gland tumors in both sexes and of uterine, mammary gland, and hematopoietic system (e.g., malignant lymphoma) tumors in females were observed. The incidence data for several tumors are shown in Table 6. Calculations using the several data sites from this study with the multistage model gave values for carcinogenic potency comparable to those calculated using the published data for inhalation by rats in the Bushy Run Research Center study (Snellings *et al*., 1984).

Table 6: Selected tumor incidences in NTP study of mice exposed to ethylene oxide for 2 years (adapted from NTP, 1986).

Organ/Sex		ppm ethylene oxide		
		100	50	Control
Alveolar/Bronchiolar Adenoma or Carcinoma				
Male	Overall	26/50[c] (52%)	19/50 (38%)	11/50 (22%)
	K-M Adjusted	68.3%	55.4%	33.2%
Female	Overall	22/49[c] (45%)	5/48(10%)	2/49 (4%)
	K-M Adjusted	58.6%	20.8%	7.7%
Malignant Lymphoma				
Female	Overall	22/49[c] (45%)	6/48 (12%)	9/49 (18%)
	K-M Adjusted	48.3%	19.0%	26.4%
Uterine Adenoma or Adenosarcoma				
Female	Overall	5/49[b] (10%)	2/47 (4%)	0/49 (0%)
	K-M Adjusted	14.3%	7.6%	0%
Mammary Gland Adenosarcoma or Adenosquamous Carcinoma				
Female	Overall	6/49 (12%)	8/48[b] (17%)	1/49 (2%)
	K-M Adjusted	17.1%	24.8%	2.9%

a Exposure groups consisted of 50 male and 50 female mice at the beginning of the study. Denominators less than 50 in the overall incidence category reflect tissues accidentally lost or that could not be examined histologically due to autolysis. K-M Adjusted incidences are Kaplan-Meier tumor incidences at the end of the study after adjusting for intercurrent mortality.

b, c Statistically significant difference versus controls: $p < 0.05$, $p < 0.01$, respectively (Fisher exact test).

In a more limited study in mice (Adkins *et al*., 1986), strain A/J female mice (6- to 8-weeks old) were exposed to 0, 70, and 200 ppm ethylene oxide for 6 hours/day, 5 days/week for only 6 months in one study and to 0 and 200 ppm in the same protocol in a second study. There were 30 animals

in each exposure group and at least 28 animals in each group survived. In each study 28% of the control animals developed pulmonary adenomas. At 70 ppm 56% developed adenomas. At 200 ppm 87% had adenomas in the first study; in the second study only 42% of the animals exposed to 200 ppm ethylene oxide developed pulmonary adenomas.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Both human (Hogstedt *et al*., 1979a, 1979b, 1986; Thiess *et al*.,1982) and animal (Dunkelberg, 1982; Snellings *et al*., 1981, 1984; Lynch *et al*., 1984; US EPA, 1985; Garman *et al*., 1985, 1986; Adkins *et al*., 1986; NTP, 1986) cancer data exist for ethylene oxide. CDHS decided that the overall evidence for human carcinogenicity due to ethylene oxide exposure could not be considered conclusive due to the small numbers of workers involved in the human studies and because of the possibility that other workplace carcinogens may have been confounders. However, CDHS also noted that though not conclusive, these studies provide substantial suggestive evidence of ethylene oxide's carcinogenicity in humans.

The animal studies listed above demonstrate the ability of ethylene oxide to induce tumors in multiple species (rats and mice) at multiple sites (brain gliomas, mononuclear cell leukemias, peritoneal mesotheliomas in rats; alveolar/bronchiolar adenomas/carcinomas, malignant lymphomas, mammary gland adenosarcomas or adenosquamous carcinomas and uterine adenomas/adenosarcomas in mice. CDHS developed a cancer unit risk for ethylene oxide based on data from the most sensitive sex, site and species, the female rat mononuclear cell leukemia data from Snellings *et al*. (1984).

Methodology

The data used to calculate cancer risk from the female rat mononuclear cell leukemia observed in the Bushy Run Research Center study (Snellings *et al*., 1984a) are given in Table 7 (US EPA, 1985). The table differs from Table 2 presented above. The denominators in Table 7.1 include only those animals whose tissues were examined, that were alive at the time the first leukemia was detected and were thus at risk for the tumor. There is an extra tumor in the 100 ppm group numerator because it was found in one of the rats removed for quality control at 18 months and was therefore excluded from Table 2. CDHS confirmed the EPA numbers by analysis of Table A-73 in the Appendices of the Bushy Run study (Snellings *et al*., 1981). Denominators obtained by approaches other than that used by the EPA do not differ significantly from their approach.

Table 7: Incidence of mononuclear cell leukemia in female rats among survivors to first tumor (Adapted from US EPA, 1985 (Table 9-33, p. 9-150)).

Ethylene oxide exposure (ppm)	Number with leukemia/corrected number exposed	Equivalent human lifetime dose (mg/kg/day)
0	22/186 (1-1.8%)	0
10	14/71 (19.7%)	0.28
33	24/72 (33.3%)	0.75
100	28/73 (38.4%)	2.11

Using the computer software Global 82 (Crump and Howe, 1982), a linearized multistage procedure was fit to the female leukemia dose-response data. Doses were first converted to human equivalents (Tyler and McKelvey, 1980; US EPA, 1985). The female rat leukemia data yielded a maximum likelihood estimate (MLE) for q_1, (the linear or slope term, which relates the probability of cancer to the dose of carcinogen administered in the equation for the multistage procedure) of 0.20 $(mg/kg\text{-}day)^{-1}$. An Upper 95% Confidence Limit (UCL) on q_1 of 0.29 $(mg/kg/day)^{-1}$ was also obtained from the data. (The values for q presented here are the same values EPA obtained using the same data).

Assuming that the percentage of ethylene oxide absorbed by inhalation is similar for rats and humans and using an average human body weight of 60 kg and an average air intake of 18 m^3 per day (California Department of Health Services 1985), a dose of 1 mg/kg/day ethylene oxide is equivalent to 3300 $\mu g/m^3$. Applying those units, the MLE and 95% UCL for the cancer unit risk are 6.1×10^{-5} and 8.8×10^{-5} $(\mu g/m^3)^{-1}$, respectively.

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ETHYLENE THIOUREA (ETU)

CAS No: 96-45-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	102.17
Boiling point	not available
Melting point	200-203 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.179 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 4.5 E-2 $(mg/kg\text{-}day)^{-1}$
[Rat thyroid tumors (Graham *et al*., 1975), contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of ethylene thiourea (ETU) in humans are known to exist.

Animal Studies

Male and female 7-day old $B6C3F_1$ and $B6AKRF_1$ mice (18/sex/group) were exposed to 215 mg/kg body weight ETU by gavage from 1 week of age until 4 weeks of age (Biogenics Research Labs, Inc., 1968; Innes *et al*., 1969). The animals were then fed diets containing 646 mg/kg diet ETU until the end of the experiment (82-83 weeks). Increases in liver tumors (hepatomas) were seen in males and females of both mouse strains used; an increased incidence of lymphomas was also seen in male and female $B6AKRF_1$ mice. Tumor incidence data is listed in Table 1.

Male and female Charles River CD rats (26 animals/sex/group) were fed diets containing 0, 175 or 330 ppm technical grade ETU (97% pure) for 18 months; 5 animals of each sex were then sacrificed (Ulland *et al*.,1972). The remaining animals were followed for 6 months. Increased incidences of thyroid carcinomas were noted in both males and females; thyroid carcinoma incidences were 0/26, 3/26 and 17/26 for control, low-dose and high-dose males, respectively, and 0/26, 3/26 and 8/26 for control, low-dose and high-dose females, respectively.

Table 1. Ethylene thiourea (ETU)-induced tumor incidence in (C57BL/6×C3H/Anf)F_1 and (C57BL/6×AKR)F_1 mice (Innes *et al*., 1969)

Sex/strain	Dose group	Tumor type	Tumor incidence
Male (C57BL/6×C3H/Anf)F_1	control	liver tumors	8/79
	treated		14/16
Female (C57BL/6×C3H/Anf)F_1	control	liver tumors	0/87
	treated		18/18
Male (C57BL/6×AKR)F_1	control	liver tumors	5/90
		lymphomas	1/90
	treated	liver tumors	18/18
		lymphomas	3/18
Female (C57BL/6×AKR)F_1	control	liver tumors	1/82
		lymphomas	4/82
	treated	liver tumors	9/16
		lymphomas	4/16

Graham *et al*. (1973, 1975) exposed male and female Charles River CD rats (initial group sizes 68 animals/sex/group) to diets containing ETU at levels of 5, 25, 125, 250 or 500 mg/kg diet. An untreated control group was included. Interim sacrifices were conducted at 2, 6, 12 and 18 months; the study was terminated at 24 months. An increased incidence of thyroid tumors (adenomas and carcinomas) was noted in males and females (combined). Tumor incidence data is listed in Table 2.

Table 2. Ethylene thiourea-induced thyroid tumor incidence in male and female (combined) Charles River CD rats (Graham *et al*., 1973, 1975)

Ethylene thiourea dietary level (mg/kg diet)	Average dose[1] (mg/kg-day)	Tumor incidence[2]
0	0	2/72
5	0.225	2/75
25	1.13	1/73
125	5.63	2/73
250	11.3	16/69
500	22.5	62/70

1. Doses as reported by Gold *et al*. (1984).
2. Tumor incidences as reported by Gold *et al*. (1984)

Male and female Charles River CD rats were exposed to diet containing 0, 175 or 350 mg/kg ETU for 78 weeks, then switched to control diet for an additional observation period of 26 weeks (Weisburger *et al*., 1981). A significantly increased incidence of thyroid follicular-cell carcinomas was noted in both male and female rats. Tumor incidences were 0/10, 2/26 and 15/26 in pooled

control, low-dose and high-dose male rats, respectively, and 0/10, 2/26 and 6/26 in pooled control, low-dose and high-dose female rats, respectively.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The results of several studies are listed in Gold *et al.* (1984). Innes *et al*. (1969) administered ethylene thiourea (ETU) to small groups of both sexes of $B6C3F_1$ and $B6AKF_1$ mice; Graham *et al*. (1973, 1975) performed relatively large multiple dose studies in Charles River CD rats of both sexes; Weisburger *et al.* (1981) and Ulland *et al.* (1972) conducted moderately sized studies in male and female Charles River CD rats. Because all male $B6C3F_1$ and female $B6AKF_1$ mice treated with ETU developed liver tumors, an upper bound estimate on potency could not be determined for these studies. The lower bound estimates of cancer potency derived from the mouse data are consistent with potencies derived from the studies in rats. Further, cancer potencies derived from the rat studies are consistent with one another. The value selected is derived from the highest quality study, Graham (1973, 1975), which had a large sample size and used multiple dose groups. The target site chosen for the analysis was the thyroid in the Charles River CD rats, the most sensitive site (see Table 2) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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FORMALDEHYDE

CAS No: 50-00-0

I. PHYSICAL AND CHEMICAL PROPERTIES (HSDB, 1998)

Molecular weight	30.03
Boiling point	-19.5°C
Melting point	-92°C
Vapor pressure	1.08 torr @ 26.1°C
Air concentration conversion	1 ppm = 1.24 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.0 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 2.1 E-2 $(mg/kg\text{-}day)^{-1}$
[Rat nasal squamous carcinoma incidence data (Kerns *et al.*, 1983; U.S. EPA 1987), linearized multistage procedure (OEHHA, 1992), with pharmacokinetic interpolation of molecular dosimetry data to the tumor incidence data.]

III. CARCINOGENIC EFFECTS

Human Studies

Epidemiological studies have shown formaldehyde exposure to be significantly associated with cancer at sites in the respiratory tract in workers and in the general population. Studies of embalmers, who have used formaldehyde, have shown increased rates of brain cancer and of leukemia.

Many studies in the epidemiological literature support a link between formaldehyde and elevated risk of cancers of the upper respiratory tract. Among the industrial cohort studies, Stayner (1988) reported a relative risk of 3.4 (90% CI: 1.2-7.9) for buccal cancer, and Blair *et al*. (1986) reported a relative risk of 3.00 (90% CI: 1.30-5.92) for nasopharyngeal cancer. Among industrial proportional mortality studies, Liebling *et al*. (1984) reported a relative risk of 8.70 (90% CI: 1.50-27.33) for buccal/pharyngeal cancer and Stayner *et al*. (1985) reported a relative risk of 7.5 (90% CI: 2.0-19) for buccal cancer. In all of these studies the elevated risk was statistically significant. The population-based case control studies reported statistically significant relationships between formaldehyde exposure and upper respiratory cancers in three studies (Vaughan *et al*., 1986a, b; Hayes *et al*., 1986; Olsen *et al*., 1984), although these cancers can appear in any of several sites.

In a subsequent report Blair *et al.* (1987) presented a summary of a further analysis resulting in a significant association between nasopharyngeal cancer and simultaneous exposure to formaldehyde and to particulate, indicating that such exposure may be a risk factor. Collins *et al.* (1988) have critiqued this finding and have added data.

The three largest - and therefore potentially most sensitive - industrial cohort studies reported elevated rates of lung cancer. The largest, Blair *et al.* (1986) with 26,561 U.S. workers, reported a statistically elevated death rate due to lung cancer, equivalent to 35% above the national average. The other two studies reporting elevated death rates due to lung cancer were Acheson *et al.* (1984a, b) with 7,680 British male workers, mostly young, and Stayner *et al.* (1988) with 11,030 U.S. workers, predominantly female. Some of the categories in the Acheson study showed statistically significant increases of lung cancer. The Stayner study found lung cancer to be elevated 14% overall, which was not statistically significant, but the exposures were well below those of the other two studies.

In the Blair *et al.* (1986) study the investigators concluded that a causal relationship between formaldehyde exposure and lung cancer was unlikely because of a lack of dose gradient for those tumors. Sterling and Weinkam (1988, 1989a, b) performed a reanalysis on the basis that Blair *et al.* (1986) failed to account for a "healthy-worker" effect in the original report. These corrected results showed that lung cancer was related to formaldehyde exposure in a dose-dependent manner, which was statistically significant. In a subsequent analysis of the same workers Blair *et al.* (1990) concluded that exposure to phenol, melamine, urea, and wood dust and other substances might account for some or all of the excess lung cancer observed.

Table 1: Cohort study on industrial exposure to formaldehyde (Blair *et al.*, 1986).

Exposure	Cancer Site	Number Observed	Number Exposed	SMR	90% Confidence Interval	
					Lower	*Upper*
0.1 - > 2.0 ppm time weighted average	brain	17	21	0.81	0.52	1.21
	leukemia	19	24	0.80	0.52	1.16
	buccal/pharynx	18	19	0.96	0.61	1.41
	lung	201	182	1.11	0.98	1.24
	larynx	12	8	1.42	0.87	2.43
	nasal	2	2.2	0.91	0.16	2.86
> 0 - 5.5 ppm-yr	lung, 20 yr latency	146	108	1.35	1.17	1.55
	hypopharynx	1	1.7	0.59	0.02	2.78
	nasopharynx	6	2.0	3.00	1.30	5.92
	oropharynx	5	2.6	1.92	0.76	4.04

Source: OEHHA (1992)

Recent epidemiological studies contribute to the conclusions only marginally. Gerin *et al.* (1989) presented the results of a large case control study with 3,726 cancer patients. The odds ratio for the highest exposure group with adenocarcinoma of the lung was nearly significant at the 95% confidence level, and there was an apparent trend of incidence of this cancer with exposure. Nevertheless, the authors concluded that there was no persuasive evidence of an increased risk of any type of cancer among men exposed to the exposure levels of formaldehyde cited by Blair *et al*. (1986) (Table 1). The study did not consider cancers of the nasal cavity, of the brain, or of leukemia. Bertazzi *et al.* (1989) presented an extension of a previous study (Bertazzi *et al.*, 1986) which had detected elevated lung cancer among 1,332 workers in a resin manufacturing plant

subject to formaldehyde exposure. In the extended study with more accurate estimates of exposure, the lung cancer rate was not elevated above expected for those exposed to formaldehyde (Bertazzi *et al.*, 1989). Linos *et al.* (1990) reported elevated rates of follicular non-Hodgkin's lymphoma and of acute myeloid leukemia among embalmers and funeral directors in a population-based case control study. The investigators did not attribute these tumors to formaldehyde exposure. Malker *et al.* (1990) found significantly elevated rates of incidence of nasopharyngeal cancer among workers in fiberboard plants and among book binders, both being subject to formaldehyde exposure.

Four recent occupational studies have investigated the relationship of formaldehyde exposure to histological changes, some of which are potentially precancerous lesions, in the nasal mucosa. Holmstrom *et al.* (1989) found that workers exposed to well-defined levels of formaldehyde developed significant changes in the middle turbinate, while those exposed to both formaldehyde and wood dust did not. Boysen *et al.* (1990) found in nasal biopses that workers exposed to formaldehyde showed a significantly higher degree of metaplastic alterations. Edling *et al.* (1988) found significant histological differences in the nasal mucosa of formaldehyde workers compared to unexposed workers but found no histological differences between those exposed to formaldehyde and those exposed to formaldehyde and wood dust. Berke (1987) found no statistical relationship between exfoliated nasal cells in formaldehyde-exposed workers and control groups. Thus, these studies provide some indication of possible histologic change due to formaldehyde exposure in humans, consistent with results in animals.

Animal Studies

A study sponsored by the Chemical Industry Institute for Toxicology (CIIT) has provided the most quantitatively useful evidence for the carcinogenicity of formaldehyde (Swenberg *et al.*, 1980a, b; Kerns *et al.*, 1983). This study used 120 male and 120 female Fischer-344 rats in each dose group, including a clean air group. The adjusted tumor incidences (adjusted for competing causes of death, including scheduled interim sacrifices) for squamous cell carcinomas in the nasal passages of males and females combined, when exposed to 0, 2.0, 5.6, or 14.3 ppm formaldehyde for 6 hours/day, 5 days/week for up to 24 months, were 0/156, 0/159, 2/153 and 94/140 (U.S. EPA, 1987). In an analogous study on mice, two mice in the high dose group (14.3 ppm) developed squamous cell carcinomas, a finding that was not statistically significant but was thought to be biologically significant due to the absence of this tumor in control animals and to concurrence with rat studies. Kerns *et al.* (1983) also reported benign tumors, including polypoid adenomas and squamous cell papillomas. Swenberg *et al.* (1980a, b) described a number of additional lesions in the nasal turbinates of rats exposed to formaldehyde for 18 months, including rhinitis, epithelial dysplasia and hyperplasia, squamous hyperplasia, and cellular atypia that occurred in a dose-related manner. Other inhalation studies (Albert *et al.*, 1982; Tobe *et al.*, 1985) have provided positive evidence for the carcinogenicity of formaldehyde.

Recent investigations of chronic toxicity have shown formaldehyde administered orally for 24 months to be carcinogenic in Sprague-Dawley rats but not in Wistar rats. Soffritti *et al.* (1989), using six exposure groups each of 50 male and 50 female Sprague-Dawley rats, with drinking water concentration of 10 to 1500 mg/L formaldehyde, reported increases in the percent of animals bearing leukemias and gastrointestinal neoplasias at the higher exposures. Til *et al.* (1989), using

three exposure groups, each of 70 male and 70 female Wistar rats, with drinking water concentrations of 20 to 1900 mg/L, reported numerous pathological changes at the highest exposure level, but no evidence of carcinogenicity at any level. Tobe *et al.* (1989), using three exposure groups, each of 20 male and 20 female Wistar rats, with drinking water concentrations of 200 to 5000 mg/L, also reported pathological changes at the highest exposures level but no significant increases in the incidence of any tumor in these small treatment groups. In a letter to the editor, Feron *et al.* (1990) questioned the conclusions and some methods of Soffritti *et al.* (1989).

Other types of exposures have produced a spectrum of results. Watanabe *et al.* (1954) presented a brief preliminary report of experimentally inducing sarcomas by repeated injections of an aqueous solution of formaldehyde in rats. Muller *et al.* (1978) induced a preneoplastic lesion of the oral mucosa by repeated exposure to formalin solution in rabbits. Homma *et al.* (1986) found that formalin solution repeatedly administered in transplanted rat bladders did not promote formation of tumors. Takahashi *et al.* (1986) found that formalin solution in diet did promote stomach tumors in Wistar rats. Iversen *et al.* (1988) found that topical skin application of formaldehyde solution in mice did not promote the formation of skin tumors.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The International Agency for Research of Cancer (1987) has reviewed the evidence for carcinogenicity and found it to be limited in humans and sufficient in animals. U.S. EPA (1987) has classified formaldehyde in Group B1, probable human carcinogen. The U.S. Occupational Safety and Health Administration (U.S. OSHA, 1987) has concluded that "formaldehyde should be regarded as an occupational carcinogen," based upon animal and human studies. Considering these previous determinations, along with the evidence of carcinogenicity, OEHHA staff (OEHHA, 1992) concluded that formaldehyde is a probable carcinogen and meets the definition of a "toxic air contaminant": an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

Formaldehyde is carcinogenic in rodents, as described above, producing squamous cell carcinomas in the nasal passages of male and female rats and male mice. Several different types of potentially precancerous abnormalities, including polypoid adenomas and squamous cell papillomas, have also been observed. The epidemiological evidence, while suggestive of a risk of human cancer due to formaldehyde exposure, was considered insufficient for risk assessment purposes on its own. OEHHA (1992) found the tumor incidence data in rats reported by Kerns *et al.* (1983) and used by U.S. EPA (1987) to be the most appropriate for use in developing a quantitative risk assessment.

Methodology

In developing a spectrum of predictions of cancer risk to humans, the OEHHA (1992) assessment applied a pharmacokinetic interpolation of the molecular dosimetry data to the animal cancer bioassay data of Kerns *et al.* (1983). The analysis used the linearized multistage procedure (GLOBAL86), and the procedure developed by Moolgavkar and others, which takes into account the proliferation of premalignant cells due to the formaldehyde exposure. Both models derive upper confidence limits (UCL) for excess cancer risk and extrapolate the risk to humans by means of three different scaling factors. Two scaling factors take into account the contact mechanism of carcinogenesis. However, they do so in different ways. One uses only a generic calculation in terms of body mass. The other takes specific account of comparative data on DNA binding in rats and monkeys to adjust the metabolic rate for humans; it assumes humans respond as do monkeys and uses the data of Casanova *et al.* (1989; 1991). The third scaling factor follows the default option of the California carcinogen guidelines (CDHS, 1985), which calculates the adjustment for rat exposures to obtain the equivalent human exposure on the basis of intake rate divided by body surface area.

Table 2: Formaldehyde inhalation bioassay data used to estimate cancer risk to rats

Exposure (ppm HCHO)[a]	Rate of DNA Binding[b] (pmol/mg-hr)	Lifetime Equivalent Metabolic Exposure[b] (ppm)	Incidence of Nasal Squamous Carcinomas[c]
0	0	0	0/156 (0%)
2	2.5	0.54	0/159 (0%)
5.6	15.9	3.4	2/153 (1.3%)
14.3	74.8	16.	94/140 (67.5%)

Source: adapted from OEHHA (1992)
[a]Fischer 344 rats inhaled indicated concentrations of formaldehyde gas 6 hours per day, 5 days per week for 24 months.
[b]Details on how these estimates were obtained are presented in OEHHA (1992)
[c]Based on data partially reported in Kerns *et al.* (1983). Numerator and denominator are those used by U.S. EPA (1987).

For the best value of UCL on unit risk for a lifetime of exposure, the OEHHA staff selected 7×10^{-3} ppm^{-1} (6.0×10^{-6} ($\mu g/m^3$)$^{-1}$), based on molecular dosimetry data in a three-stage model and using the standard surface-area scaling factor, 1.2. The range of calculated values of UCL on unit risks is 0.3×10^{-3} ppm^{-1} to 40×10^{-3} ppm^{-1} (0.25×10^{-6} to 33×10^{-6} ($\mu g/m^3$)$^{-1}$).

In a review of epidemiological studies for workers exposed to formaldehyde the study by Blair *et al.* (1986) was selected as the most reliable for quantitative comparisons. That study, the largest and best documented study available, evaluated mortality in a cohort of more than 26,000 workers. The observed risk of death by lung cancer in exposed workers was 15×10^{-3} over their career. Based on extrapolation of rat cancer risk predictions to humans for a 40-hour work week for 20 years and an exposure level of 1.0 ppm, the prediction of 95% upper confidence limits on respiratory tract cancer was 32×10^{-3} for the three-stage tissue-dose model with generic contact

scaling factor. Thus, the upper range of human cancer risk predictions from the rat bioassay data (Kerns *et al.*, 1983) was consistent with the occupational exposure cancer risk data.

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HEXACHLOROBENZENE

CAS No: 118-74-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	284.8
Boiling point	323-326°C
Melting point	231°C
Vapor pressure	1.09 E-05 mm Hg at 20°C
Air concentration conversion	1 ppm = 11.65 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 5.1 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.8 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from potency derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

No adequate epidemiological studies of cancer in people exposed to hexachlorobenzene (HCB) are available. The only reported study found increases in porphyria, neurological, dermatological and orthopedic disorders and thyroid enlargement among 161 individuals (63 women, 98 men) studied out of a group of approximately 4000 who had suffered hexachlorobenzene poisoning 25 years previously as a result of eating HCB-treated wheat seed (Peters *et al.*, 1982, 1983). No increases in cancer incidence were reported; however, it should be noted that the methodology used in the study was not designed to evaluate excess cancer occurrence.

Animal Studies

A number of feeding studies have been conducted in hamsters, rats and mice. Hexachlorobenzene has been found to induce tumors in the liver, adrenal gland, thyroid gland, parathyroid gland, kidney, lymphoid tissue and endothelial tissue.

Cabral *et al.* (1977) fed male and female Syrian golden hamsters diets containing 0, 50, 100 or 200 mg/kg diet HCB for the life of the animals. Treatment group sizes for the control, low-dose, mid-dose and high-dose groups were 40, 30, 30 and 59, respectively, for males and 40,30,30 and 60, respectively, for females. Treatment-related increases in the incidence of liver tumors (hepatomas, hemangioendotheliomas) and thyroid adenomas were observed in both males and females. Tumor incidence data is listed in Table 1.

Table 1. Hexachlorobenzene-induced tumor incidence in male and female Syrian golden hamsters (Cabral *et al.*, 1977)

Dietary HCB concentration (mg/kg diet)	Calculated daily intake (mg/kg-day)	Tumor type	Tumor incidence	
			males	females
0	0	hepatomas	0/40	0/39
50	4		14/30	14/30
100	8		26/30	17/30
200	16		49/57	51/60
0	0	hemangioendotheliomas	0/40	0/39
50	4		1/30	0/30
100	8		6/30	2/30
200	16		20/57	7/60
0	0	thyroid adenomas	0/40	0/39
50	4		0/30	2/30
100	8		1/30	1/30
200	16		8/57	3/60

Outbred Swiss mice were fed diets containing 0, 50, 100, or 200 mg/kg hexachlorobenzene for 101-120 weeks; all surviving animals were killed at 120 weeks (Cabral *et al.*, 1979). Initial group sizes were 50 animals/sex for the control and 200 mg/kg diet groups, and 30/sex for the 50, 100 and 300 mg/kg diet groups. A dose-response related increase in the incidence of liver tumors (unspecified histological type) was noted in both male and female animals. An increased incidence of liver tumors was also found in a group of 30 males and 30 females fed diet containing 300 mg/kg diet HCB for 15 weeks followed by observation until 120 weeks. Tumor incidence data is listed in Table 2.

Table 2. Hexachlorobenzene-induced liver tumors in male and female Swiss mice (Cabral *et al.*, 1979)

Dose group (mg/kg diet)	Tumor incidence	
	males	females
0	0/47	0/49
50	0/30	0/30
100	3/29	3/30
200	7/44	14/41
300 (15 weeks exposure)	1/16	1/26

Smith and Cabral (1980) exposed female Agus and Wistar rats to diets containing 100 mg/kg HCB for up to 90 or 75 weeks, respectively. An increased incidence of liver tumors (histological type

not specified) due to HCB exposure was observed in both Agus and Wistar rats; tumor incidence was 14/14 and 4/6, respectively, compared to 0/12 and 0/4, respectively, in the control animals.

Male and female Syrian golden hamsters were exposed to diet containing 0, 200 or 400 mg/kg diet HCB for 90 days; 25-50 animals/group were sacrificed on the 91st day (Lambrecht *et al.*, 1982). The remaining 25 animals/group were placed on control diet and sacrificed at 6 week intervals up to 1 year. Hepatoma incidence in the 200 and 400 mg/kg diet groups was 1/13 and 1/20, respectively, for males and 1/15 and 1/7, respectively for females. No hepatomas were noted in 43-50 control animals for each sex.

Male and female Sprague-Dawley rats (94/sex/group) were fed diets containing 0, 75 or 150 mg/kg diet HCB for up to 2 years (Lambrecht *et al.*, 1983a, b, 1986). Four animals/sex/group were killed at 0, 1,2,3,4,8,16,32 and 64 weeks. Treatment-related increases in the incidence of hepatic tumors (hepatomas, hemangiomas, hepatocarcinomas and bile duct adenomas/carcinomas) and renal-cell adenomas were noted in both male and female animals. Tumor incidence data is noted in Table 3.

Table 3. Hexachlorobenzene-induced hepatic tumors in male and female Sprague-Dawley rats (Lambrecht *et al.*, 1983 a,b; 1986)

Dose group (mg/kg diet)	Tumor type	Tumor incidence	
		males	females
0	hepatoma/hemangioma	0/54	0/52
75		10/52	23/56
150		11/56	35/55
0	hepatocarcinoma	0/54	0/52
75		3/52	36/56
150		4/56	48/55
0	bile duct adenoma/carcinoma	0/54	1/52
75		2/52	19/56
150		2/56	29/55
0	renal-cell adenomas	7/54	1/52
75		41/52	7/56
150		42/56	15/55

Arnold *et al.* (1985) conducted two studies on the effects of chronic feeding of HCB in Sprague-Dawley rats. In the first study, male and female Sprague-Dawley rats were fed diets containing 0, 0.32, 1.6, 8 or 40 mg/kg diet HCB for 3 months after weaning. Group sizes were 40/sex except for the control and high-dose groups (64 and 66/sex, respectively). After 3 months, the F_0 rats were bred and 50 pups (F_1) of each sex were randomly selected from each group. The F_1 generation animals were fed their parent's diet from weaning for their lifetime (130 weeks). A significant positive trend was noted in the incidence of parathyroid adenomas in males ($p < 0.01$); the incidence in high-dose males was also significantly greater than controls ($p < 0.05$). A significant positive trend was also noted in the incidence of adrenal pheochromocytomas in both

males and females ($p < 0.05$ and $p < 0.01$, respectively); the incidence in high-dose females was also significantly greater than controls ($p < 0.01$). Tumor incidence data is listed in Table 4.

Table 4. Hexachlorobenzene-induced tumor incidence in the male and female exposed F_1 progeny of exposed F_0 Sprague-Dawley rats (Arnold *et al.*, 1985)

Dose group (mg/kg diet HCB)	Average dose[1]	Tumor type	Tumor incidence	
			males	females
0	0	parathyroid adenomas	2/48	
0.32	0.01		4/48	
1.6	0.07		2/48	
8	0.35		1/49	
40	1.72		12/49	
0	0	adrenal pheochromocytomas	10/48	2/49
0.32	0.01		12/48	4/49
1.6	0.07		7/48	4/50
8	0.35		13/49	5/49
40	1.72		17/49	17/49

1. As reported by CDHS (1988)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results from the following 3 studies provide the basis for cancer potency derivation. Cabral *et al.* (1977) treated groups of male and female Syrian golden hamsters with hexachlorobenzene in feed over the lifetime of the animals. Significant dose-related increases in hepatomas were observed in both sexes (see Table 1). Lambrecht *et al.* (1983a, b; 1986) exposed male and female Sprague-Dawley rats to hexachlorobenzene in feed for 2 years. Treated male and female rats exhibited significant increases in the incidence of hepatomas and renal-cell adenomas. Female rats also demonstrated significant increases in the incidence of hepatocellular carcinomas. No hepatocellular carcinomas were noted in control animals (see Table 3). Arnold *et al.* (1985) also observed a significant dose related increase in the occurrence of adrenal pheochromocytomas in the male and female and parathyroid adenomas in the male exposed F_1 progeny of exposed F_0 Sprague-Dawley rats (see Table 4).

Methodology

Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that the value derived from that data set is not appropriate (CDHS, 1985). For hexachlorobenzene, similar cancer potencies were derived using data from several tumor sites in different test species. Cancer potency factors (q_1^*) were derived by applying a linearized multistage procedure (CDHS, 1985) to the dose-response data for induction of hepatomas in male Syrian golden hamsters (Cabral *et al.*,

1977), and hepatocellular carcinomas (Lambrecht *et al.*, 1983a, b) and pheochromocytomas (Lambrecht *et al.*, 1983a, b; Arnold *et al.*, 1985) in female Sprague-Dawley rats. Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors. Assumed body weight values used for humans, hamsters and mice were 70 kg, 0.1 kg and 0.035 kg, respectively (CDHS, 1988). Lambrecht *et al.* (1983a, b) reported average body weights of 0.265 kg for female Sprague-Dawley rats; unpublished data cited by US EPA (1985) indicates that average body weights of female Sprague-Dawley rats in the study by Arnold *et al.* (1985) were 0.353 kg. A human cancer potency value (q_{human}) of 1.7 $(mg/kg\text{-}day)^{-1}$ was calculated from the male hamster hepatoma incidence data (Cabral *et al.*, 1977) and the female rat hepatocellular carcinoma incidence data (Lambrecht *et al.*, 1983a, b). A human cancer potency value of 1.8 $(mg/kg\text{-}day)^{-1}$ were calculated from female rat pheochromocytomas incidence data (Lambrecht *et al.*, 1983a, b; Arnold *et al.*, 1985). On the basis of the results stated above, a cancer potency of 1.8 $(mg/kg\text{-}day)^{-1}$ was selected for hexachlorobenzene (CDHS, 1988). The unit risk factor was derived by OEHHA/ATES from the low dose exposure cancer potency value using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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HEXACHLOROCYCLOHEXANE (TECHNICAL GRADE)

CAS No: 608-73-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	290.9
Boiling point	288°C (α-HCH); 323.4°C (γ-HCH)
Melting point	158°C (α-HCH); 113°C (γ-HCH)
Vapor pressure	0.02 mm Hg @ 20°C (α-HCH)
Air concentration conversion	1 ppm = 11.9 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 4.0 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

The International Agency for Research on Cancer (IARC) concluded in 1987 that the evidence for carcinogenicity of hexachlorocyclohexane (HCH; all isomers) was inadequate in humans. However, U.S.EPA (1988) designated α-HCH and technical grade HCH as B2 (probable human) carcinogens. Several case reports suggest an association between HCH isomers, including β- and γ-HCH, and exposure and leukemia, aplastic anemia, liver cancer, soft-tissue sarcomas, and lung cancer (IARC, 1987). In all of these case reports, the exposures are not well documented. In addition, exposures to other chemicals, including some pesticides, probably occurred in these cases.

Animal Studies

The incidence of liver tumors in male and female mice has been shown to be increased in two studies of technical HCH (Kashyap *et al*., 1979; Hanada *et al*., 1973). Hanada *et al*. (1973) exposed male and female dd mice (10-11 per group; 14 controls) to 100, 300, or 600 mg/kg diet of α-, β-, γ-, or technical HCH for 32 weeks, followed by a 6-week period without chemical exposure. The incidence of hepatomas was significantly increased in animals treated with increasing doses of α-, or technical HCH (Table 1).

In the study by Kashyap *et al*. (1979), Swiss mice (30/sex/group) were exposed to 0 or 100 mg/kg diet for 80 weeks. Mice were also exposed to technical HCH by gavage (10 mg/kg/day) or skin painting (0.25 mg in 0.1 mg olive oil). A significant increase in liver hepatocarcinomas and lymphoreticular tumors of type B was observed in mice exposed to technical HCH in the diet or by gavage (Table 2).

Table 1. Liver hepatoma incidence in dd mice treated with hexachlorocyclohexane (HCH) (Hanada *et al*. (1973).

HCH Isomer	Sex	Hepatoma incidence mg/kg diet HCH		
		100	300	600
α-HCH	males	1/8	7/7	7/7
	females	0/8	2/3	6/8
β-HCH	males	0/9	0/8	0/8
	females	0/9	0/8	0/4
γ-HCH	males	0/10	0/9	3/4
	females	0/8	0/7	1/3
Technical HCH	males	0/10	4/4	4/4
	females	0/8	3/5	5/5

Table 2. Tumor incidence in mice treated with technical hexachlorocyclohexane (HCH) (Kashyap *et al*., 1979).

HCH Treatment Group	Sex	Animals/ group	Liver tumors	Total tumors
Control	m	25	4	9
	f	26	1	5
100 mg/kg/day (diet)	m	23	16	22
	f	25	9	21
10 mg/kg/day (gavage)	m	26	12	17
	f	28	7	16
0.25 mg/0.1 mg (olive oil) (gavage)	m	25	5	11
	f	18	3	7

m = male, f = female

Wolff *et al*. (1987) reported on the carcinogenic effects of γ-HCH in several strains of mice. Female yellow, black, and pseudoagouti mice (36-96 per group) were exposed to 0 or 160 ppm γ-HCH in the diet for up to 24 months. Different response rates were observed between strains, indicating significant genetic variability in response to γ-HCH. In yellow mice, a significant increase in the incidence of Clara cell hyperplasia, papillary lung tumors and hepatocarcinomas and adenomas was observed (Table 3). The higher incidence of tumors in the obese yellow mice indicate that bioaccumulation of γ-HCH in obese animals may influence carcinogenicity. Similar experiments were not done using technical HCH.

Table 3. Tumor incidence in yellow mice exposed to γ-HCH (Lindane) (Wolff *et al*., 1987)

Concentration of γ-HCH (ppm)	Lung Tumors	Liver Adenomas
0	4/95	8/93
160	18/95	33/94

Thorpe and Walker (1973) showed an increase in liver tumors of male CF1 mice fed 400 ppm γ-HCH for 110 weeks, compared with controls. The time-weighted dose was estimated as 52 mg/kg/day by US EPA (1988). In this experiment, control mice exhibited an incidence of 11/45 for liver tumors, compared to 27/29 for the 52 mg/kg/day group.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The studies by Hanada *et al*. (1973) and Kashyap *et al*. (1979) both show a carcinogenic effect on the liver in mice. The study by Nagasaki *et al*. (1975) also showed a positive carcinogenic effect in mice, but these data were considered less reliable since the tumor incidence was zero in all but the highest dose group, where it was 100%. In addition, the study by Kashyap *et al*. (1979) was among those of the longest duration available for HCH (80 weeks). The potency values from the Kashyap *et al*. (1979) and Hanada *et al*. (1973) studies are the same for liver tumors in mice. Therefore, these studies were used by CDHS (1988) to determine the cancer potency for HCH.

Methodology

A linearized multistage procedure was used to estimate the cancer potency of technical HCH from the Kashyap *et al*. (1979) and Hanada *et al*. (1973) data in male Swiss mice (Crump *et al*., 1982). The concentrations of technical HCH given in the feed were 0 or 100 mg/kg diet (Kashyap *et al*., 1979), and 0, 100, 300, or 600 mg/kg diet (Hanada *et al*., 1973). The tumor incidence data are shown in Tables 1 and 2 above. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for HCH.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. The default lifespan for mice is 104 weeks. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 4.0 $[mg/kg\text{-}day]^{-1}$ was derived (CDHS, 1988). An airborne unit risk factor of 1.1E-3 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

V. REFERENCES

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HYDRAZINE

CAS No: 302-01-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	32.05
Boiling point	113.5°C
Melting point	2.0°C
Vapor pressure	14.44 mm Hg @ 25°C
Air concentration conversion	1 ppm = 1.31 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.9 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 1.7 E+1 $(mg/kg\text{-}day)^{-1}$
[Calculated by US EPA (1991) from the male rat nasal cavity tumor data of MacEwan *et* al. (1980) using a linearized multistage procedure (Global 82), extra risk]

Oral Cancer Potency Factor: 3.0 E+0 $(mg/kg/day)^{-1}$
[Calculated by US EPA (1991) from the male mouse liver tumor data of Biancifiori (1970) using a linearized multistage procedure (Global 82), extra risk]

III. CARCINOGENIC EFFECTS

Human Studies

A published letter (Roe, 1978) presented mortality data from two hydrazine manufacturing plants (belonging to one of nine companies in the trade). This study included 423 workers employed at one plant between 1963 and 1975 (151 workers) and at a second plant (272 workers) between 1945 and 1970. Five cancer deaths were reported (three of the stomach, one prostatic and one neurogenic). A follow-up study of this cohort extended the observation period to 1982 (Wald *et al*., 1984). The only excess cancer mortality was the result of two lung cancer cases in the highest exposure group (relative risk = 1.2, 95% confidence interval 0.2 - 4.5). The author concluded that neither group of workers demonstrated an increased risk of cancer associated with occupational exposure to hydrazine. No other studies on human hydrazine exposure have been published.

Animal Studies

Several studies have tested the ability of hydrazine sulfate administered by gavage or in drinking water to induce cancer. Lung adenomas and adenocarcinomas and liver hepatomas and hepatocarcinomas were observed in both mice and rats. These studies have been reviewed by IARC (1974) and US EPA (1988). Lung tumors, reticulum-cell sarcomas and myeloid leukemias have also been observed to occur in mice exposed to hydrazine by intraperitoneal injection (Juhász *et al*., 1966; Kelly *et al*., 1969; Mirvish *et al*., 1969). MacEwan *et al*. (1981) reported that

inhalation exposure to hydrazine induced lung adenomas in mice, nasal cavity tumors and thyroid adenocarcinomas in rats and nasal polyps in hamsters.

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Inhalation

MacEwan *et al*. (1981) exposed C57BL/6 mice, F344 rats, Syrian golden hamsters and beagle dogs to hydrazine vapor (97% pure) by inhalation for 6 hours/day, 5 days/week for 1 year followed by a variable observation period (12-38 months). Exposure levels were 0.05, 0.25 and 1.0 ppm for mice, 0.05, 0.25, 1.0 and 5.0 ppm for rats, 0.25, 1.0 and 5.0 ppm for hamsters and 0.25 and 1.0 ppm for dogs. Lung adenomas were reported in 12/379 female mice ($p < 0.05$) exposed to 1.0 ppm hydrazine. Male and female rats demonstrated nasal cavity tumors after exposure to 1.0 ppm (11/98 and 4/97, respectively) and 5.0 ppm (72/99 and 36/98, respectively). Male rats also developed thyroid adenocarcinomas (13/99) after exposure to 5.0 ppm hydrazine. Nasal polyps were induced in male hamsters exposed to 5.0 ppm hydrazine (16/160, $p < 0.01$). No significant tumor increase was seen in either dog exposure group. This study was selected as the basis of a cancer potency factor for exposure to hydrazine by inhalation because it demonstrated a dose response, used a relevant exposure route and used hydrazine vapor instead of hydrazine sulfate.

Oral

Biancifiori (1970) administered hydrazine sulfate by gavage to groups of 24 to 30 8-week-old CBA/Cb/Se mice of each sex at doses of 0.0, 0.14, 0.28, 0.56, or 1.13 mg/day, 6 days/week for 25 weeks. Animals were observed throughout their lifetimes. Liver carcinomas were induced in a dose-related manner in both sexes and lung metastases were observed in some of the mice treated with 1.13 mg/kg/day (Table 1). Pulmonary tumors were reportedly present in many of the treated mice, but incidences were not reported because the purpose of the study was to describe hepatic tumors.

Table 1. Tumor incidence in male CBA/Cb/Se mice exposed by gavage to hydrazine sulfate (Biancifiori, 1970)

Administered dose (ppm)	Human equivalent dose (mg/kg)/day[1]	Liver tumor incidence
0	0	3/30
0.14	0.044	1/26
0.28	0.103	7/25
0.56	0.222	12/25
1.13	0.403	15/25

1. Human equivalent dose calculated by US EPA (1991).

Methodology

Inhalation

A linearized multistage procedure (Global 82) was used to calculate a slope factor of 1.7 E+1 $(mg/kg/day)^{-1}$ from the male F344 rat nasal cavity adenoma and adenocarcinoma incidence data of MacEwan *et al*. (1980). Male F344 rats were the most sensitive species and sex to the carcinogenic effects of inhaled hydrazine. Administered doses were 1.0 and 5.0 ppm; human equivalent doses were 0.01 and 0.05 mg/kg/day. Human equivalent doses were calculated on the basis of a 365 day treatment and an experimental period of 910 days. Rat body weight was assumed to be 350 g, and the animal lifespan was assumed to be 910 days. Calculation of the unit risk from the slope factor assumed a body weight of 70 kg and an inspiration rate of 20 m^3/day. EPA has stated that the unit risk should not be used if the air concentration exceeds 2 $\mu g/m^3$, since above this concentration the unit risk may not be appropriate.

Oral

A linearized multistage procedure (Global 82) was used to calculate a slope factor of 3.0 E+0 $(mg/kg/day)^{-1}$ from the male CBA/Cb/Se mouse liver tumor incidence data of Biancifiori (1970) (Table 1). Human equivalent doses were calculated to reflect a treatment period of 175 days and an experimental period of 607 days, the mean length of the experiment for each treatment group. Mouse body weight was assumed to be 0.03 kg and the animal lifespan was assumed to be 730 days.

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LEAD AND LEAD COMPOUNDS (INORGANIC)

CAS No.: 7439-92-1

I. PHYSICAL AND CHEMICAL PROPERTIES

Molecular weight	207.2 (Budavari, 1989)
Boiling point	1740° C (Budavari, 1989)
Melting point	327.4° C (Budavari, 1989)
Vapor pressure	1.77 mm Hg at 1000° C (Budavari, 1989)
Air concentration conversion	not available

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor:	1.2 E-5 $(\mu g/m^3)^{-1}$	
Slope Factor:	(inhalation)	4.2 E-2 $(mg/kg\text{-}day)^{-1}$
	(oral)	8.5 E-3 $(mg/kg\text{-}day)^{-1}$

[Calculated by OEHHA (1997) from rat kidney tumor incidence data (Azar *et al.*, 1973) using a linearized multistage procedure.]

III. CARCINOGENIC EFFECTS

Human Studies

Epidemiological studies and case reports of people occupationally exposed to lead provide some evidence of carcinogenicity but are not convincing due to lack of controlling for confounders such as smoking and to the simultaneous exposure of some workers to known human carcinogens including arsenic and cadmium. These studies have been reviewed by several agencies (IARC, 1980; U.S. EPA, 1986; 1989a; 1989b; ATSDR, 1990).

The epidemiologic study by Selevan *et al.* (1985) suggested that human cancer may be induced in the same organ in which cancer is induced in animals. A cohort of 1,987 lead smelter workers was studied. The study confirmed previous reports of occupationally-induced, chronic, fatal renal disease after long term exposure to lead and yielded a Standardized Mortality Ratio (SMR) of 204 for kidney cancer, but the numbers were small (6 cases observed) and the SMR for kidney cancer was not statistically significant.

Recently the study has been updated to include 11 years of follow-up and 363 additional deaths (Steenland *et al.*, 1992). No additional deaths from nonmalignant kidney disease had occurred but 3 additional deaths from kidney cancer had occurred. The updated SMR from kidney cancer was 193 (9 total kidney cancer deaths, 95% confidence interval (CI = 0.88, 3.67), i.e., not statistically significant at the 5% level). The SMR for kidney cancer for those with the highest lead exposure was statistically significant (SMR = 239 based on 8 cancers, 95% CI = 1.03, 4.71). The study suffers from lack of detailed data on lead exposure levels and from potential confounding exposures to cadmium, arsenic, and tobacco smoke.

In an epidemiologic study of 7,121 deceased California plumbers and pipefitters, Cantor *et al.* (1986) found increased cancer incidence for all neoplasms and for cancers of several sites including the respiratory system, kidney, and stomach. In addition to lead, these workers were exposed to carcinogens such as asbestos and chromium. Since excess mesotheliomas were observed (16 observed, 2 expected), asbestos exposure likely contributed to the observed increase in stomach and respiratory system cancer. Asbestos, chromium, and cigarette smoking are likely contributors to lung cancer but are not generally considered causes of kidney cancer.

There are 2 case reports of renal cancer in men occupationally exposed to toxic levels of lead (Baker *et al.*, 1980; Lilis, 1981). Baker *et al.* (1980) thought that the histology in the renal tumor in their case report was similar to that of kidney tumors in lead-exposed animals. Despite the long history of human lead exposure and the chronic nephropathy induced by lead, the data on lead-induced, human renal cancer is not definitive.

In regard to induction of cancer in organs other than the kidney, the largest occupational cohort studied for lead-induced cancer included approximately 6,800 employees of 6 lead smelters and recycling plants and 10 battery manufacturing plants in the United States (Cooper and Gaffey, 1975; Cooper, 1976; Kang *et al.*, 1980; Cooper, 1981; Cooper *et al.*, 1985; Cooper, 1988). Statistically significant increases in cancer have been reported for total malignant neoplasms in lead production workers (Cooper and Gaffey, 1975), total malignant neoplasms and cancers of both the digestive tract and the respiratory tract in lead production workers and in battery workers (Kang *et al.*, 1980), no sites (Cooper, 1981; 1988), and total malignancies in the battery workers (Cooper at al., 1985) principally due to cancers of the respiratory and digestive tracts. In these studies several factors including cigarette smoking could not be ruled out as confounders.

Ades and Kazantzis (1988) studied 4,293 men at a zinc-lead-cadmium smelter in Great Britain. An effect of lead exposure on lung cancer was noted but lead exposure was highly correlated with exposure to arsenic, a known respiratory carcinogen, and no data on cigarette smoking were reported.

Fu and Boffetta (1995) have conducted a meta-analysis of the published studies on cancer and workplace exposures to inorganic lead compounds. The studies include the 2 case reports, 16 papers dealing with cohort studies, and 7 papers dealing with case-control studies. The meta-analysis showed a statistically significant, excess relative risk of cancer overall (RR = 1.11, 95% CI = 1.05-1.17), of stomach cancer (RR = 1.33, CI = 1.18-1.49), of lung cancer (RR = 1.29, CI = 1.10-1.50), and of bladder cancer (RR = 1.41, CI = 1.16=1.71). The relative risk for kidney cancer did not reach statistical significance (RR = 1.19, CI = 0.96-1.48). A separate analysis of studies involving workers heavily exposed to lead found higher relative risks for stomach cancer (RR = 1.50, CI = 1.23-1.43, based on 4 studies) and lung cancer (RR = 1.42, CI = 1.29-1.62, based on 4 studies). The meta-analysis is further indication of a relationship between lead exposure and cancer, but it is limited by the paucity of information in the various studies on confounders such as cigarette smoking, dietary habits, and other occupational carcinogens at many of the workplaces studied (Fu and Boffetta, 1995).

There are corroborative findings relevant to the potential of lead to be both an initiator and a promoter of carcinogenicity (Goyer, 1992). Results of these studies will not be discussed here.

Animal Studies

There are a large number of carcinogenicity studies in rodents in which lead compounds were administered by the oral route, either in feed or in drinking water. Although other types of tumors are occasionally seen, the principal finding has been kidney tumors, both benign and malignant, in rats. Important studies are summarized in Table 1.

No long-term studies in animals to investigate carcinogenicity due to lead inhalation have been conducted. Intratracheal instillation of lead oxide was employed in one study of cancer (Kobayashi and Okamoto, 1974). No tumors were seen in 20 hamsters after 10 intratracheal instillations of 1 mg of lead oxide, which gave a comparatively low total dose of 10 mg. In that study, however, simultaneous administration of lead with benzo[a]pyrene (10 instillations of 1 mg), which by itself also did not cause tumors, did act to produce lung tumors. Lead might be acting as a promoter or co-carcinogen for benzo[*a*]pyrene-initiated carcinogenicity.

Table 1: Kidney tumors induced by lead compounds

Author(s)	Pb Compound	Species	Sex	Route	Time[a]	Concentration	Total Lead Dose (g)	Tumor Incidence
van Esch and Kroes (1969)	subacetate	mouse	M	diet	24 mo	0.1%	2	6/26
			F			0.1%	2	2/25
van Esch and Kroes (1969)	subacetate	hamster	M, F	diet	24 mo	0.1%	7	M 0/22, F 0/24
						0.5%	35	M 0/22, F 0/24
Schroeder *et al.* (1970)	nitrate	rat	M	water	life	25 ppm	0.5	0/52
Zawirska and Medras (1968)	acetate	rat	M	po / feed	18 mo	3 mg/day,	1	58/94
			F			then 4 mg/day	1	14/32
Nogueira (1987)	acetate	rat	M	feed	6 mo	0.5%	9	0/12
						1.0%	17	9/10
Azar *et al.* (1973)	acetate	rat	F	diet	24 mo	0-2000 ppm	0-26	up to 13/20
Boyland *et al.* (1962)	acetate	rat	M	diet	12 mo	1.0%	34	15/16
Kasprzak *et al.* (1985)	subacetate	rat	M	feed	18 mo	1.0%	38	13/29
Koller *et al.* (1985)	acetate	rat	M	water	18 mo	2600 ppm	38	13/16
van Esch *et al.* (1962)	subacetate	rat	M, F	diet	24 mo	0.1%	10	M 5/12, F 6/13
			M, F			1.0%	97	M 6/7, F 7/9
					24 mo			
Mao and Molnar (1967)	subacetate	rat	M	diet	life	1.0%	97	31/40

[a] Time is in months unless otherwise noted.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The U.S. EPA, IARC, and the State of California have all determined that, based on animal studies, lead is a carcinogen. The relevant animal studies have been reviewed by U.S. EPA and IARC (IARC, 1980; 1987; U.S. EPA, 1986; 1989a; 1989b). U.S. EPA has classified lead and lead compounds in class B2, probable human carcinogens. This conclusion is based on sufficient animal evidence and inadequate human evidence. IARC has concluded: "There is sufficient evidence that lead subacetate is carcinogenic to mice and rats and that lead acetate and lead phosphate are carcinogenic to rats." There are inadequate human data. IARC classifies lead in Group 2B, possibly carcinogenic to humans.

The quantitative cancer risk assessment is based on the best available animal data set for risk assessment, male rat kidney tumors. The U.S. EPA Air Quality Criteria for Lead document (U.S. EPA, 1986; 1989a) examined lead's carcinogenicity but it also did not contain a formal quantitative risk assessment. OEHHA relied extensively on these U.S. EPA documents in the preparation of its quantitative cancer risk assessment.

Methodology

A large number of animal studies have shown kidney tumors following oral exposure to lead compounds (Tables 1), but there are no studies of carcinogenicity due to lead inhalation. The best tumor dose-response data for use in quantitative cancer risk assessment are those of Azar *et al.* (1973). In the Azar *et al.* study, lead as lead acetate was given to groups of male and female rats in the feed at concentrations of 0, 10, 50, 100, 500, 1000, and 2000 ppm (nominal concentrations) for 2 years. Kidney tumors, mainly adenomas, were seen in a dose-dependent relationship in the 3 highest dose groups in males. Tumors were also seen in the 2000 ppm dose group in females (7/20 or 35%). Cancer risk at ambient levels was estimated by extrapolating at least 5 orders of magnitude from these data by means of the best fitting linearized multistage model.

The data used to calculate cancer risk from the rat kidney tumors (Azar *et al.*, 1973) are given in Table 2. Doses were first converted to human equivalent doses (HED) (Anderson *et al.*, 1983). Using the computer software GLOBAL86 (Howe *et al.*, 1986), a linearized multistage model was fit to the male kidney tumor dose-response data. The male rat kidney tumor data yielded a maximum likelihood estimate (MLE) for q_1 (the linear or slope term, which relates the probability of cancer to the dose of carcinogen administered in the equation for the multistage model) of 0 $(mg/kg/day)^{-1}$, an MLE for q_2 of $2.5 \times 10^{-3} (mg/kg/day)^{-2}$, and an Upper 95% Confidence Limit (UCL) on q_1 (also known as q_1^* and as the cancer potency) of 8.5×10^{-3} $(mg/kg/day)^{-1}$.

Available human data indicate that approximately 50% of inhaled lead is absorbed compared to approximately 10% of ingested lead (summarized by Owen, 1990). If the percentage of lead absorbed by inhalation is similar for rats and humans and if the standard assumption that an average adult human has a body weight of 70 kg and an average air intake of 20 m^3 per day is used, an oral intake of 1 mg/kg/day lead is equivalent to an inhalation exposure of 3,500 $\mu g/m^3$ for 24 hr. Using

the latter units, the 95% UCL for q_1 equals 2.4×10^{-6} $(\mu g/m^3)^{-1}$, which assumes equivalent absorption by the 2 routes. If there is approximately 5 times higher absorption by the respiratory tract compared to the gastrointestinal tract (Owen, 1990), the inhalation risk can be multiplied by 5 and the corrected inhalation unit risk is 1.2×10^{-5} $(\mu g/m^3)^{-1}$.

To derive a range of risks, the study by Koller *et al.* (1985), which showed the greatest sensitivity to lead's carcinogenicity, was selected. In that study, 13 out of 16 male rats drinking water containing 2600 ppm lead acetate developed renal tumors, compared to 0 of 10 in controls. The resulting human equivalent dose (HED) was calculated as 60.1 mg/kg-day. Using the GLOBAL86 program, an MLE for q_1 of 0.0279 $(mg/kg\text{-}day)^{-1}$ and a 95% UCL, q_1^* of 0.0455 $(mg/kg\text{-}day)^{-1}$ were obtained. The latter potency was divided by 3500 to obtain a preliminary inhalation unit risk of 1.3×10^{-5} $(\mu g/m^3)^{-1}$, which, when corrected for the 5-fold greater absorption by inhalation compared to ingestion in humans (Owen 1990), yielded a final inhalation unit risk of 6.5×10^{-5} $(\mu g/m^3)^{-1}$.

Therefore, the 95% UCL obtained for the range of inhalation unit risks is 1.2×10^{-5} $(\mu g/m^3)^{-1}$ to 6.5×10^{-5} $(\mu g/m^3)^{-1}$. The best value of the cancer unit risk for air was selected as 1.2×10^{-5} per $\mu g/m^3$.

Table 2: Kidney tumors in rats fed lead[a]

Lead in food (ppm)		Animal dose (mg/kg-day)	HED[b] (mg/kg-day)	Number of rats[c]		%	% died
Added	Measured			exp[d]	tumors		
0	3	0.225	0.038	20[f]	0	0	50
0	5	0.39	0.067	100	0	0	37
10	18	1.40	0.238	50	0	0	36
50	62	4.78	0.818	50	0	0	36
100	141	10.88	1.86	50	0	0	36
500	548	42.27	7.22	50	5	10	52
1000[e]	1130	79.65	13.6	20[f]	10	50	50
2000[e]	2102	162	27.2	20[f]	16	80	80

[a] Data from Azar *et al.* (1973).
[b] Human Equivalent Dose = daily dose $\times (70/0.35)^{1/3}$.
[c] Among similar size groups of female rats, kidney tumors were seen only in 7 of 20 animals in the 2000 ppm group.
[d] Number of animals exposed to indicated level of lead in food.
[e] The rate of body weight gain was depressed in both groups. Since mortality was not increased in the 1000 ppm group, it can be considered a Maximally Tolerated Dose (MTD).
[f] The groups with only 20 rats per dose level were also studied for 2 years but were begun several months after the other dose groups.

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LINDANE (γ-Hexachlorocyclohexane)

CAS No: 58-89-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	290.9
Boiling point	323.4°C
Melting point	113°C
Vapor pressure	9.4E-6 mm Hg @ 20°C
Air concentration conversion	1 ppm = 11.9 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.1E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.1 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor reported by US EPA (1987)]

III. CARCINOGENIC EFFECTS

Human Studies

The International Agency for Research on Cancer (IARC) concluded in 1987 that the evidence for carcinogenicity of hexachlorocyclohexane (HCH; all isomers) was inadequate in humans. Several case reports suggest an association between lindane exposure and leukemia, aplastic anemia, liver cancer, soft-tissue sarcomas, and lung cancer (IARC, 1987). In all of these case reports, the exposures are not well documented. In addition, exposures to other chemicals, including some pesticides, probably occurred in these cases.

Animal Studies

Wolff *et al*. (1987) reported on the carcinogenic effects of lindane in several strains of mice. Female yellow, black, and pseudoagouti mice (36-96 per group) were exposed to 0 or 160 ppm lindane in the diet for up to 24 months. Different response rates were observed between strains, indicating significant genetic variability in response to lindane. In yellow mice, a significant increase in the incidence of lung and liver tumors was observed (Table 1). The higher incidence of tumors in the obese yellow mice indicate that bioaccumulation of lindane in obese animals may influence carcinogenicity.

Thorpe and Walker (1973) showed an increase in liver tumors of male CF1 mice fed 400 ppm lindane for 110 weeks, compared with controls. The time-weighted dose was estimated as 52 mg/kg/day by US EPA (1988). In this experiment, control mice exhibited an incidence of 11/45 for liver tumors, compared to 27/29 for the 52 mg/kg/day group.

Table 1. Tumor incidence in yellow mice exposed to γ-HCH (lindane) (Wolff *et al*., 1987)

Dietary Concentration of γ-HCH (ppm)	Tumor Type and Incidence	
	Lung Carcinomas	Liver Adenomas
0	4/95	8/93
160	18/95	33/94

A study by Goto *et al*. (1972) showed a positive effect of lindane on cancer in mice. However, this experiment used only 10 animals per treatment group and was of a short duration. The NCI (1977) study on male mice showed a significant increase in cancer incidence in mice exposed to 80, but not 160 ppm γ-HCH. The absence of a clear dose-response precluded this data from use in determining the cancer potency for lindane.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The US EPA (1988) selected the study by Thorpe and Walker (1973) as the basis for the cancer potency for lindane. This was considered to be the best study for development of a cancer potency factor for lindane because of the large sample size of mice surviving for a full lifespan, and the large numbers of tumors in the treatment group. Thorpe and Walker (1973) showed an increase in liver tumors in male CF1 mice fed 400 ppm lindane in the diet for 110 weeks, compared with controls. Control mice exhibited an incidence of 11/45 for liver tumors, compared to 27/29 for the lindane-treated group ($p < 0.01$). Some lung metastases were also reported in the male and female mice treated with lindane.

Methodology

A linearized multistage procedure was used to estimate the cancer potency of lindane from the Thorpe and Walker (1973) data in male CF1 mice (Crump *et al*., 1982). The concentrations of lindane given in the feed were 0 or 160 ppm. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for lindane.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 1.1 $[mg/kg\text{-}day]^{-1}$ was reported (US EPA, 1987). An airborne unit risk factor of 3.1E-4 $(\mu g/m^3)^{-1}$ was calculated from the q_{human} value by OEHHA/ATES using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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METHYL *TERT*-BUTYL ETHER (MTBE)

CAS No: 1634-04-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 2001)

Molecular weight	88.15
Boiling point	55.2°C
Melting point	-108.6°C
Vapor pressure	250 mm Hg at 25°C
Air concentration conversion	1 ppm = 3.6 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.6 E-7 $(\mu g/m^3)^{-1}$
Slope Factor: 1.8 E-3 $(mg/kg\text{-}day)^{-1}$
[Cancer slope factor (CSF) derived by OEHHA (1999a) from the geometric mean of the potency estimates obtained for male rat kidney adenomas and carcinomas (Chun *et al*. 1992), male rat Leydig interstitial cell tumors and female rat leukemia and lymphomas (Belpoggi *et al*. 1995, 1998) using potency values derived from the lower 95% confidence limit on the 10% tumor dose (LED_{10}) with pharmacokinetic adjustments; inhalation unit risk factor derived from the CSF by OEHHA (1999b).]

III. CARCINOGENIC EFFECTS

Human Studies

No studies regarding the carcinogenic effects of human exposure to MTBE were found in an earlier search by ATSDR (1996) or more recently by OEHHA (1999a).

Animal Studies

Oral

Male and female Sprague-Dawley rats (60/sex/group) were exposed to MTBE by gavage at doses of 0, 250 or 1,000 mg/kg body weight/day, four days/week for 104 weeks (Belpoggi *et al*., 1995, 1997, 1998). Animals were maintained until natural death; the last animal died at 174 weeks of age. A dose-related increase in the combined incidence of lymphomas and leukemia was observed in female rats (Table 1). The authors reported that the increase was highly significant ($p < 0.01$) in the high-dose group and marginally significant in the low-dose group, when analyzed using a log-ranked test. When analyzed using the Fisher exact test, the combined incidence of lymphomas and leukemia in high-dose females was significantly different from controls at the $p = 0.001$ level. Historical control incidence rates in this laboratory for lymphomas and leukemias (combined) was < 10% in female Sprague-Dawley rats (Belpoggi *et al*., 1995). Testicular Leydig cell tumor incidence was also significantly increased [$p = 0.05$, using a prevalence analysis for nonlethal tumors (Hoel and Walburg 1972)] in high-dose males.

Table 1: Tumors in Sprague-Dawley Rats exposed to MTBE by gavage (Belpoggi *et al*., 1995, 1997, 1998)

Tumor site	Tumor type	Tumor incidence Dose (mg/kg/day)		
Females		0	250	1000
Hemolymphoreticular tissues (including mesenteric lymph nodes)	Lymphomas and leukemias (Belpoggi *et al*., 1995)	2/58[b] (3.4%)	6/51[b] (11.8%)	12/47[b,c,d, e] (25.5%)
	Lymphomas and leukemias of lymphoid origin (Belpoggi *et al*., 1998)	2/58[b] (3.4%)	7/51[b] (13.7%)	12/47[b,d,e] (25.5%)
Males				
Testes	Leydig interstitial cell tumors (Belpoggi *et al*., 1995)	2/26[f] (7.7%)	2/25[f] (8.0%)	11/32[f, g, h] (34.4%)
	Leydig interstitial cell adenomas (Belpoggi *et al*., 1998)	3/26[f] (11.5%)	5/25 [f] (20.0%)	11/32[f, h] (34.4%)

[a] Administered in olive oil, four days per week, for 104 weeks.
[b] Number of lesion-bearing animals/total alive at 56 weeks of age, when the first leukemia was observed.
[c] Incidence relative to control group was significant ($p < 0.01$) using a log-ranked test (Mantel 1966, Cox 1972), as reported by Belpoggi *et al*. (1995).
[d] Incidence relative to control group was significant by the Fisher exact test ($p = 0.001$).
[e] Dose-related trend was significant by the Cochran-Armitage trend test ($p < 0.01$).
[f] Number of lesion-bearing animals/total alive at 96 weeks of age, when the first Leydig cell tumor was observed.
[g] Incidence relative to control group was significant ($p = 0.05$) level using prevalence analysis for nonlethal tumors (Hoel and Walburg 1972), as reported by Belpoggi *et al*. (1995).
[h] Incidence relative to control group was significant by the Fisher exact test ($p < 0.05$).

A pathology review was later published (Belpoggi *et al*., 1998) in which slides from the original study were re-examined, and diagnostic criteria reviewed. This was undertaken by an independent panel of the Cancer Research Centre (where the study authors were based), assisted by an outside pathologist. Tumor incidences according to the review are also presented in Table 1. Both observed types of tumor were reexamined:

Testicular tumors: Diagnosis was carried out according to criteria developed by the National Toxicology Program (NTP), and adenomas and hyperplasia were reported separately. In addition, adenomas were further characterized as having single or multiple histiotypes, and the number of

multifocal adenomas in each dose group was reported. The results confirmed the diagnosis of the Leydig cell tumors as adenomas, as initially reported. According to the NTP diagnostic criteria, the incidence of Leydig cell adenomas was 3, 5, and 11 in the control, low- and high-dose groups, respectively, compared to the originally reported incidences of 2, 2, and 11 in control, low- and high-dose animals. The review indicated that all four multifocal adenomas observed occurred in the high-dose group. No dose-related increase in atrophy or testicular tissue degeneration was observed. Therefore, the tumors were not considered likely to be secondary to cell death.

Lymphoid tumors: The cell type of origin and tumor sites were reported. All neoplasms were of lymphoid origin. Corrected incidences were 2, 7 and 12 in the control, low- and high-dose groups, respectively, compared to the previously reported incidence data of 2, 6 and 12 in the same groups. Cancers were classified as lymphoblastic lymphomas, lymphoblastic leukemias and lymphoimmunoblastic lymphomas. The latter category was the most prevalent, accounting for 1, 6 and 8 of the tumors observed in the respective dose groups. The data on site distribution indicated that most animals with lymphoid cancers were affected at multiple sites. The tissues involved in treated animals were lung, liver, spleen and lymph node, and "other", with the lung being the most commonly affected site in treated animals.

Inhalation

Male and female Fischer 344 rats (50 animals/sex/group) were exposed to target concentrations of 0, 400, 3000, or 8000 ppm MTBE by inhalation (actual concentrations of 403, 3023, or 7977 ppm) (Chun *et al*., 1992; Bird *et al*., 1997). The animals were exposed for 6 hours/day, 5 days/week for 24 months, except for the mid- and high-dose males, which were terminated at 97 and 82 weeks, respectively, due to a dose-dependent increased mortality rate from chronic progressive nephropathy. Low-dose males also experienced an increase in nephropathy that was associated with a slight increase in mortality and a decrease in survival. Survival times for females were not significantly different between exposed and control rats. However, there were slightly more deaths due to chronic progressive nephropathy in the mid- and high-dose females than in the low-dose and control females. Exposure-related increases in kidney and liver weights were reported in mid- and high-dose females, but not in males. Chun *et al*. (1992) concluded that the maximum tolerated dose (MTD) was exceeded in both sexes at high- and mid-dose levels, based on increased mortality. Other observed effects of MTBE exposure included anesthetic effects in rats of both sexes in the mid- and high-dose groups.

A detailed histopathology examination was performed on all animals in the control and high-dose groups, and on all animals that died or were sacrificed moribund. Only a limited histopathology examination was performed on non-moribund animals from the low- and mid-dose groups that survived to terminal sacrifice; for males, only the liver, kidneys, testes and gross lesions were evaluated, while for females, only the liver and gross lesions were examined microscopically (Bird *et al*. 1997).

At the request of the MTBE Task Force, Experimental Pathology Laboratories, Inc. (1993) reevaluated the histopathologic slides of kidneys from all male and female rats used in the Chun *et al*. (1992) study, and confirmed the study pathologist's conclusion that MTBE increased the severity of chronic progressive nephropathy in rats of both sexes. No histopathologic reevaluation

of the kidney tumors was performed. In males, a statistically significant increase in renal tubular adenoma and carcinoma combined) was observed in the mid-dose group (Table 2). In high-dose males renal tubular adenomas were increased, however, this increase did not reach statistical significance (Table 2). The sensitivity of the bioassay to detect a dose-related increase in renal tumors in the high-dose group is likely to have been reduced by the high rate of early mortality, and the early termination of this treatment group at week 82. Despite the reduced sensitivity of the bioassay, a statistically significant increase in Leydig interstitial cell testicular tumors was observed in mid- and high-dose males, with a clear dose-response evident (Table 2). Historical laboratory control values for Leydig testicular tumors in Fischer rats ranged from 64 to 98% (Bird *et al*. 1997).

Table 2: Tumor incidence in male Fischer 344 rats exposed to MTBE by inhalation (Chun *et al*., 1992; Bird *et al*., 1997)

Tumor site and type		Concentration (ppm)			
		0	400	3000	8000
Kidney	renal tubular adenoma	1/35[c]	0/32[c]	5/31[c]	3/20[c]
	renal tubular carcinoma	0/35[c]	0/32[c]	3/31[c]	0/20[c]
	renal tubular adenoma and carcinoma (combined)	1/35[c]	0/32[c]	8/31[c,d]	3/20[c]
		(3%)	(0%)	(26%)	(15%)
Testes	Leydig interstitial cell tumors	32/50	35/50	41/50[e]	47/50[f]
		(64%)	(70%)	(82%)	(94%)

[a] Mid- and high-dose animals were terminated at 97 and 82 weeks, respectively, due to a dose-dependent increased mortality rate from chronic progressive nephropathy.
[b] Administered as MTBE vapor six hours per day, five days per week.
[c] Survival-adjusted tumor incidence rates were used to attempt to control for excess early mortality in the mid- and high-dose groups (US EPA, 1995c).
[d, e, f] Incidence relative to control group was significant by the Fisher Exact test ([d] $p < 0.01$, [e] $p < 0.05$, [f] $p < 0.001$).

In female Fischer 344 rats exposed to MTBE vapor, a single rare renal tubular cell adenoma was observed in one mid-dose animal; no treatment-related increases in tumor incidence were observed (Chun *et al*. 1992, Bird *et al*. 1997). However, MTBE treatment of females was associated with several nonneoplastic kidney lesions. Both female and male rats exposed to MTBE experienced a dose-related increase in mortality from chronic progressive nephropathy. Increases in microscopic kidney changes indicative of chronic nephropathy were seen in all treated males and in mid- and high-dose females. All treated males had increases in the severity of mineralization and interstitial fibrosis of the kidney, while increases in mild to moderate glomerulosclerosis, interstitial fibrosis, and tubular proteinosis were observed in females.

Groups of 50 male and 50 female eight-week old CD-1 mice were exposed to 0, 400, 3000 or 8000 ppm MTBE vapor by inhalation (corresponding to analytical mean concentrations of 402, 3014 or 7973 ppm or 1442, 10816, or 28843 mg/m^3) (Burleigh-Flayer *et al*., 1992; Bird *et al*., 1997). The animals were exposed for six hours/day, five days/week for 18 months. Increased mortality and decreased mean survival time were observed only for male mice in the high-dose group. A slightly

increased frequency of obstructive uropathy, a condition that occurs spontaneously in this mouse strain, was observed in high-dose males. However, deaths due to the condition were within the range noted for historical controls. Body weight gain and absolute body weights were decreased in high-dose males and females. Dose-dependent increases in liver weights were observed in both sexes. Kidney weights were increased in high-dose females and in low- and mid-dose males.

Burleigh-Flayer *et al*. (1992) concluded that the MTD was exceeded in both sexes at the high-dose level. Other observed effects of MTBE exposure included anesthetic effects in mice of both sexes in the mid- and high-dose groups.

A detailed histopathology examination was performed on all animals in the control and high-dose groups, and on all animals that died or were sacrificed moribund. Only a limited histopathology examination was performed on non-moribund animals from the low- and mid-dose groups that survived to terminal sacrifice; for males, only the liver, spleen and submandibular lymph nodes were evaluated, while for females, only the liver, uterus and stomach were examined microscopically (Bird *et al*. 1997).

In females, a statistically significant increased incidence of hepatocellular adenomas was observed in the high-dose group (Table 3). The incidence of hepatocellular adenomas and carcinomas (combined) was also increased in high-dose females; however, only two hepatocellular carcinomas were reported, one each in the low- and high-dose groups. In males, a statistically significant increase in hepatocellular carcinomas was observed in the high-dose group (Table 3). Bird et al. (1997) noted that the combined incidence of adenomas and carcinomas in high-dose males was similar to the historical incidence for male CD-1 mice of 33%. However, after correcting for the number of animals alive at 49 weeks, when the first hepatocellular adenoma was observed in males, the incidence in the high-dose group was 43%
(16/37, see Table 3), representing a clear increase above the cited historical incidence in male CD-1 mice. Burleigh-Flayer et al. (1992) concluded that the increased incidence of liver tumors in the high-dose groups (adenomas in females and carcinomas in males) could be attributed to MTBE exposure. The ability of this study to detect increases in tumor incidence was likely decreased by the shortened study length (18 versus 24 months).

Table 3: Tumor incidence in CD-1 mice exposed to MTBE by inhalation (Burleigh-Flayer *et al*. 1992, Bird *et al*. 1997)

Tumor site and type	Dose[b] (ppm)			
	0	400	3000	8000
Females				
Liver hepatocellular adenoma	2/50	1/50	2/50	10/50[c]
hepatocellular carcinoma	0/50	1/50	0/50	1/50
hepatocellular adenoma and carcinoma (combined)	2/50	2/50	2/50	11/50[d]
Males				
Liver hepatocellular adenoma	11/47[e]	11/47[e]	9/46[e]	12/37[e]
hepatocellular carcinoma	2/42[f]	4/45[f]	3/41[f]	8/34[c,f]
hepatocellular adenoma and carcinoma (combined)	12/47[e]	12/47[e]	12/46[e]	16/37[e]

[a] Male mice in the high-dose group experienced early mortality.
[b] Administered as MTBE vapor six hours per day, five days per week.
[c,d] Incidence relative to control group was significant by the Fisher Exact test ([c] $p < 0.05$, [d] $p < 0.01$).
[e] Number of lesion-bearing animals per total alive at 49 weeks, when the first hepatocellular adenoma was observed.
[f] Number of lesion-bearing animals per total alive at 63 weeks, when the first hepatocellular carcinoma was observed.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

No human studies suitable for derivation of a cancer potency for MTBE have been reported. However, there is evidence for the carcinogenicity of MTBE at multiple sites in both sexes of rats (oral and inhalation exposure) (Chun *et al*., 1992; Belpoggi *et al*., 1995, 1997, 1998; Bird *et al*., 1997) and mice (inhalation exposure) (Burleigh-Flayer *et al*. 1992; Bird *et al*., 1997). These studies provide data from which cancer potency values can be derived.

Methodology

OEHHA (1999a) derived cancer slope factors (CSFs) from the rat oral and inhalation exposure (Chun *et al*., 1992; Belpoggi *et al*., 1995, 1997, 1998; Bird *et al*., 1997) and mouse inhalation exposure (Burleigh-Flayer *et al*. 1992; Bird *et al*., 1997) tumor incidence data (Table 4). The CSF is a potency value derived from the lower 95% confidence limit on the 10% dose that is predicted to give a 10% tumor incidence (LED_{10}). A multistage polynomial was used to fit data in the observable range. The CSF is equal to $0.1/LED_{10}$, in units of $(mg/kg\text{-}day)^{-1}$. For the curve fitting to estimate the LED_{10}, a $p \geq 0.05$ criterion for the Chi-squared goodness of fit statistic of the optimized polynomial was employed. Interspecies scaling for oral doses (and internal doses calculated from a single-species pharmacokinetic model) was based on $(body\ weight)^{3/4}$.

For inhalation exposures OEHHA and other risk assessors have in the past used an assumption of equivalence between different species of exposures to a given atmospheric concentration. This provides roughly similar scaling in effect, due to the way that breathing rate and related parameters affecting uptake scale with body weight. More recently, physiologically-based pharmacokinetic (PBPK) modeling has been seen as a preferable approach to both dose estimation and interspecies scaling of inhalation exposures, where data are available to support this. Since pharmacokinetic data are available for MTBE in the rat, the modeling approach was feasible in this case for that species only.

Due to the lack of a clear mode of action of TBA or other MTBE metabolites in MTBE-induced carcinogenesis in experimental animals, OEHHA treated the parent compound MTBE as the cause of the observed effects in animal studies for the purpose of determining dose metrics. In order to estimate internal doses of MTBE, in addition to simple continuous applied doses, a simplified PBPK model was employed. This model was based on both the Borghoff *et al*. (1996a) model, in that it has five compartments for MTBE and five compartments for TBA, and the Rao and Ginsberg (1997) model with its MTBE metabolic parameters and slowly perfused compartment/blood partition coefficient for TBA. The PBPK model employs compartments loosely representing "Fat, Liver, Kidneys, Muscle, and rapidly perfused tissues termed as Vessel Rich Group (VRG)". The model's fundamental structure was based on that developed by Hattis *et al*. (1986) for perchloroethylene and was formulated in Stella software (ithink v. 3.0.6b for the Power Macintosh, High Performance Systems Inc., Hanover, New Hampshire 03755). The model units for the whole animal were moles, L, moles/L, hour, moles/hour, L/hour, and ppm in alveolar air. Simulations of up to 32 hours were run at approximately 1,000 steps per simulated hour, using the Runge-Kutta four computation method. The model parameters were obtained from Borghoff *et al*. (1996a) or Rao and Ginsberg (1997). In addition to simulations of the pharmacokinetic data of Miller *et al*. (1997) with a model 0.22 kg rat, simulations of cancer bioassay doses were conducted assuming 0.35 kg for female and 0.5 kg for male lifetime average body weights. Physiological and metabolic parameters were scaled to these body weights as described in Borghoff *et al*. (1996a).

The data for kidney tumors in the high dose (8,000 ppm) male rats in the study by Chun *et al*. (1992) were excluded so that an adequate fit could be obtained. Results in the inhalation studies (Chun *et al*. 1992, Burleigh-Flayer *et al*. 1992) were effectively the same (within a factor of two) for the different sites in rats and mice, except that the potency for testicular interstitial cell tumors in male rats is about five times higher (Table 4a). Comparison between different routes and experiments for the rat was facilitated by examining the data calculated using the pharmacokinetic model to convert the inhalation exposures to equivalent oral doses. In this case it was apparent that all the results are comparable, with the testicular interstitial cell tumors in the Chun *et al*. (1992) males again showing a slightly higher value than those found at other sites or in the testis in the Belpoggi *et al*. (1995, 1997, 1998) oral study.

Carcinogen risk assessment guidelines used by OEHHA normally recommend selection of human cancer potency estimates based on the most sensitive site and species, unless there is evidence to indicate that the most sensitive site(s) are not relevant to human cancer induction, or represent data sets with unusually wide error bounds. As an alternative, where several equally plausible results

are available and are sufficiently close to be regarded as concordant, the geometric mean of all such estimates may be used.

Pharmacokinetic modeling, which would allow the comparison of different routes and correct for nonlinearities in the relationship between applied and internal dose, was not available for the mouse. Therefore, the potency estimates obtained in the rat were preferred for risk assessment purposes. Because the results in rats and mice are comparable, the use of the rat data was consistent with the policy of selecting appropriately sensitive species as the basis for the estimate of potency in humans.

Table 4: Dose Response Parameters for MTBE Carcinogenicity Studies

a) Inhalation studies - ppm in air as dose metric

Species	Sex	Tumor site and type	LED_{10} (ppm)	CSF (ppm^{-1})
mouse[a]	female	hepatocellular adenoma + carcinoma	320	3.2×10^{-4}
	male	hepatocellular adenoma + carcinoma	140	7.0×10^{-4}
rat[b]	male	renal tubular cell adenoma + carcinoma	240	4.2×10^{-4}
		testicular interstitial cell tumors	46	2.2×10^{-3}

[a] Burleigh-Flayer *et al*. 1992, Bird *et al*. 1997
[b] Chun *et al*., 1992; Bird *et al*., 1997.
Assumed: Data reassessment by U.S. EPA (1994c, 1995c).
Duration correction based on $(t_e/t_l)^3$: t_l = 104 weeks for both rats and mice.
Interspecies correction: ppm equivalency.

b) Rat oral and inhalation studies - Equivalent oral dose as dose metric

Route	Sex	Tumor site and type	LED_{10} (mg/kg-day)	CSF $(mg/kg/day)^{-1}$
Inhalation[a]	Male	Male renal tubular cell adenoma + carcinoma	55	1.8×10^{-3}
		Testicular interstitial cell tumors	11	8.7×10^{-3}
Gavage[b]	Male	Leydig cell tumors		
		Original 1995 report	76	1.38×10^{-3}
		Revised 1998 data	64	1.55×10^{-3}
	Female	Leukemia/lymphoma		
		Original 1995 report	49	2.03×10^{-3}
		Revised 1998 data	48	2.09×10^{-3}

[a] Chun *et al*., 1992.
[b] Belpoggi *et al*., 1995, 1998.
Assumed: Data reassessment by U.S. EPA (1994c, 1995c) for Chun *et al*. (1992) study.
Table 4 (continued): Dose Response Parameters for MTBE Carcinogenicity Studies

Duration correction based on $(t_e/t_l)^3$: t_l = 104 weeks for rats.

Interspecies correction: $BW^{3/4}$.

In terms of the relevance to human cancer and the mechanism of the observed effects, the results of the studies by Chun *et al*. (1992) and Burleigh-Flayer *et al*. (1992) are limited by the relatively severe mortality seen in the highest dose groups, and the less-than lifetime exposure given the mice and the male rats. These experimental flaws are not so severe as to exclude the use of the data in risk assessment, nor more prohibitive than the experimental flaws associated with many studies on other compounds that have been successfully used for this purpose. There are, however, additional problems in the case of the testicular interstitial cell tumors observed in male rats by Chun *et al*. (1992). The study authors stated that the control incidence of these tumors was lower than the historical incidence observed in animals from the colony from which these experimental animals were obtained. In view of this, the slightly divergent value for the potency estimate obtained with this data set was regarded with lower confidence than the other values obtained in this analysis, and was not included in the determination of a recommended potency.

In view of the closeness of the other values obtained in the rat, and their similar confidence levels, the preferred value for the cancer potency was therefore the geometric mean of the potency estimates obtained for the male rat kidney adenomas and carcinomas combined (1.8×10^{-3} (mg/kg-day)$^{-1}$) (Chun *et al*. 1992), and the male rat Leydig interstitial cell tumors (1.55×10^{-3} (mg/kg-day)$^{-1}$) and the leukemia and lymphomas in female rats (2.09×10^{-3} (mg/kg-day)$^{-1}$) (Belpoggi *et al*. 1995, 1998) (Table 4b). The combined use of these data yields an estimated CSF of 1.8×10^{-3} (mg/kg-day)$^{-1}$.

Since a pharmacokinetic model was not available for MTBE uptake, distribution and metabolism in humans, default assumptions were used to extrapolate from risk estimates in the experimental animals (rats) to the human situation. The CSF was calculated as an "oral equivalent" potency, in mg/kg-day. It is assumed that low oral doses would be essentially 100% absorbed, so no correction is required when this potency is used to estimate risks from oral exposures. However, in order to estimate risks from inhalation exposures it is necessary to have an estimate of the percentage uptake of inhaled MTBE at low atmospheric concentrations. OEHHA (1999b) assumed that humans absorb 50% of inhaled MTBE at low doses. This estimate is derived primarily from the 42 to 49% respiratory uptake observed among 10 healthy male volunteers inhaling 5 to 50 ppm for 2 hours (Nihlen *et al.,* 1998). This represents a small study of short duration exposures to relatively high concentrations of MTBE, and respiratory uptake among humans inhaling low concentrations for long periods is unknown. As absorption at low concentrations may in some cases be greater than that at higher concentrations, the assumption of 50% absorption should be viewed as a best estimate rather than an upper-bound estimate or health-protective assumption.

On this basis, and assuming a 70 kg human inhaling 20 m^3 per day, the oral CSF described above was converted to an inhalation potency estimate (cancer unit risk factor or URF) of 9.3×10^{-7} ppb^{-1}, or 2.6×10^{-7} ($\mu g/m^3$)$^{-1}$ (OEHHA, 1999b).

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4, 4'-METHYLENE BIS(2-CHLOROANILINE) (MOCA)

CAS No: 101-14-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	267.15
Boiling point	not available
Melting point	110°C
Vapor pressure	1.3×10^{-5} mm Hg at 60°C
Air concentration conversion	1 ppm = 10.9 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.3 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.5 E+0 $(mg/kg\text{-}day)^{-1}$
[Female beagle dog urinary bladder tumor data (Stula *et al*., 1977) , contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

IARC (1993) has reviewed several descriptive studies on the potential carcinogenic effects of 4, 4'-methylene bis(2-chloroaniline) (MOCA) in humans. An epidemiological study by Ward *et al.* (1990) examined cancer incidence in workers employed at a chemical plant in Michigan where MOCA was produced between 1968 and 1979. All 532 workers employed in 1968-79 and an additional 20 workers employed in 1980-81 who had possible exposure due to plant site contamination were included. Median duration of employment was 3.2 months. Quantitative exposure was not available; however, worker exposure may have been substantial, since worker urinary levels of MOCA several months after the end of production ranged up to 50,000 µg/l. Telephone interviews were conducted with 452 workers, and 385 participated in a urine screening examination. Three asymptomatic bladder tumors were identified. The screening procedure was supplemented for some workers with cytoscopy after a 28-year old worker was found to have a non-invasive papillary transitional-cell tumor. Low-grade papillary transitional cell carcinoma was diagnosed in 2 of 200 examined workers; one was less than 30 years old. Mean interval time from first exposure to study initiation was 11.5 years, while the latency period for most bladder carcinogens is about 20 years (Ward *et al.*, 1990). This finding increases the concern that MOCA is a human bladder carcinogen, since bladder carcinoma in young men is very uncommon. A limitation of this study was that expected numbers of bladder tumors could not be calculated, as no data exists on the incidence of bladder tumors diagnosed by cytoscopy in an asymptomatic nonexposed population.

Animal Studies

Male and female HaM/ICR mice and male Charles River CD-1 rats (25/sex/species/group) were exposed to MOCA hydrochloride in the diet for 18 months by Russfield *et al*. (1975). Mice were fed diet containing 0, 1000 or 2000 mg/kg diet MOCA hydrochloride; rats were fed diet containing 0, 500 or 1000 mg/kg diet MOCA hydrochloride. Surviving animals were killed after 24 months; about 55% of the control and treated animals were still alive at 20-22 months. Hemangiomas or hemangiosarcomas were noted in 0/10 control, 3/13 low dose and 8/20 high dose male mice; hepatomas were noted in 0/20 control, 9/21 low dose and 7/14 high dose female mice ($p < 0.01$, Fisher exact test), and in 0/22 control, 1/22 low dose and 4/19 high dose rats ($p < 0.05$, Cochran-Armitage trend test).

Male and female Charles River CD rats (50/sex/group) were fed diet containing 0 or 1000 mg/kg diet MOCA in a standard diet (23% protein) for life (Stula *et al*., 1975). Average experiment duration was 80 weeks for treated and control males, 89 weeks for female controls and 78 weeks for treated females. Six animals from each group were killed for an interim evaluation at one year. Lung carcinomas were observed in 21/44 treated males ($p < 0.05$, χ^2 test) and in 27/44 treated females ($p < 0.05$, χ^2 test); a lung squamous-cell carcinomas was also observed in one treated male and female. Pleural mesotheliomas occurred in 4/44 treated males and 2/44 treated females. Hepatocellular adenomas and carcinomas occurred in 3/44 and 3/44 treated males and 2/44 and 3/44 treated females, respectively. No lung tumors, pleural mesotheliomas or hepatocellular adenomas and carcinomas were noted in control animals.

Male Charles River CD rats were fed a "protein-adequate" diet containing 0, 250, 500 or 1000 mg/kg diet MOCA (group sizes 100, 100, 75 and 50, respectively) for 18 months followed by a 32 week observation period (Kommineni *et al*., 1979). MOCA exposure was associated with decreased survival; mean survival time was 89, 87, 80 and 65 weeks for controls, low-dose, mid-dose and high-dose animals, respectively. Dose-related increases in the incidences of lung tumors, mammary adenocarcinomas, Zymbal gland adenocarcinomas and hepatocellular carcinomas were noted. Tumor incidence data is listed in Table 1.

Table 1. 4, 4'-methylene bis(2-chloroaniline) (MOCA)-induced tumor incidence in male Charles River CD rats (Kommineni *et al*., 1979)

Tumor type	dietary MOCA (mg/kg diet)			
	0	250	500	1000
lung tumors	1/100	23/100	28/75	35/50
Zymbal gland carcinomas	1/100	8/100	5/75	11/50
mammary adenocarcinomas	1/100	5/100	8/75	14/50
hepatocellular carcinomas	0/100	3/100	3/75	18/50

Stula *et al*. (1977) exposed a group of 6 female beagle dogs to a daily dose of 100 mg MOCA by capsule 3 days/week for 6 weeks, then 5 days/week for up to 9 years. A second group of 6 females served as untreated controls. One treated dog died at 3.4 years of age because of an infection. The other animals were killed at 8.3-9 years. Transitional-cell carcinomas of the urinary bladder

occurred in 4 of 5 treated dogs ($p < 0.025$, Fisher exact test), and a composite tumor (transitional-cell carcinoma/adenocarcinoma) of the urethra was noted in one dog. No urinary tract tumors were noted in the untreated controls. Tumor incidence data is listed in Table 2.

Table 2. 4, 4'-Methylene bis(2-chloroaniline) (MOCA) -induced urinary bladder tumor incidence in female beagle dogs (Stula *et al*., 1977)

Average Dose[1] (mg/kg-day)	Tumor Incidence[2]
0	0/6
7.31	4/5

1. Doses as reported by Gold *et al*. (1984).
2. Tumor incidences as reported by Gold *et al*. (1984)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results from a number of studies using Charles River CD and Wistar rats, as well as female beagle dogs, are listed in Gold *et al*. (1984). 4, 4'-Methylene bis(2-chloroaniline) induced papillary transitional cell carcinomas of the urinary bladder in dogs, whereas the liver was the most common target site in the rat studies. Dogs are more sensitive to the carcinogenic effects of the compound than rats. The compound is similar in structure to benzidine, a human bladder carcinogen, which appears to be significantly more potent in humans than rodents. Results from the Stula *et al*. (1977) dog study are used as the basis of potency estimation, despite the small numbers of animals used, because dogs may be better predictors of human carcinogenicity of this compound than rodents (Cal/EPA, 1992). Dose-response data are listed in Table 2.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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METHYLENE CHLORIDE

CAS No: 75-09-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	84.9
Boiling point	39.7°C
Melting point	-95.1°C
Vapor pressure	400 mm Hg @ 24°C
Air concentration conversion	1 ppm = 3.47 mg/m^3@ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.0 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 3.5 E-3 $(mg/kg\text{-}day)^{-1}$
[Calculated from female mouse lung tumors (NTP, 1986; Mennear *et al.* 1988) using a linearized multistage procedure (CDHS, 1989) with high-to-low dose adjustment for saturation of mixed-function oxidase pathway (Cohn, 1987)]

III. CARCINOGENIC EFFECTS

Human Studies

Friedlander and colleagues studied male workers employed by the Eastman Kodak Company at its film-making operation in Rochester, New York, where MC was used as the primary solvent (Friedlander *et al.,* 1978; Hearne and Friedlander, 1981; Friedlander *et al.,* 1985; Friedlander *et al.*, 1986; Hearne *et al.,* 1987). Industrial hygiene surveys conducted there had found airborne levels of methylene chloride in the workroom ranging, in general, from 30 to 100 ppm. As control groups, the researchers considered (1) males in New York State not including New York City and (2) other males employed by Kodak in Rochester.

The 1985 report from Friedlander and colleagues noted that overall, significantly fewer deaths occurred during the follow-up period (January 1964 through December 1984) than expected based on the New York State data (165 vs. 231.1) (Friedlander *et al.,* 1985). However, the number of deaths among exposed workers was similar to that of the other Kodak employees (165 versus 167.0). Thirty-nine deaths from malignant neoplasms were observed in the exposed cohort compared to 54.7 expected based on the New York State data or 43.2 expected on the basis of the data from other Kodak employees. The follow-up rate for this report was 94% for the exposed cohort (N = 751). The above findings are consistent with the "healthy worker effect," in which working populations tend to experience lower mortality than the general population.

Using the statistical tests (one-tailed and two-tailed test of significance) employed by investigators, no cancer site displayed a significantly elevated death rate. Nevertheless, eight deaths from pancreatic cancer were observed compared to 3.0 expected based on the New York data or 2.6

based on the other employees' data. Although this finding was not considered significant based on the two-tailed test described above, an exact one-sided Poisson test using the other Kodak employees as the control group yields a *p*-value of 0.0053 and suggests a possible relationship between the exposure to MC and pancreatic cancer mortality. Somewhat smaller-than-expected death rates were observed for certain tumor sites, including the colon, and the genital and urinary organs; these observations did not reach statistical significance.

In the subset of the cohort which had been exposed for a minimum of 20 years by 1964 (N = 252), fewer cancer deaths were observed than expected when compared to the New York State data (23 vs. 33.8) or to the data from other Kodak employees (23 versus 27.0). A slight excess of deaths from pancreatic neoplasms was observed here (4 compared to 1.9 or 1.6 expected). None of these differences were statistically significant.

Hearne *et al.* (1987) presented estimates of exposure and expanded the exposed cohort to 1,013 men who had at least one year of experience in the methylene chloride operation between January 1964 and December 1970. The 1985 report analyzed approximately 14,000 person-years of follow-up in the exposed cohort; this 1987 report presented data from 19,465 person-years, with a follow-up of 99% for the exposed cohort. Again, compared to either control group, no statistically significant difference was found between observed and expected deaths for respiratory or hepatic cancer mortality, based on a one-sided test, ($p < 0.05$). Among the nonhypothesized outcomes, workers exposed to methylene chloride still experienced more than a two-fold greater rate of mortality from pancreatic cancer (8 observed vs. 3.2 or 3.1 expected [New York State or Kodak controls]). The SMR for this site was 2.5 with 95% confidence limits of 1.1 to 4.9. DHS staff calculations indicate an exact one-sided Poisson test using the New York State data as a control yields a p-value of 0.017. Thus, the results still suggest a possible relationship between exposure to methylene chloride and pancreatic cancer mortality. Exposure estimates were based on over 1,200 area and task-specific air samples collected between 1945 and 1986 and more than 900 full-shift personal samples collected between 1980 and 1986. The majority of the cohort was exposed to peak concentrations of 500 ppm, an average of three times per day, 10 or 40 days per year (depending on occupational classification). Other solvents, including 1,2-dichloropropane and 1,2-dichloroethane, were present at lower levels in the workroom.

In a series of reports, Ott and colleagues (Ott *et al.,* 1983a-e) evaluated the health of employees working at a fiber production plant in Rock Hill, South Carolina, where methylene chloride was used as a part of a solvent system. Workers in this plant were exposed to a mixture of methylene chloride and methanol from one process and to acetone from a second process. Median 8-hr TWA methylene chloride concentrations in the plant's two main work areas were 140 and 475 ppm. Health evaluations of these employees were compared to those of employees at a similar fiber production plant in Narrows, Virginia, where only acetone was used. One of the reports (Ott *et al.,* 1983b) evaluated whether exposure to methylene chloride was associated with cancer deaths. Smoking habits were not considered in the analyses, although age was controlled for. Compared with United States death rates, no excess mortality from any cause in either cohort was evident. A slight deficit in the observed deaths from cancer was noted among exposed white workers (7 observed versus 12.4 expected). The cancer mortality experience of the methylene chloride-exposed workers was not significantly difference from that of the reference cohort. One death

from pancreatic cancer was reported in the exposed cohort. Of the seven cancer deaths in the reference cohort, one was from pancreatic cancer (Bond, 1988).

This study is of somewhat limited usefulness for evaluating the association between exposure to methylene chloride and cancer mortality. It had limited power to detect increases in malignancy rates in the exposed cohort. In that cohort, only 54 deaths, of which 7 were from cancer, were reported. There were no deaths observed among the 108 nonwhite women in the study. In addition, the follow-up period was probably insufficient for any carcinogenic effects from exposure to methylene chloride to be manifested.

The International Agency for Research on Cancer (IARC, 1986) in their review of epidemiological studies has concluded that no excess risk of death from malignancies was observed, but noted that the studies had a limited power to detect excess risk. To date, epidemiological studies on methylene chloride do not provide sufficient evidence either to prove or disprove human carcinogenicity.

Animal Studies

There are five long-term rodent bioassays examining the effects of inhaling methylene chloride: two using Spartan/Sprague-Dawley (SD) rats (Burek *et al.,* 1984; U.S. EPA, 1985a; Nitschke *et al.,* 1988a), one with Fischer-344 (F344) rats (NTP, 1986), one using $B6C3F_1$ mice (NTP, 1986), and one with Ela:Eng (Syr) Syrian hamsters (Burek *et al.,* 1984). The NTP (1986) studies have also been published by Mennear *et al.* (1988). Bioassays exposing animals orally to MC in drinking water were conducted in F344 rats and $B6C3F_1$ mice (Serota *et al.,* 1986a-b).

In the Dow (1980) study, male and female Spartan/Sprague-Dawley (SD) rats were exposed to methylene chloride by inhalation for two years (Burek *et al.,* 1984; U.S. EPA, 1985a). During the first two months of the study, there was an outbreak of sialodacryoadenitis virus infection involving control and exposed rats. This virus has been associated with acute inflammation and diffuse coagulative necrosis of the parotid and submandibular salivary glands and Harderian gland (Burek *et al.,* 1984). The carcinogenic end points in this study were sarcomas arising in the cervical/salivary gland area in males and benign mammary tumors in both sexes (Table 1). Burek *et al.* (1984) suggested that the combinations of this viral infection and exposure to high concentrations of methylene chloride may have been associated with the salivary gland tumors. However, F344 rats exposed to higher methylene chloride concentrations and the same viral agent did not develop similar tumors in the salivary gland region (NTP, 1986; Mennear *et al.,* 1988). Control and exposed female rats all had a high incidence (above 80%) of benign mammary tumors.

Table 1: Methylene chloride-induced tumor incidence in Sprague-Dawley rats.

Dose (ppm)	Cervical/salivary gland region sarcomas in male rats	Benign mammary tumors	
		Males	Females
0	1/93 (1%)	7/95 (7%)	79/96 (82%)
500	0/94	3/95 (3%)	81/95 (85%)
1500	5/91 (5.5%)	7/95 (7%)	80/96 (83%)
3500	11/88 (12.5)*	14/95 (15%)	83/97 (86%)
HLC[1]	0-2%	10%	80%

[1] historical laboratory control

* $p < 0.05$, Fisher's exact probability test

In another inhalation study at Dow (Nitschke *et al.,* 1988a) 90 SD rats/sex were exposed to 0 (control), 50, 200, and 500 ppm methylene chloride, 6 hours/day, 5 days/week, for 20 (males) or 24 (females) months. Most of the animal husbandry conditions were similar to the previous rat study with the exception that the animals were housed in conventional animal rooms overnight and during the weekends instead of in the chamber rooms. Female rats kept in chambers 100% of the time were reported to have higher incidence of mammary tumors than in conventional animal rooms (Nitschke *et al.,* 1988a). In this study there was a nonsignificant increase in the number of benign mammary tumors per tumor bearing female rat. No other tumors were observed.

An inhalation study of Ela:Eng (Syr) Syrian hamsters (Burek *et al.,* 1984) were performed under similar experimental exposure conditions as the 1980 Dow SD rat study. In males, there were no exposure-related increases in mortality rates, although mortality was high at 24 months (82% in control, 85% in the 3500 ppm exposed group). In females, control animals had 100% mortality at 24 months which was higher than any of the exposed groups (90.3% in the 3500 ppm exposed group). No exposure-related neoplasms or nonneoplastic lesions were observed.

The strongest evidence for the carcinogenicity of methylene chloride to rodents was provided by the NTP inhalation bioassays (NTP, 1986; Mennear *et al.,* 1988). Fifty F344 rats and $B6C3F_1$ mice of both sexes/group were exposed to methylene chloride for 6 hours/day, 5 days/week for 102 weeks (concentrations: 0, 1000, 2000, and 4000 ppm for rats; 0, 2000, and 4000 ppm for mice). Rats were housed in cages in exposure chambers and remained in the chambers during nonexposure periods.

Under the conditions of the study, benign mammary tumors were induced in F344 rats, and the female rats exhibited a dose-related response ($p < 0.001$) (Table 2). NTP interpreted the incidence of benign mammary tumors in female rats as "clear evidence of carcinogenicity" and in male rats as "some evidence of carcinogenicity". An elevated incidence of leukemia was observed in the 2000 ppm and 4000 ppm exposed female rats but this was also observed in controls. NTP considered this to be "equivocal".

Table 2: Methylene chloride-induced benign mammary tumors incidence in F344/N rats.

Dose (ppm)	Benign mammary tumors	
	males[1]	female[2]
0	1/50 (2%)	5/50 (10%)
1000	1/50 (2%)	11/50 (22%)
2000	4/50 (8%)	13/50 (26%)
4000	9/50 (18%)*	23/50 (46%)*
Historical Control (Fibroadenoma)		
a. Laboratory	0%	16%
b. NTP	3%	28%

[1] Fibroadenoma, adenoma, or fibroma.
[2] Fibroadenoma or adenoma.
* ($p < 0.001$), Fisher exact test.

In $B6C3F_1$ mice, exposure to methylene chloride by inhalation (NTP, 1986; Mennear *et al.,* 1988) was associated with an increased incidence and multiplicity of alveolar and bronchiolar tumors (adenoma and carcinoma) in the lungs of both sexes. The incidence and multiplicity of liver tumors were also increased in both sexes. Male mice had an increased incidence of hepatocellular carcinomas and of adenomas or carcinomas (combined) at the high exposure level, while female mice had dose-related increases in hepatocellular adenoma and hepatocellular carcinoma (Table 3). The survival in both male and female high dose groups was significantly ($p < 0.001$, trend test) decreased as compared to controls.

Table 3: Methylene chloride-induced neoplasms incidence in $B6C3F_1$ mice

Dose (ppm)	Alveolar /Bronchiolar Adenomas(A) or Carcinomas(C) or combined		Hepatocellular Adenomas or Carcinomas or combined	
	Male	Female	Male	Female
0	A: 3/50(6%)	2/50(4%)	10/50(20%)	2/50(4%)
	C: 2/50(4%)	1/50(2%)	13/50(26%)	1/50(2%)
	A, C 5/50(10%)	3/50(6%)	22/50(44%)	3/50(6%)
2000	A: 19/50(38%)*	23/48(48%)*	14/49(29%)	6/48(13%)
	C: 10/50(20%)	13/48(27%)*	15/49(31%)	11/48(23%)*
	A, C 27/50(54%)*	30/48(63%)*	24/49(49%)	16/48(33%)*
4000	A: 24/50 (48%)*	28/48(58%)*	14/49(29%)	22/48(46%)
	C: 28/50(56%)*	29/48(60%)*	26/49(53%)	32/48(67%)*
	A, C 40/50(80%)*	41/48(85%)*	33/49(67%)	40/48(83%)*
Historical control	A: --	--	13%	1%
a. Laboratory	C: --	--	15%	4%
	A, C 31%	10%	28%	5%
b. NTP	A: --	--	10%	4%
	C: --	--	21%	5%
	A, C 17%	7%	30%	8%

* Fisher Exact Test ($p < 0.001$).

Significant treatment-related increases in the combined incidence of liver tumors, hepatocellular adenomas, and carcinomas occurred in $B6C3F_1$ mice exposed orally (via drinking water), 7 days/week for two years, to lower doses (125 and 185 mg/kg/day) of methylene chloride, but were not significant in the highest (250 mg/kg/day) exposure group (Serota *et al*., 1986b). Serota *et al*. (1986a) considered the increase in liver tumors (combined neoplastic nodule and hepatocellular carcinoma) in rats to be insignificant because the incidence was within the laboratory's historical control range.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Methylene chloride has been observed to induce lung (alveolar and bronchiolar) and liver (hepatocellular adenoma or carcinoma) tumors in both sexes of $B6C3F_1$ mice and subcutaneous sarcomas of the ventral cervical-salivary gland region in male Sprague-Dawley rats, as described above. CDHS (1989) decided that the tumor incidence data from studies by Dow (1980), NTP (1986) and Mennear *et al*. (1988) were suitable for use in developing a quantitative risk assessment.

Methodology

DHS staff used female mouse lung tumor incidence (the most sensitive sex, species and tumor site of the 1986 NTP inhalation bioassay) to calculate the low-dose risk from exposure to MC. DHS staff fitted several low-dose risk assessment models to the mouse lung tumor data, including the multistage (GLOBAL82 and GLOBAL86), time-dependent multistage (Weibull 82), probit, logit, Weibull, gamma multihit, and two-stage models. DHS staff also applied a physiologically based pharmacokinetic model to estimate the internal dose. This model adjusts the expected exposure concentration and suggests lower human risks than predicted by an unadjusted or applied dose approach. The application of the pharmacokinetic approach to risk assessment is based on information developed by the U.S. EPA (1987) and U.S. Consumer Product Safety Commission (Cohn, 1987). DHS staff recommended that the range of risks for ambient exposures to methylene chloride be based on the upper 95% confidence limit predicted from fitting either the multistage (GLOBAL82) model or the time-dependent multistage (Weibull 82) model to the animal data. The unit risk for a lifetime of continuous exposure to methylene chloride is 0.3 to 3×10^{-6} $(\mu g/m^3)^{-1}$. The lower estimate (0.3×10^{-6} $(\mu g/m^3)^{-1}$) incorporates a complete pharmacokinetic adjustment as calculated by U.S. EPA (1987). DHS staff believe that the complete pharmacokinetic adjustment retains considerable uncertainty. In contrast, the applied dose value (3×10^{-6} $(\mu g/m^3)^{-1}$) does not incorporate any pharmacokinetic information with the likely result of overestimating the risk. The high-to-low dose adjustment used by the U.S. Consumer Product Safety Commission (Cohn, 1987) generates a risk of 4×10^{-6} ppb^{-1} which incorporates information regarding saturation of the mixed-function oxidase pathway. After reviewing the full range of values, DHS staff concluded that the most likely estimate of the risk of methylene chloride exposure is the adjusted value of 4×10^{-6} ppb^{-1} (1.0×10^{-6} $(\mu g/m^3)^{-1}$).

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4, 4'-METHYLENEDIANILINE

CAS No: 101-77-9

4, 4'-METHYLENEDIANILINE DIHYDROCHLORIDE

CAS No: 13552-44-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

4, 4'-Methylenedianiline

Molecular weight	198.26
Boiling point	398-399 °C at 768 mm Hg
Melting point	91.5-92 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 8.109 mg/m^3

4, 4'-Methylenedianiline didihydrochloride

Molecular weight	271.21
Boiling point	not available
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 11.09 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.6 E+0 $(mg/kg\text{-}day)^{-1}$
[Male mouse liver tumors (NTP, 1983), contained in Gold *et al*. (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 4,4' methylenedianiline in humans are known to exist.

Animal Studies

Griswold *et al*. (1968) exposed a group of 20 female Sprague-Dawley rats to 30 mg 4,4' methylenedianiline dihydrochloride in 1 ml sesame oil by gavage every third day for 30 days (total dose, 300 mg/rat). The animals were then observed for a further 9 months. A group of 140 female Sprague-Dawley rats served as a negative control group. No treatment-related increase in tumor incidence was noted; however, the study duration was short, a small number of animals was used,

only one sex was used, and the primary aim of the study was to develop methods of detecting carcinogens inducing mammary tumors.

The potential carcinogenicity of 4,4' methylenedianiline dihydrochloride was studied using Fischer 344 (F344) rats and $B6C3F_1$ mice (50 animals/sex/species/group) (NTP, 1983). Animals were exposed to 150 mg/l or 300 mg/l 4,4' methylenedianiline dihydrochloride in drinking water for 103 weeks followed by one week without treatment. Untreated control groups were included. A significantly increased incidence of thyroid follicular-cell adenomas was observed in male and female mice and rats. Significantly increased incidences of hepatocellular adenomas and carcinomas were observed in female and male mice; increased incidences of neoplastic nodules were observed in male rats. Tumor incidence data is listed in Table 1.

Table 1 4,4' methylenedianiline dihydrochloride-induced tumor incidences in male and female F344 rats and $B6C3F_1$ mice (NTP, 1983; Weisburger *et al*., 1984)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male mice	control	0	thyroid tumors	0/50
	low dose	24.5		3/50
	high dose	49.5		16/50
	control		liver tumors	17/50
	low dose			43/50
	high dose			37/50
female mice	control	0	thyroid tumors	0/50
	low dose	29.4		1/50
	high dose	59.1		15/50
	control		liver tumors	4/50
	low dose			15/50
	high dose			23/50
male rats	control	0	thyroid tumors	1/50
	low dose	7.36		4/50
	high dose	14.7		10/50
	control		hepatic neoplastic nodules	1/50
	low dose			12/50
	high dose			25/50
female rats	control	0	thyroid tumors	0/50
	low dose	8.41		5/50
	high dose	16.7		22/50

1. Doses as reported by Gold *et al*. (1987).
2. Tumor incidences as reported by Gold *et al*. (1987).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

4, 4'-Methylenedianiline

The potency for this compound was derived from the potency for the dihydrochloride using a molecular weight conversion:

$$q_h \text{ (anhydrous)} = q_h \text{ (hydrate)} \times \frac{\text{MW (hydrate)}}{\text{MW (anhydrous)}}$$

where q_h is the human potency and MW is the molecular weight. This conversion assumes that the intake of equivalent moles of the two forms of the chemical (e.g. the anhydrous and hydrate forms) results in equivalent concentrations of the active species *in vivo*.

4, 4'-Methylenedianiline didihydrochloride

Results are listed for the drinking water studies by NTP (1983) in male and female B6C3F$_1$ mice and F344 rats. Significant increases in tumors of the liver or thyroid or both are observed for all sex/species combinations tested, with male mice the most sensitive. The cancer potency listed is based on the combined incidence of benign and malignant liver tumors in male mice (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Analysis of the data set using the computer program TOX_RISK (Crump *et al*., 1991) indicated that inclusion of the high dose group resulted in a *p*-value of = 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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MICHLER'S KETONE (4,4′-BIS(DIMETHYLAMINO) BENZOPHENONE)

CAS No: 90-94-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	268.35
Boiling point	>360 °C (with decomposition)
Melting point	172 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 10.98 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.5 E-4 ($\mu g/m^3$)$^{-1}$
Slope Factor: 8.6 E-1 (mg/kg-day)$^{-1}$
[Female rat liver tumor data (NCI, 1979), contained in Gold *et* al. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of Michler's ketone in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice were fed diets containing Michler's ketone (NCI, 1979). Mice were fed diets containing 1250 or 2500 mg/kg diet Michler's ketone for 78 weeks; animals were then maintained on control diet for an additional 13 weeks. Rats were fed diets containing 250 or 500 mg/kg diet Michler's ketone for males, 500 or 1000 mg/kg diet for females; the treatment period for both sexes was 78 weeks. The treatment period was followed by an observation period; 28 weeks for male rats and high dose female rats and 29 weeks for low dose female rats. Treatment group sizes were 50 animals/sex/species/group; control group sizes were 20 animals/sex/species.

Significant dose-related increases in incidences of liver tumors (hepatocellular adenomas and carcinomas) were observed in rats and female mice, and of hemangiosarcomas in male mice. Tumor incidence data is listed in Table 1.

Table 1. Michler's ketone-induced tumor incidence in male and female F344 rats and $B6C3F_1$ mice (NCI, 1979)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
Male mice	control	0	hemangiosarcomas	0/20
	low dose	128		5/50
	high dose	257		20/50
Female mice	control	0	liver tumors	0/20
	low dose	139		41/50
	high dose	278		49/50
Male rats	control	0	liver tumors	0/20
	low dose	7.4		17/50
	high dose	14.4		43/50
Female rats	control	0	liver tumors	0/20
	low dose	18		46/50
	high dose	37		48/50

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The results from feeding studies by NCI (1979) are listed by Gold *et al*. (1984). Rats are more sensitive than mice to induction of tumors due to exposure to Michler's ketone, with male and female rats having similar sensitivity. The cancer potency factor for Michler's ketone was derived from dose-response data for liver tumors in female rats as listed in Table 1 (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

California Environmental Protection Agency (Cal/EPA) 1992. Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, Berkeley, CA.

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NAPHTHALENE

CAS No: 91-20-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 2003 except as noted)

Molecular weight	128.2
Boiling point	218ºC
Melting point	80.5 ºC
Vapor pressure	0.078 Torr @ 25ºC (Sonnenfeld *et al*., 1983); 0.10 Torr @ 27ºC (CRC, 1994)
Air concentration conversion	1 ppm = 5.24 mg/m^3 (NIOSH, 2004)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.4 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 1.2 E-1 $(mg/kg\text{-}day)^{-1}$

[Male rat nasal respiratory epithelial adenoma and nasal olfactory epithelial neuroblastoma incidence data (NTP, 2000), linearized multistage procedure (OEHHA, 2004).]

III. CARCINOGENIC EFFECTS

Animal Studies

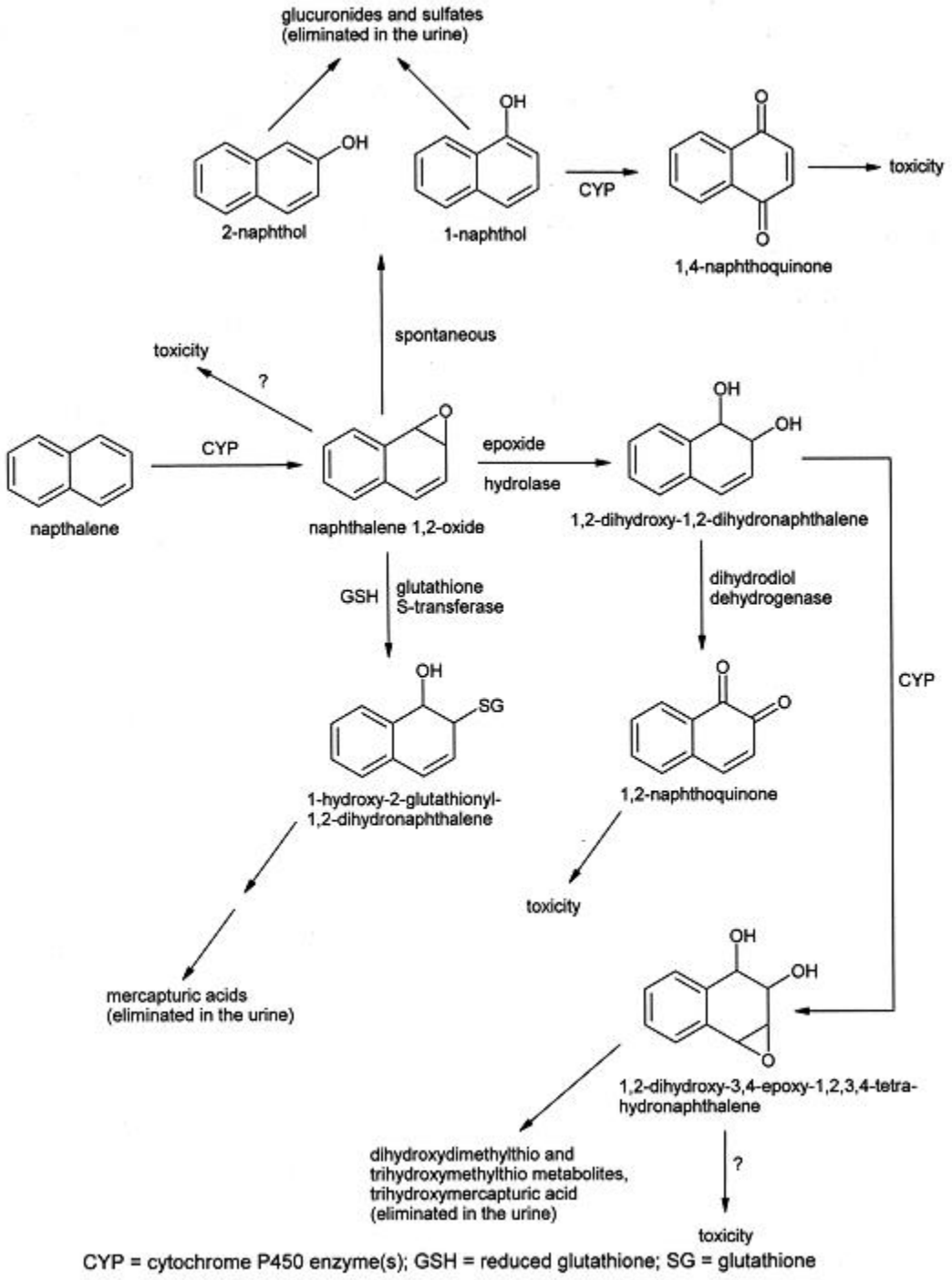
Metabolism

The metabolism of naphthalene is similar to that of many other aromatic hydrocarbons (reviews: Buckpitt and Franklin, 1989; Buckpitt *et al*., 2002). Initially, naphthalene is oxidized by the cytochrome P450 monooxygenase system to naphthalene oxide enantiomers. The primary site of metabolism is the liver, but oxidation also occurs in the lung and kidneys. Naphthalene oxides may be converted to dihydrodiols by epoxide hydrolase enzymes. Naphthalene oxides also undergo nonenzymatic conversion to 1-naphthol, which may be subsequently conjugated or may be further oxidized to 1,4-naphthoquinone. The naphthalene dihydrodiols may also be oxidized to 1,2-naphthoquinone (Figure 1). Toxicity is apparently related to protein binding by quinone metabolites and/or their participation in redox cycles leading to oxidative stress including DNA damage (O'Brien, 1991).

Naphthalene-1,2-epoxide

Naphthalene is oxidized to two reactive enantiomers: (1*R*, 2*S*)-naphthalene oxide and (1*S*, 2*R*)-naphthalene oxide. A purified cytochrome P450 monooxygenase (CYP2F2) from mouse liver that metabolized naphthalene rapidly with high stereoselectivity was used to clone and sequence the cDNA coding for a 50-kDa protein present at high levels in mouse lung and liver. The protein had 82% sequence homology to a cDNA cloned earlier from human lung (Ritter *et al*., 1991). The human CYP2F1 and mouse CYP2F2 were expressed in HEPG2 cells and yeast,

Figure 1. Metabolic Scheme for Naphthalene (adapted from ATSDR, 2003)



CYP = cytochrome P450 enzyme(s); GSH = reduced glutathione; SG = glutathione

respectively. In human lymphoblastoid cells the CYP2F1 demonstrated a naphthalene turnover of about 0.035 nmol/min/nmol P450 or about 0.1% the rate observed with the mouse CYP2F2 (Shultz *et al*., 1999). The human CYP2F1 showed slight stereopreference in the generation of the (1S, 2R) naphthalene oxide enantiomer (7.7:1). The recombinant mouse CYP2F2 exhibited a high degree of stereoselectivity for the (1*R*, 2*S*) enantiomer (66:1), a very high V_{max} (107 nmol/min/nmol P450), and a low K_m (3 μM). This high level of activity is consistent with the metabolism and toxicity of naphthalene in the mouse lung. CYP2F2 also oxidizes a number of other substrates including the lung toxicant 1-nitronaphthalene.

Characterization of naphthalene oxidizing P450 enzymes in the rat lung has been more difficult. A CYP2F4 has been cloned from the rat lung that has 93 percent identity with the mouse and 83 percent with the human (Buckpitt *et al*., 2002). While further characterization of the rat enzyme is necessary the results overall indicate that there are likely major interspecies catalytic differences in these CYP2F enzymes between mouse, rat and human. It is unknown whether CYP2F is responsible for the activation of naphthalene in the nasal epithelium. The rate of metabolism appears to be substantial in olfactory postmitochondrial supernatants from mice and rats, 87 and 43.5 nmol/min/mg protein, respectively (Buckpitt *et al*., 1992). However, there are several P450 isoforms in the nasal mucosa including CYP1A2, 2A, 2B, 2C, 2G1, 2J, and 3A and catalytic activities with naphthalene have not been established.

In contrast to the results of *in vitro* enzymatic studies, Willems *et al*. (2001) estimated overall kinetic parameters for intact mice and rats exposed to concentrations of naphthalene that were used in the NTP cancer bioassays in conjunction with a physiologically based pharmacokinetic model. The V_{max} (nmol/min/mg microsomal protein) and Km (μM) for the male and female rats were 16.5, 6.0; and 24.6, 3.2, respectively. For male and female mice the V_{max} and K_m values were 38.7, 1.5; and 54.8, 5.8, respectively. While some differences in metabolic saturation capacity are apparent the values overall are similar. The overall metabolic capacities based on these figures are higher than indicated by in vitro derived kinetic parameters of Quick and Shuler (1999). The values above do not distinguish between lung and liver.

1-Naphthol

Naphthalene-1,2-epoxide undergoes spontaneous rearrangement to 1-naphthol. Like naphthalene, 1-naphthol is subject to oxidation by cytochrome P450 enzymes. Wilson *et al*. (1996) studied the metabolism and cytotoxicity of naphthalene and 1-naphthol in vitro with human hepatic microsomes and mononuclear leukocytes (MNL). 1-Naphthol was observed to be more toxic than naphthalene (49.8 ± 13.9% vs. 19.0 ± 10.0% cell death; $p < 0.01$). CYP2E1-induced rat liver microsomes increased the metabolism of naphthalene giving increased yields of both naphthalene dihydrodiol and 1-naphthol. The cytotoxicity of naphthalene but not 1-naphthol was increased by CYP2E1 induction. The metabolites of 1-naphthol; 1,2-naphthoquinone and 1,4-naphthoquinone were directly toxic to MNL and depleted glutathione to one percent of control level. Both quinone metabolites of 1-naphthol were also genotoxic to human lymphocytes. Buckpitt *et al*. (1986) found that in vivo, reactive metabolites from [^{14}C]-1-naphthol became covalently bound to proteins in lung, liver, and kidney, but that the amount of binding was similar to that seen after administration of naphthalene. Zheng *et al*. (1997) incubated murine Clara cells with naphthalene and found adducts generated from the 1,2-quinone metabolite vs. the 1,2-epoxide had a ratio of 32:1. They found no evidence for formation of the 1,4-naphthoquinone. Conversely, Doherty *et al*. (1985)

incubated microsomal preparations and reported that the reactive metabolite generated from 1-naphthol was not trapped by ethylene diamine, which reacts rapidly with 1,2-naphthoquinone, and hence was likely 1,4-naphthoquinone. Current thinking is that 1-naphthol is oxidized to 1,4-naphthoquinone, which binds to proteins and plays a role in toxicity of naphthalene, particularly in the lung (Buckpitt *et al*., 2002).

1,2-Dihydroxy-1,2-dihydronaphthalene

Naphthalene-1,2-oxides are hydrolyzed to naphthalene dihydrodiols via epoxide hydrolase (EH). While generally less toxic than their parent epoxides dihydrodiols may serve as precursors to diol epoxides that represent ultimate carcinogens for many PAHs. The formation of diol epoxides and/or diepoxides from naphthalene is supported by the observation of trihydroxytetrahydro-urinary metabolite derivatives (Buckpitt *et al*., 2002). In addition to this microsomal oxidation of naphthalene dihydrodiol, a competing biotransformation by cytosolic dihydrodiol dehydrogenase (DD) generates the catechol, 1,2-dihydroxynaphthalene, which is readily autoxidized to 1,2-naphthoquinone. During oxidation via single electron steps reactive oxygen species (ROS) are generated together with an *o*-semiquinone anion radical intermediate. 1,2-Naphthoquinone can be reduced by NAD(P)H back to the catechol creating a futile redox cycle, which may lead to oxidative stress including DNA damage (Penning *et al*. 1999). As noted above, studies in isolated Clara cells indicated that the 1,2-naphthoquinone was the major metabolite, which bound covalently to proteins (Zheng *et al*., 1997). 1,2-Naphthoquinone is mutagenic in the Salmonella microsome assay (Bolton *et al*., 2000) and forms *N*-7 adducts with deoxyguanosine *in vitro* (McCoull *et al*., 1999). 1,2-Naphthoquinone is a key metabolite in naphthalene toxicity and may be more important in humans than rodents due to the higher activities of both EH and DD in human tissues compared to rodent tissues (Penning *et al*., 1999; Kitteringham *et al*., 1996)

Conjugates of Naphthalene Metabolites

Naphthalene-1,2-oxides are converted via the action of glutathione *S*-transferase to 1-hydroxy-2-glutathionyl-1,2-dihydronaphthalenes. These are subsequently converted to mercapturic acids (*S*-conjugates of *N*-acetyl-L-cysteine) and excreted in the urine (25 to 35 percent of dose in mice and rats). In mice the ratio of diastereomeric mercapturates derived from (1*R*, 2*S*):(1*S*, 2*R*) epoxide ranged from 1:1 to 3:1 (1-200 mg/kg i.p.) whereas in rats the ratio was always less than 1:1 at all doses. For inhalation exposures the ratios were higher in mice 6:1 to 3:1 (15-100 ppm) but unchanged in rats (Pakenham *et al*., 2002). Three mercapturic acids have been identified in urine derived from the following conjugates: 1) 1*S*-hydroxy-2*S* –glutathionyl; 2) 1*R*-hydroxy-2*R*-glutathionyl; and 3) 1*R*-glutathionyl-2*R*-hydroxy. There are no substantial species differences in the percentage of dose eliminated as diastereomeric mercapturates. The ratios of the diastereomers do vary with species, administration route and dose level. Overall these urinary mercapturates appear to provide a useful biomarker of internal naphthalene dose.

Alternative biomarkers are the albumin and hemoglobin cysteinyl adducts of naphthalene-1,2-oxide, 1,2- and 1,4-naphthoquinones formed after administration of naphthalene to rats (Waidyanatha *et al*., 2002). In human coke oven workers only albumin adducts of 1,2-naphthoquinone (1,2-NQ-Alb) were found to significantly exceed background levels seen in control steel industry workers (Waidyanatha *et al*., 2004). This study also observed that 1,2-NQ-Alb levels were significantly correlated with urinary levels of naphthalene, 1-naphthol, 2-naphthol,

and 1-pyrenol but negatively correlated with age, suggesting a diminished cytochrome P450 metabolism of about three percent/year.

The conjugation of dihydroxy dihydronaphthalene metabolites and their subsequent urinary elimination as mercapturates is generally considered a detoxication process. However, reaction of these metabolites with glutathione may give rise to naphthoquinone thioethers that possess a variety of toxic properties (Monks and Lau, 1992,1998; Monks *et al*., 1992). ESR studies have shown the formation of GSH-conjugated semiquinone free radicals of 3-(glutathion-*S*-yl)-1,4-naphthoquinone and 2,3 (di-glutathion-*S*-yl)-1,4-naphthoquinone in rat hepatocytes (Takahashi *et al*., 1987; Rao *et al*., 1988). Conjugation of naphthoquinones with glutathione or *N*-acetylcysteine may exacerbate redox cycling by reducing the redox potential of the conjugate vs. the parent quinone. Quinone thioethers participate in protein crosslinking; serve as substrates for DT-diaphorase, or as inhibitors of important enzymes such as NADP-linked 15-hydroxyprostglandin dehydrogenase and glutathione sulfotransferase (GST). Some quinone thioethers also exhibit nephrotoxicity as indicated by menadione 3-thioethers (e.g., 2-methyl-3-(*N*-acetylcysteine-*S*-yl)-1,4-naphthoquinone) induction of renal proximal tubular necrosis in rats (Lau *et al*., 1990).

In addition to the GST mediated conjugation of naphthalene dihydrodiols and naphthoquinones, 1-naphthol and 2-naphthol arising from the rearrangement of the naphthalene-1,2-oxides are also conjugated and eliminated in the urine as sulfates and glucuronides.

Genotoxicity

Naphthalene

Naphthalene has been tested for genotoxicity in a variety of *in vitro* and *in vivo* genotoxicity assays. Those studies have recently been reviewed by ATSDR (2003). Naphthalene has not demonstrated genotoxicity in *Salmonella* reverse mutation assays. Those studies are listed in Table 1. All studies were performed in the presence and absence of metabolic activation (rat liver S9), and were negative.

Naphthalene has also been tested in other bacterial mutation assay systems. These studies are listed in Table 2. All studies were performed in the presence and absence of metabolic activation (rat liver S9), and were negative except for the study by Arfsten *et al*. (1994). This study used Vibrio fischeri (strain M169) in a Mutatox assay (reversion to luminescence). Naphthalene was negative in the absence of S9, but positive in the presence of S9.

Naphthalene has not demonstrated genotoxicity activity in mammalian *in vitro* DNA damage and gene mutation assays. The relevant studies are listed in Table 3.

Table 1. Naphthalene *Salmonella* reverse mutation studies

Test strains	Reference
TA98, TA100, TA1535, TA1537	McCann *et al*., 1975
TM677	Kaden *et al*., 1979
TA98, TA100, TA1535, TA1537	Florin *et al*., 1980
TA1537, TA1538	Gatehouse, 1980
TA98, TA100, UTH8413, UTH8414	Connor *et al*., 1985
TA98, TA100, TA1535, TA1537, TA1538	Godek, 1985
TA98, TA100, TA1535, TA1537	Mortelmans *et al*., 1986
TA98, TA1535	Narbonne *et al*., 1987
TA98, TA100	Bos *et al*., 1988
TA98, TA100, TA1535, TA1537	NTP, 1992a
TA98, TA100, TA1535, TA1537	Sakai *et al*., 1985

Table 2. Other naphthalene bacterial mutation studies

Assay system	Species/strain	Reference
SOS response	*E. coli* K12 inductest (λ lysogen GY5027; *uvr*B-, *env*A-)	Mamber *et al*., 1984
	S. typhimurium TA1535/p5K1002 (uMuC-IacZ)	Nakamura *et al*., 1987
SOS chromotest assay	*E. coli* PQ37 (*sfi*A::*lac*Z fusion)	Mersch-Sundermann *et al*., 1993
Pol A- or Rec	*E. coli* WP2/WP10 (*uvr*A-, *rec*A-)	Mamber *et al*., 1983
	E. coli WP2/WP67 (*uvr*A-, *pol* A-)	
	E. coli WP2/WP3478 (*pol* A-)	
Mutatox (reversion to luminescence)	*Vibrio fischeri* M169	Arfsten *et al*. 1994

Table 3. Naphthalene mammalian *in vitro* DNA damage and gene mutation studies

Assay	Cell type	Reference
Alkaline elution (single strand DNA breaks)	Rat primary hepatocytes	Sina *et al*., 1983
Unscheduled DNA synthesis	Rat primary hepatocytes	Barfknecht *et al*., 1985
hprt and *tk* loci mutations	Human MCL-5 B-lymphoblastoid cells	Sasaki *et al*., 1997

Naphthalene also induced chromosomal aberration in CHO cells in the presence but not absence of rat liver S9. Additionally, naphthalene caused an increase in the frequency of CREST micronuclei (indicative of chromosomal breakage) in human MCL-5 B-lymphoblastoid cells (Sasaki *et al*., 1997). These cells express microsomal epoxide hydrolase (EH) and CYP1A2, CYP2A3, CYP3A4, and CYP2E1 P450 isoforms.

Data on the induction by naphthalene of DNA damage *in vivo* are mixed. Single strand DNA breaks (measured by alkaline elution) were not induced in hepatocytes from female rats exposed to a single oral dose of naphthalene (Kitchin *et al*., 1992, 1994). In contrast, naphthalene caused DNA fragmentation in liver and brain tissue from rats given daily oral doses for up to 120 days (Bagchi *et al*., 1998), mice given single oral doses (Bagchi *et al*., 2000, 2002), and *p*53-deficient mice given single oral doses (Bagchi *et al*., 2002).

Naphthalene did not cause micronucleus induction (indicative of chromosomal damage) in the bone marrow cells of mice exposed to naphthalene either by gavage (Harper *et al*., 1984) or by intraperitoneal injection (i.p.) (Sorg, 1985). However, naphthalene was reported to induce chromosomal aberrations in preimplantation mouse embryos in an abstract by Gollahon *et al*. (1990).

Naphthalene has been demonstrated to have genotoxic effects in nonmammalian assay systems. Delgado-Rodriguez *et al*. (1995) reported positive results for naphthalene in the *Drosophila melanogaster* wing spot assay. This assay detects both somatic mutations and mitotic recombination in cells of the wing imaginal discs, based on the induced loss of heterozygosity for two recessive wing cell markers. Micronuclei induction was reported in the erythrocytes of salamander larvae (*Pleurodeles waltl*) exposed to naphthalene in their tank water (Djomo *et al*., 1995).

Naphthalene metabolites

1-Napthol, 2-Napthol

1-Naphthol was reported to be negative in the *Salmonella* reverse mutation assay by McCann *et al*. (1975) (test strains TA98, TA100, TA1535 and TA1537) and Norbonne *et al*. (1987) (test strains TA98 and TA1535). 1-Naphthol and 2-napthol also did not induce UDS in primary rat hepatocytes (Probst *et al*., 1981).

1,2-Napthoquinone

Flowers-Geary *et al*. (1996) tested 1,2-napthoquinone in the *Salmonella* reverse mutation assay (test strains TA97a, TA98, TA100 and TA104) in the presence and absence of rat liver S9. 1,2-Napthoquinone caused a 2.5-fold increase in revertants in strain TA104, a strain that is sensitive to oxidative DNA damage, compared to controls. 1,2-Napthoquinone also caused SCEs in human lymphocytes in the absence of metabolic activation (Wilson *et al*., 1996).

1,4-Napthoquinone

1,4-Napthoquinone was negative in the *Salmonella* reverse mutation assay (test strains TA98, TA100, TA1535 and TA1537) (Sakai *et al*., 1985). 1,4-Napthoquinone also did not induce mutations at either the *hprt* or *tk* loci in the human B-lymphoblastoid MCL-5 cell line (Sasaki *et al*., 1997). However, 1,4-napthoquinone did cause SCEs in human lymphocytes in the absence of metabolic activation (Wilson *et al*., 1996), and caused a significant increase in the frequency of

both $CREST^+$ (indicative of chromosomal loss) and total micronuclei in the human B-lymphoblastoid MCL-5 cell line (Sasaki *et al*., 1997).

Naphthalene 1,2-epoxide

Naphthalene 1,2-epoxide did not cause SCEs in human lymphocytes in the absence of metabolic activation (Wilson *et al*., 1996).

Naphthalene Atmospheric Reaction Products

Naphthalene is one of the more abundant PAH air pollutants in California. Atmospheric naphthalene occurs partially in the vapor phase and enters into rapid gas-phase reactions with hydroxyl radical (HO, daytime) and nitrate radicals (NO_3, nighttime). Reaction products include 1-nitronaphthalene (1NN), 2-nitronaphthalene (2NN), 1-hydroxy-2-nitronaphthalene (1H2NN), and 2-hydroxy-2-nitronaphthalene (2H2NN). Sasaki *et al*. (1997) evaluated the genotoxicity of these reaction products in the human B-lymphoblastoid MCL-5 cell line. 2-Nitronaphthalene caused a significant increase both in the mutation frequency at the thymidine kinase (*tk*) locus, and in the total micronucleus number (indicative of chromosomal damage).

The above data indicate that naphthalene generally has not been shown to cause gene mutations, but has been demonstrated to cause chromosomal damage and may cause DNA damage. The naphthalene metabolite 1,4-napthoquinone also causes chromosomal damage, and 1,2-napthoquinone causes both gene mutations and chromosomal damage, as does the atmospheric reaction product 2-nitronaphthalene.

Cancer Bioassays

The National Toxicology Program (NTP) conducted inhalation cancer studies of naphthalene using male and female $B6C3F_1$ mice (NTP, 1992). Animals were exposed to 0 (70 males, 69 females), 10 (69 males, 65 females) or 30 ppm naphthalene (135 males, 135 females) for 6 hours/day, 5 days/week for 104 weeks.

The survival rates of exposed female mice were similar to that of controls (86%, 88% and 76% for controls, 10 and 30 ppm exposure groups, respectively). However, survival of male control mice was significantly less than that of exposed male mice (37%, 75% and 89% for controls, 10 and 30 ppm exposure groups, respectively). NTP stated that the reduced control survival was due to wound trauma and secondary infections due to fighting among the group-housed mice.

Almost all of the male and female mice in the NTP 1992 mouse inhalation studies demonstrated an increased incidence of nasal respiratory epithelium hyperplasia and olfactory epithelium metaplasia (Table 4).

Table 4. Incidence of nonneoplastic nasal lesions in male and female B6C3F$_1$ exposed to naphthalene by inhalation for 104 weeks (NTP, 1992).

Lesion type	Sex	Naphthalene concentration		
		0 ppm	10 ppm	30 ppm
respiratory epithelium hyperplasia	male			
overall rate		0/70 (0%)	66/69 (96%)	134/135 (99%)
average severity grade[a]		0	2.6	2.8
olfactory epithelium metaplasia				
overall rate		0/70 (0%)	66/69 (96%)	134/135 (99%)
average severity grade[a]		0	2.5	2.6
respiratory epithelium hyperplasia	female			
overall rate		0/69 (0%)	65/65 (100%)	135/135 (100%)
average severity grade[a]		0	2.5	2.7
olfactory epithelium metaplasia				
overall rate		0/69 (0%)	65/65 (100%)	135/135 (100%)
average severity grade[a]		0	2.5	2.4

a: Average severity grade based on 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.

Increased incidences of alveolar/bronchiolar adenomas and carcinomas were observed in male B6C3F$_1$ mice. Alveolar/bronchiolar adenoma or carcinoma incidences in the male mice as cited by NTP were 7/70, 17/69 and 31/135 for controls, and the 10 and 30 ppm exposure groups, respectively. The increased tumor incidences observed for the 10 and 30 ppm groups were significant when a pairwise comparison to control was performed using the Fisher exact test (p = 0.019 and 0.016 for the 10 and 30 ppm groups, respectively). However, NTP noted that an evaluation of the dose-response trend (p = 0.530) and pairwise comparisons between the controls and exposure groups (p = 0.212 and 0.394 for the 10 and 30 ppm exposure groups, respectively) using a logistic regression test indicated a lack of statistical significance. This was explained by NTP as being the result of the early control mortality due to fighting which lowered considerably the number of control animals at risk of developing lung tumors. NTP also noted that the alveolar/bronchiolar adenoma and carcinoma incidence (adjusted rate 26% in the high dose group) was within the historical control range for male B6C3F$_1$ mice (total incidence 19.7%, range 10-30%). NTP therefore concluded that the marginally increased alveolar/bronchiolar adenoma and carcinoma incidence in the male mice was more likely to be related to survival difference between exposed and control groups, than directly related to naphthalene exposure.

Increased incidences of alveolar/bronchiolar adenomas and carcinomas were also observed in female B6C3F$_1$ mice. The incidences of alveolar/bronchiolar adenoma or carcinoma, combined, in the female mice as cited by NTP were 5/69, 2/65 and 29/135 for controls, and the 10 and 30 ppm exposure groups, respectively. The tumors were primarily adenomas; one carcinoma was observed in high dose female mice. The increased tumor incidence in the 30 ppm exposure group females was statistically significant when compared to controls. NTP concluded that this provided *some evidence* of carcinogenicity.

These results were generally considered at the time to provide only equivocal evidence of carcinogenic activity, when considered in conjunction with earlier studies by various routes, which, although of lower power, also had negative or equivocal results (Adkins *et al*., 1986; Kennaway, 1930; Schmahl, 1955). However, the observation of possible tumor responses in the

mice prompted the National Toxicology Program to undertake naphthalene inhalation cancer studies in rats.

NTP (2000) exposed groups of 49 male and female Fischer 344N (F344) rats to naphthalene by inhalation at concentrations of 0, 10, 30 or 60 ppm for 6.2 hours/day, five days/week for 105 weeks. Survival of the male and female exposure groups were similar to that of controls.

These studies found clear evidence of carcinogenic activity in male and female rats, based on increased incidences of rare tumors, respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose, in both sexes. Respiratory epithelial adenoma incidence occurred with a positive dose-response trend in male rats and was significantly increased in all exposed male rat groups. Male rat respiratory epithelial adenoma incidence as cited by NTP was 0/49, 6/49, 8/48 and 15/48 for controls, and the 10, 30 and 60 ppm exposure groups, respectively. Respiratory epithelial adenoma incidences in female rats exposed to 30 or 60 ppm were also increased, but the increase in the 60 ppm animals was not significant, and the increase in the 30 ppm animals was of borderline significance ($p = 0.053$ by Poly-3 test). Female rat respiratory epithelial adenoma incidence as cited by NTP was 0/49, 0/49, 4/49 and 2/49 for controls, and the 10, 30 and 60 ppm exposure groups, respectively.

Olfactory epithelial neuroblastomas occurred in males exposed to 30 and 60 ppm naphthalene and in all dose groups of naphthalene-exposed females. Neuroblastoma incidences occurred with positive dose-response trends in males and females. The incidence in females exposed to 60 ppm was significantly greater ($p < 0.001$ by Poly-3 test) than that in controls. Male rat olfactory epithelial neuroblastoma incidence as cited by NTP was 0/49, 0/49, 4/48 and 3/48 for controls, and the 10, 30 and 60 ppm exposure groups, respectively. Female rat olfactory epithelium neuroblastoma incidence as cited by NTP was 0/49, 2/49, 3/49 and 12/49 for controls, and the 10, 30 and 60 ppm exposure groups, respectively.

NTP also noted that nasal olfactory epithelial neuroblastomas and nasal respiratory epithelial adenomas have not been observed in male or female control rats in the NTP historical control database for animals fed NIH-07 feed in 2-year inhalation studies or in the more recent, smaller database for control rats fed NTP-2000 feed. Additionally, almost all of the male and female mice in the NTP 1992 inhalation studies demonstrated increased nasal respiratory epithelium hyperplasia and olfactory epithelium metaplasia (Table 1). These tissue types correspond to the tumor sites observed in rats exposed to naphthalene by inhalation.

Human Studies

Although a number of reports exist which describe non-cancer health effects in humans (OEHHA, 2000), no studies of carcinogenic effects in humans were identified.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Unit risk values for naphthalene were calculated based on data in female mice, male rats and female rats from the studies of NTP (1992, 2000). The mouse lung alveolar/bronchiolar adenoma or carcinoma incidence data, rat nasal respiratory epithelial adenoma data and nasal olfactory epithelial neuroblastoma data used to calculate unit risk values are listed in Tables 5, 6 and 7, respectively.

Table 5. Incidence of lung alveolar/bronchiolar adenoma or carcinoma in female $B6C3F_1$ mice exposed to naphthalene via inhalation (from NTP, 1992)

Chamber Concentration (ppm)	Average Concentration[a] (mg/m^3)	Lifetime Average Dose[b] (mg/kg-day)	Tumor Incidence[c] (%)	Statistical Significance[d]
0	0	0	5/67 (7)	$p < 0.001$
10	9.36	12.3	2/61 (3)	$p = 1$
30	28.1	36.8	29/129[e] (22)	$p < 0.01$

[a] Average concentration calculated by multiplying chamber concentration by six hours/24 hours, 5 days/7 days and 5.24 mg/m^3/ppm.

[b] Lifetime average doses were determined by multiplying the average concentrations during the dosing period by the female mouse breathing rate (0.038 m^3/day) divided by the female mouse body weight (0.029 kg). The dosing period of 104 weeks was equivalent to the standard lifespan of the test animals (104 weeks for rodents), so no correction for less than lifetime exposure was required.

[c] Effective rate. Animals that died before the first occurrence of tumor (day 471) were removed from the denominator.

[d] The *p*-value listed next to dose groups is the result of pairwise comparison with controls using the Fisher exact test. The *p*-value listed next to the control group is the result of trend tests conducted by NTP (1992) using the logistic regression, life table, and Cochran-Armitage methods (all three methods produced the same result).

[e] One carcinoma was observed in the high dose group.

Table 6. Incidence of nasal respiratory epithelial adenoma in male F344/N rats exposed to naphthalene via inhalation (from NTP, 2000)

Chamber Concentration (ppm)	Average Concentration[a] (mg/m^3)	Lifetime Average Dose[b] (mg/kg-day)	Tumor Incidence[c] (%)	Statistical Significance[d]
0	0	0	0/44 (0)	$p < 0.001$
10	9.67	5.69	6/42 (14)	$p < 0.05$
30	29.0	17.1	8/44 (18)	$p < 0.01$
60	58.0	34.1	15/41 (37)	$p < 0.001$

[a] Average concentration calculated by multiplying chamber concentration by 6.2 hours/24 hours, 5 days/7 days, and 5.24 mg/m^3/ppm.

[b] Lifetime average doses were determined by multiplying the average concentrations during the dosing period by the male rat breathing rate (0.262 m^3/day) divided by the male rat body weight (0.445 kg). The dosing period of 105 weeks was at least the standard lifespan of the test animals (104 weeks for rodents), so no correction for less than lifetime exposure was required.

Table 6 (cont.). Incidence of nasal respiratory epithelial adenoma in male F344/N rats exposed to naphthalene via inhalation (from NTP, 2000)

[c] Effective rate. Animals that died before the first occurrence of tumor (day 552) were removed from the denominator.

[d] The *p*-value listed next to dose groups is the result of pairwise comparison with controls using the Fisher exact test. The p-value listed next to the control group is the result of the Poly-3 trend test, as reported by NTP (2000).

Table 7. Incidence of nasal olfactory epithelial neuroblastoma in F344/N rats exposed to naphthalene via inhalation (from NTP, 2000)

Chamber Concentration (ppm)	Average Concentration[a] (mg/m^3)	Lifetime Average Dose[b] (mg/kg-day)	Tumor Incidence[c] (%)	Statistical Significance[d]
Males				
0	0	0	0/49 (0)	$p = 0.027$
10	9.67	5.69	0/48 (0)	$p = 1$
30	29.0	17.1	4/48 (8)	$p = 0.056$
60	58.0	34.1	3/48 (6)	$p = 0.117$
Females				
0	0	0	0/49 (0)	$p < 0.001$
10	9.67	6.82	2/49 (4)	$p = 0.247$
30	29.0	20.4	3/49 (6)	$p = 0.121$
60	58.0	40.9	12/48 (25)	$p < 0.001$

[a] Average concentration calculated by multiplying chamber concentration by 6.2 hours/24 hours, 5 days/7days, and 5.24 mg/m^3/ppm.

[b] Lifetime average doses were determined by multiplying the average concentrations during the dosing period by the rat breathing rate (males: 0.262 m^3/day; females: 0.182 m^3/day) divided by the rat body weight (males: 0.445 kg; females: 0.258 kg). The dosing period was at least the standard lifespan of the test animals (104 weeks for rodents), so no correction for less than lifetime exposure was required.

[c] Effective rate. Animals that died before the first occurrence of tumor (males, day 399; females, day 429) were removed from the denominator.

[d] The p-value listed next to dose groups is the result of pairwise comparison with controls using the Fisher Exact test. The p-value listed next to the control group is the result of the Poly-3 trend test, as reported by NTP (2000).

Methodology

The default approach, as originally delineated by CDHS (1985), is based on a linearized form of the multistage model of carcinogenesis (Armitage and Doll, 1954). Cancer potency is estimated from the upper 95% confidence bound, q_1^*, on the linear coefficient q_1 in a model relating lifetime probability of cancer (p) to dose (d):

$$p = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \ldots)] \quad (1)$$

The parameter q_1^* is estimated by fitting the above model to dose response data using MSTAGE (Crouch, 1992).

For a given chemical, the model is fit to one or more data sets. The default approach is to select the data for the most sensitive species and sex. For carcinogens that induce tumors at multiple sites, or at the same site but arising from different cell types, in a particular species and sex, cancer potency is taken to be the sum of potencies from the different sites or cell types. This approach assumes that tumors arising at different sites or from different cell types are independent. Because of the statistical uncertainty in individual estimates of potency, the terms are summed statistically as follows. A distribution of estimates corresponding to the 0.1 through 99.9 percentiles of the linear term (q_1) of the multistage model (Equation 1) is generated for each treatment-related tumor site in a given species and sex using the computer program MSTAGE (Crouch, 1992), modified to tabulate percentile values. (Distributional values stem from the assumption that twice the log likelihood function is χ^2 distributed). The discretized distributions were used to obtain a distribution of the sum of q_1s for each site affected by the chemical using Monte Carlo simulation (100,000 trials; Crystal Ball 2000 software, Decisioneering, Inc., Denver, Colorado). The upper 95 percent confidence bound on the summed q_1s is taken as q_1* for the combined tumor sites.

To estimate animal potency, q_{animal}, the parameter q_1* is adjusted to account for short duration of an experiment by assuming that the lifetime incidence of cancer increases with the third power of age. However, the durations of the studies examined here (NTP, 1992; 2000) were at least the standard lifespan of the test animals (104 weeks for rodents), so this correction was not required. Thus, for the calculations based on the NTP (1992; 2000) studies, q_1* is equivalent to q_{animal}.

Interspecies extrapolation from experimental animals to humans is normally based on the following relationship (Anderson *et al*., 1983), where bw_h and bw_a are human and animal body weights, respectively, and potency (e.g., q_{animal}) is expressed on a dose per body weight basis:

$$q_{human} = q_{animal} \times \left(\frac{bw_h}{bw_a} \right)^{\frac{1}{3}} \qquad (2)$$

Alternatively, when performing calculations based on applied dose in terms of air concentrations, the assumption has sometimes been made that air concentration values are equivalent between species (CDHS, 1985). However, using the interspecies scaling factor shown above is preferred because it is assumed to account not only for pharmacokinetic differences (*e.g.*, breathing rate, metabolism), but also for pharmacodynamic considerations. Therefore, lifetime average doses in mg/kg-day were determined (details provided below) and used in the calculation of q_{animal} in $(mg/kg\text{-}day)^{-1}$. The interspecies scaling factor was applied to q_{animal} to obtain q_{human} in $(mg/kg\text{-}day)^{-1}$. Unit risk in $(mg/m^3)^{-1}$was determined from q_{human} in $(mg/kg\text{-}day)^{-1}$ by applying a conversion factor (the ratio of human breathing rate [20 m^3/day] to human body weight [70 kg]).

Male and female rats (NTP, 2000) were exposed 6.2 hours/day, five days/week for 105 weeks. Female mice (NTP 1992) were exposed six hours/day, five days/week for 104 weeks. Average concentrations during the dosing period were calculated by multiplying the reported chamber concentrations by 6 or 6.2 hours/24 hours, five days/seven days and 5.24 mg/m^3/ppm. The average body weight of female mice was estimated to be approximately 0.029 kg based on data for controls reported by NTP (1992). The average body weights of male and female rats were calculated to be

0.445 kg and 0.258 kg, respectively, based on data for controls reported by NTP (2000). Inhalation rates (I) in m^3/day for mice and rats were calculated based on Anderson *et al.* (1983):

$$I_{mice} = 0.0345 \times (bw_{mice}/0.025)^{2/3} \quad (3)$$

$$I_{rats} = 0.105 \times (bw_{rats}/0.113)^{2/3} \quad (4)$$

Breathing rates were calculated to be 0.038 m^3/day for female mice, 0.262 m^3/day for male rats, and 0.182 m^3/day for female rats. Lifetime average doses were determined by multiplying the average concentrations during the dosing period by the appropriate animal breathing rate divided by the corresponding animal body weight. The dosing periods in the NTP studies were at least the standard lifespan of the test animals (104 weeks for rodents), so no correction for less than lifetime exposure was required.

An alternative dose description approach, using pharmacokinetic analyses based on models described in the literature (Willems *et al.*, 2001; Quick and Shuler, 1999; Sweeney *et al.*, 1996; Frederick *et al.*, 1998, 2001; NTP, 2000) was evaluated. Although no data were available on the metabolism of naphthalene by rodent nasal tissues, simulations were conducted using parameters for rats and mice assuming either lung-like or liver-like scaling. The model predictions evaluated included amounts of naphthalene metabolized in each of the seven nasal compartments and their sum and the areas under the concentration × time curves (AUCs) for the olfactory and ventral respiratory compartments. Since all of these metrics appeared linear and in relative proportion to the applied doses, they did not indicate any substantial difference from the default potency analysis. If the assumptions used are correct, the concentrations used in the NTP studies were below those at which saturation of metabolism or other pharmacokinetic effects become important in the nasal and lung regions.

Application of an uptake rate for naphthalene was also considered. NTP (2000) estimated inhalation uptakes of 22 to 31 percent for rats and 65 to 73 percent for mice based on pharmacokinetic data and PBPK modeling. However, in the subsequent publication of NTP's PBPK modeling of inhaled naphthalene, uptakes are estimated to be 85 to 94 percent in rats and 92 to 96 percent in mice (Table 3, Willems *et al.*, 2001). Until more reliable estimates become available we assume there are no significant differences in uptake between mice and rats used in the NTP bioassay. Also we assume similar uptake in humans exposed to low levels of naphthalene.

Table 8 provides the q_{animal}, q_{human} and unit risk values, calculated using the linearized multistage procedure as described above, based on data for female mice (NTP, 1992) and male and female rats (NTP, 2000).

U.S. EPA (2003) and others (*e.g.* Gaylor *et al.*, 1994) have more recently advocated a benchmark dose method for estimating cancer risk. This involves fitting an arbitrary mathematical model to the dose-response data. A linear or multistage procedure is often used, although others may be chosen in particular cases, especially where mechanistic information is available which indicates that some other type of dose-response relationship is expected, or where another mathematical model form provides a better fit to the data. A point of departure on the fitted curve is defined: for animal carcinogenesis bioassays this is usually chosen as the lower 95% confidence bound on the

dose predicted to cause a 10% increase in tumor incidence (LED_{10}). Linear extrapolation from the point of departure to zero dose is used to estimate risk at low doses either when mutagenicity or other data imply that this is appropriate, or in the default case where no data on mechanism are available. The slope factor thus determined from the experimental data is corrected for experimental duration and interspecies extrapolation in the same way as the q_1^* adjustments described for the linearized multistage procedure. In the exceptional cases where data suggesting that some other form of low-dose extrapolation, such as the assumption of a threshold, is appropriate, a reference dose method with safety factors as required may be used instead.

Table 8. Cancer potency and unit risk values for naphthalene derived using the linearized multistage procedure based on data from NTP (1992) and NTP (2000).

Sex, Species	Site, Tumor Type	q_{animal} $(mg/kg\text{-}day)^{-1}$	q_{human}[a] $(mg/kg\text{-}day)^{-1}$	Human Unit Risk Value[b] $(mg/m^3)^{-1}$	Goodness-of-Fit Test[c]
Female mice	Lung alveolar/bronchiolar adenoma/carcinoma	0.004382	0.059	0.017	$p = 0.1428$
Male rats	Nasal respiratory epithelial adenoma	0.01919	0.10	0.030	$p = 0.4192$
	Nasal olfactory epithelial neuroblastoma	0.004651	0.025	0.0072	$p = 0.4224$
	All naphthalene-related tumor sites in male rats	0.02219	0.12	0.034	NA[d]
Female rats	Nasal olfactory epithelial neuroblastoma	0.007636	0.049	0.014	$p = 0.6342$

[a] The interspecies extrapolation was applied to q_{animal} in $(mg/kg\text{-}d)^{-1}$ to determine q_{human} $(mg/kg\text{-}day)^{-1}$, as described above.

[b] Unit risk was determined by multiplying the human cancer potency in $(mg/kg\text{-}day)^{-1}$ by the human breathing rate divided by human body weight, as described above.

[c] A *p*-value of greater than 0.05 for the chi-square goodness-of-fit test indicates an adequate fit.

[d] Not applicable.

The benchmark dose methodology was applied to the tumor incidence data for naphthalene in the NTP (1992; 2000) studies. Genetic toxicology results for naphthalene are mixed: *Salmonella* reverse mutation assays were generally negative, but some test results with eukaryotic systems *in vivo* or *in vitro* were positive (NTP, 2000). However, it was considered on balance that the weight of evidence, including metabolism to 1-naphthol via an epoxide intermediate (NTP, 1992, citing Bock *et al.*, 1976 and others; NTP, 2000), and the reactivity of naphthoquinones to cellular components (Zheng *et al*., 1997) favors the interpretation that the mechanism of naphthalene carcinogenicity likely involves a reactive metabolic intermediate which causes direct damage to DNA. A low dose linearity assumption is therefore appropriate when extrapolating from the point of departure to obtain an estimate of the cancer risk at low doses.

Model fits, points of departure and unit risks calculated using the benchmark methodology and U.S. EPA's Benchmark Dose Software version 1.3 are shown in Table 9. In all three cases, the model used was either a multistage polynomial, or a quantal linear model, which is identical to the multistage procedure in cases where the higher terms are not significant.

Table 9: Unit risk and human cancer potency values for naphthalene based on NTP (1992) and NTP (2000), derived using benchmark methodology.

Sex, Species	Site, Tumor Type	Model Fit:[a]	LED_{10} [ED_{10}] (mg/m^3)	Animal Unit Risk Value[b] $(mg/m^3)^{-1}$	Human Unit Risk Value[c] $(mg/m^3)^{-1}$ [Human Cancer Potency][c] $(mg/kg\text{-}d)^{-1}$
Female mice	Lung alveolar/bronchiolar adenoma/carcinoma	$\chi^2 = 1.42$ $p = 0.23$	17.1 [22.8]	0.0058	0.017 [0.059]
Male rats	Nasal respiratory epithelial adenoma	$\chi^2 = 2.82$ $p = 0.42$	9.3 [12.5]	0.0108	0.028 [0.099]
	Nasal olfactory epithelial neuroblastoma	$\chi^2 = 2.82$ $p = 0.42$	38.5 [67.6]	0.0026	0.0068 [0.024]
	All naphthalene-related tumor sites in male rats	NA	8.1[d] [10.6]	0.012	0.031 [0.11]
Female rats	Nasal olfactory epithelial neuroblastoma	$\chi^2 = 1.73$ $p = 0.63$	18.1 [26.4]	0.0055	0.014 [0.050]

[a] A *p*-value of greater than 0.05 for the chi-square goodness-of-fit test indicates an adequate fit.

[b] Animal unit risk was calculated using the relationship $0.1/LED_{10}$.

[c] The interspecies extrapolation from rodent unit risks to human unit risks was based on the $(mg/kg\text{-}d)^{-1}$ equivalents of the animal unit risks, as described above. The following parameters were used to derive the $(mg/kg\text{-}day)^{-1}$ equivalents of the animal unit risks: bw_{animal} = 0.029 kg for female mice, 0.445 kg for male rats, and 0.258 kg for female rats; I_{animal} = 0.038 m^3/d for female mice, 0.262 m^3/d for male rats and 0.182 m^3/d for female rats. Human cancer potency was derived by applying the interspecies scaling factor to the $(mg/kg\text{-}day)^{-1}$ equivalents of the animal unit risks. The interspecies scaling factor is $(bw_{human}/bw_{animal})^{1/3}$, or 13.4 for female mice, 5.4 for male rats, and 6.5 for female rats. Human unit risks were then derived by multiplying human cancer potency by the human breathing rate (20 m^3/day) divided by the human body weight (70 kg).

[d] The LED_{10} in mg/m^3 for the multi-tumor analysis in rats was calculated by assuming a linear dose response relationship: $LED_{10} = -\ln(0.9)/(q_{animal} \times [I_{animal}/bw_{animal}])$. By inspection, this assumption appears reasonable for the dose-response curves considered, in the ED_{10} range. For the current case, q_{animal} is the cancer potency in rats ($0.02219\ [mg/kg\text{-}day]^{-1}$) generated using the multi-tumor analysis described above, I_{animal} is the breathing rate in male rats (0.262 m^3/day), and bw_{animal} is the male rat body weight (0.445 kg).

Using either of these methodologies, the 95% upper confidence bound on the unit risk value for purposes of calculating cancer risks associated with exposure to naphthalene is in the range 0.014-0.034 $(mg/m^3)^{-1}$, based on the incidence data in female mice and male and female rats from the NTP (1992; 2000) studies.

The male rat was the most sensitive sex and species tested by NTP (1992; 2000) in the inhalation carcinogenesis studies of naphthalene. NTP considered the increased incidences of nasal respiratory epithelial adenoma and nasal olfactory epithelial neuroblastoma, which are rare tumors, to provide clear evidence of the carcinogenic activity of naphthalene. The unit risk value of 0.034 $(mg/m^3)^{-1}$, or 3.4×10^{-5} $(\mu g/m^3)^{-1}$, based on the tumor incidence data in male rats, is therefore considered the most appropriate for use in risk assessment.

V. REFERENCES

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NICKEL AND NICKEL COMPOUNDS

CAS No: 744-02-0 (nickel)

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	59 (nickel)
Boiling point	2730°C
Melting point	1455°C
Vapor pressure	not applicable
Air concentration conversion	not applicable

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.6 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 9.1 E-1 $(mg/kg\text{-}day)^{-1}$

[Calculated from Ontario nickel refinery sinter plant worker lung cancer mortality data (Chovil *et al.,* 1981; Roberts *et al.,* 1984; Muir *et al.,* 1985), using excess relative risk estimates (CDHS, 1991)].

III. CARCINOGENIC EFFECTS

Human Studies

Epidemiologic studies of the carcinogenic effects of nickel generally center around cohort studies of refinery workers which have found increased risk of lung cancer and nasal sinus cancer. While other types of studies have been done, cohort studies of nickel refinery workers warrant special consideration for use in quantitative risk assessment in view of the high cancer risks detected and the availability of at least some exposure information. There are many studies of welders, for example, but exposure data are limited and the increase in lung cancer risks may have been more attributable to chromium than to nickel (Stern, 1983). A comprehensive quantitative risk analysis was undertaken by the US Environmental Protection Agency (US EPA) for the 1986 Health Assessment Document (US EPA, 1986). The following sections review the lung cancer findings for the cohort studies used in the US EPA risk assessment, and their subsequent follow-up by the International Committee on Nickel Carcinogenesis in Man (ICNCM). These studies also report increased risk of nasal cancer. However, the excess number of lung cancers were generally much greater than the excess numbers of nasal cancers.

Enterline and Marsh (1982) studied a West Virginia cohort consisting of 1,855 workers employed by the International Nickel Company (INCO) at a nickel refinery and alloy manufacturing plant in Huntington, West Virginia. Cohort members had at least one year service prior to 1948 when the calcining operations ceased. The cohort was followed to the end of 1977. Among the subset of 266 men that worked in the nickel refinery there were 113 deaths, eight of which were from lung cancer. The corresponding lung cancer standardized mortality ratio (SMR) for 20 or more years after first exposure was only 1.12 (90% confidence limits 0.56 and 2.02). Air levels of nickel were in the range of 0.01-5.0 mg/m^3.

The ICNCM (1990) reported a further five years of follow-up of this cohort up to 1982. Among workers hired before 1947 and who had 15 or more years since first exposure in calcining, there were eight lung cancer deaths yielding an SMR estimate of 1.15 (90% confidence limits 0.57 - 2.07). Two nasal cancer deaths were reported with 0.9 expected.

The Ontario cohort involved refinery workers at Copper Hill, Ontario (Chovil *et al.,* 1981; Roberts *et al.,* 1984; Muir *et al.,* 1985). A subcohort with high exposure to nickel consisted of 495 workers with five or more years' work history at a sinter plant operated by the INCO between 1948 and 1963. Workers were followed up from 1963 to the end of 1978, a minimum of 15 years. Eighty-five cohort members died during the follow-up period, of which 37 were lung cancer deaths. The SMR for lung cancer was 8.71, (90% confidence limits 6.49 and 11.45).

The ICNCM (1990) reported a further follow-up of this cohort up to 1984. There were a total of 63 lung cancer deaths and 6 nasal cancer deaths among the Copper Cliff sinter plant workers with 15 or more years since first exposure. Of the 63 lung cancer deaths, 33 had five or more years of exposure and yielded an SMR of 7.89 (90% confidence limits 5.78 - 10.56). For those who commenced work prior to 1952, the SMR estimate was 8.55 (90% confidence limits 6.15 - 11.59). These estimates are close to the SMR of 8.71 obtained from the earlier report by Chovil *et al.* presented above. Exposure data were given by Roberts *et al.* (1984) who estimated a level of 400 mg/m^3 in 1950, falling to 100 mg/m^3 "toward the end of the plant's productive life in 1958." Calculations based on the data give an average of 158 mg/m^3 for measurements made before 1952 and an average level of 73 mg/m^3 for measurements made after 1952.

Studies of a Welsh nickel refinery cohort involved 967 refinery workers, some of whom started working as early as 1910 at a nickel refinery in Clydach Wales, operated by INCO. Several publications provide some form of dose-response data. These studies include: 1) Doll et al. (1977) in which lung cancer mortality is presented by year of first employment; 2) Peto et al. (1984) study which categorized the cohort members by duration of exposure in the calcining furnaces, and 3) analyses by various exposure variables by Breslow and Day (1987) and Kaldor et al. (1986).

The Doll et al. (1977) study followed the employees up until the end of 1971 and calculated man-years at risk from 1934-1971. There were 689 total deaths in the cohort, including 145 lung cancer deaths, yielding a lung cancer SMR of 5.28 (90% CI: 4.58-6.03). The risk of lung cancer was increased in workers exposed before 1930.

The Peto *et al.* (1984) study updated dates of first employment in cases where additional information had come to light since the publication of the Doll *et al.* (1977) paper. Employees were classified into low and high exposure groups based on the number of years each employee spent at the furnaces or in the copper sulfate work areas. The lung cancer SMR for the low exposure group was 3.7 while that for the high exposure group was 14.0. Again, this paper provided no nickel exposure data. The ICNCM reported further follow-up of the cohort to 1984. There were 172 lung cancer deaths and 74 nasal cancer deaths among those hired prior to 1930. The overall lung cancer SMR was 3.93 (90% confidence limits 3.45-4.46). For those men hired before 1920, the SMR was 5.49 (90% confidence limits 4.57-6.60). This is the only cohort in which the excess number of nasal cancer deaths (73.6) was significant in number compared to the

excess number of lung cancer deaths (128.2). In the other cohorts reviewed, the excess number of lung cancer cases are much larger than the excess number of nasal cancers.

Exposure data are available for the Welsh cohort from a paper by Morgan (1985) in which a historical description of nickel monitoring at Clydach was presented. The main problem with the exposure data for this cohort is that the earliest data are for 1932. There were no measurements prior to 1930 when exposures were said to be higher.

Studies on a Norwegian nickel refinery worker cohort were described in two papers (Magnus *et al.,* 1982; Pedersen *et al.,* 1973). This cohort involved 2,247 refinery workers employed for at least three years prior to 1969 in Kristiansand, Norway. Follow-up was accomplished to the end of 1979, for a minimum of 10 years. Eighty-two lung cancer cases were observed, giving an SMR of 3.73 and 90% confidence limits 3.08 and 4.48. SMRs unadjusted for smoking habits ranged from 2.28 for those followed up for 3-14 years, to 4.30 for those followed up for more than 35 years. Exposure data for this site were estimated by the US EPA based on INCO estimates of exposure at the Clydach Wales plant. No exposure data were available from the Norwegian smelter itself. The US EPA (1986) took as their exposure estimate the range from 3 to 35 mg Ni/m^3 assuming air levels would be similar to those in the Welsh smelter, and further assumed exposure over one quarter of a lifetime as no record of number of years worked was provided for the Norwegian cohort.

The ICNCM report presented further follow-up of this cohort to 1984. There were 77 lung cancer cases among the refinery workers with an SMR estimate of 2.62 (90% confidence limits 2.15 - 3.16). Three deaths from nasal cancer were reported with 0.66 expected. It was thought that the excess lung cancer risk among electrolysis workers should be attributed to soluble nickel exposure. No actual measurements of exposure were presented.

Table 1 presents a range of exposure estimates and confidence limits around the SMRs for the West Virginia, the Ontario, the Welsh and the Norwegian cohort studies. The ICNCM follow up studies of these cohorts did not alter the relative magnitude of the precision estimates. The precision of the relative risk estimates is assessed by the upper confidence limit of the excess relative risk estimate divided by the point estimate (Table 1).

Table 1: Lung cancer risks in four cohort studies (from US EPA, 1986)

Study	Number of subjects	Lung cancer deaths	Lung cancer SMR	90% confidence limits(CI)	Ratio of upper CI of (SMR-1) to (SMR-1)*
W. Virginia	1855	8	1.12	0.56, 2.02	8.5
Ontario	495	37	8.71	6.49, 11.45	1.4
Wales	967	145	5.28	4.58 – 6.03	1.2
Norway	2247	82	3.73	3.08, 4.48	1.3

* Note: the (SMR-1) is an estimate of excess relative risk

The Ontario cohort study was determined to be the most appropriate for quantitative cancer risk assessment (CDHS, 1991). The main reason for choosing this cohort was that it was the only cohort with actual measurements of exposure associated with a relevant causal period with sufficient

latency (available from 1948 on which is the most relevant period for the lung cancer deaths ascertained between 1963 and 1978).

Animal Studies

At the time that the CDHS (1991) report "Health Risk Assessment for Nickel" was written, inhalation exposure cancer bioassays had only examined insoluble forms of nickel for their carcinogenic potential. Likewise, only soluble forms of nickel had been evaluated by oral administration. Evidence of carcinogenic potential following inhalation exposure has been shown for nickel subsulfide (Ni_3S_2) and suggested for nickel carbonyl. Inhalation exposure to metallic nickel resulted in very poor survival which was too short to properly evaluate carcinogenicity. Many rats exposed to metallic nickel by inhalation developed squamous metaplasia and peribronchial adenomatoses (Hueper and Payne, 1962). Exposure to metallic nickel by intratracheal instillation produced a significant increase in lung tumor incidence. Pott *et al.* (1987) administered nickel powder in a total intratracheal dose of 6 or 9 mg Ni/animal to female Wistar rats. Following treatment, animals were maintained for up to an additional 2.5 years. The lung tumor incidence in the saline control, 6 mg Ni (0.3 mg Ni × 20), and 9 mg Ni (0.9 mg × 10) treatment groups were 0%, 26% and 25%, respectively. The results from the nickel oxide (NiO) studies assessing the carcinogenicity of nickel oxide following inhalation exposure are negative in hamsters (Wehner *et al.,* 1975, 1981) and inconclusive in rats (Takenaka *et al.,* 1985; Glaser *et al.,* 1986; Horie *et al.,* 1985). These studies were also plagued by very poor survival rates. Intratracheal instillation of nickel oxide resulted in lung tumor induction. Female Wistar rats received a total dose of 0, 50, or 150 mg Ni/animal. Animals were maintained for an additional 2.5 years. The lung tumor incidence in the saline control, 50 (5 mg Ni × 10) and 150 mg Ni (15 mg Ni × 10) were 0%, 27% and 32%, respectively (Pott *et al.,* 1987).

Two studies produced positive results in evaluating the pulmonary tumorgenicity of nickel subsulfide, one utilizing inhalation exposure (Ottolenghi *et al.*, 1974) and the other, intratracheal administration. In the Ottolenghi *et al.* study 122 male and 104 female Fischer-344 rats were exposed to 0.97 mg/m^3 nickel subsulfide via inhalation for 78-80 weeks (6 hours/day, 5 days/week). The control group, 120 male and 121 female rats, was exposed to clean air. The study design included two subtreatments in a 2^4 factorial arrangement. The two subtreatments were: 1) pre-exposure for one month to 0.97 mg/m^3 nickel subsulfide 6 hr/day, 5 day/week; and 2) injection of the pulmonary infarction agent, hexachlorotetrafluorobutane. Animals found moribund or succumbing during the study and those killed at the end of the observation period (i.e., 30 weeks) were necropsied. A small number of animals (18 in the exposed and 26 in the control groups) were not examined because of autolysis or cannibalism.

The results demonstrated a significant increase in lung tumors (adenomas, adenocarcinomas, squamous cell carcinomas, and fibrosarcomas) in the exposed 110 male and 98 female rats examined as compared with the control 108 male and 107 female rats examined (Table 2).

Table 2: Neoplastic Changes in Lungs of Rats Exposed to Nickel Subsulfide

Tumors	Controls		Nickel Subsulfide Exposed	
	Males	Females	Males	Females
Adenoma	0/108 (0%)	1/107 (1%)	8/110 (7%)[b]	7/98 (7%)[a]
Adenocarcinoma	1/108 (1%)	0/107 (0%)	6/110 (5%)[a]	4/98 (4%)[b]
Squamous cell carcinoma	0/108 (0%)	0/107 (0%)	2/110 (2%)	1/98 (1%)
Fibrosarcoma	0/108 (0%)	0/107 (0%)	1/110 (1%)	0/98 (0%)

[a] $p < 0.01$, Fisher's Exact Test
[b] $p < 0.05$, Fisher's Exact Test

The two subtreatments, described above, did not alter the effects produced by nickel subsulfide treatment (Ottolenghi *et al.*, 1974). Sex of the exposed animal also did not appear to alter the effects produced by the nickel subsulfide treatment. The study results of Ottolenghi *et al.* (1974) for nickel subsulfide were selected for a quantitative risk assessment.

At the time the CDHS (1991) risk assessment was conducted, injection administration (intramuscular) was the only route of exposure from which data were available for comparison of carcinogenic potency of a variety of nickel compounds. Injection studies by Sunderman (1984) and Skaug *et al.* (1984) demonstrate that based on the incidence of sarcomas produced at the injection site, nickel subsulfide and nickel oxide possess approximately equal potency following this route of exposure. None of the studies utilizing oral exposure has produced evidence of carcinogenic potential. However, it should be noted that only nickel sulfate ($NiSO_4$) has been adequately evaluated in rats by this route.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Nickel subsulfide has been observed to induce lung tumors in male and female rats (Ottolenghi *et al.,* 1974). This study and the Ontario cohort study (Chovil *et al.,* 1981; Roberts *et al.,* 1984; Muir *et al.,* 1985; ICNCM, 1990), which demonstrated an increased risk of lung cancer associated with occupational nickel exposure in humans, were determined to be the most appropriate for use in developing a quantitative cancer risk assessment

Methodology

In the Ottolenghi *et al.* study, the low survival rate of the nickel subsulfide exposed group was examined. Mortality was about the same during the first year of study between the control and the nickel-exposed group but in the 76th week when the first tumor was observed, the exposed group had a 6% higher mortality rate (23% vs. 17% for controls). Taking this into account, the subsequent mortality [(0.94 (exposed group mortality) – 0.23) × 208 (animals examined) = 148 animals] in the nickel-exposed group due to tumors was 29/148 or approximately 20%. Based on these assumptions, nearly all of the differences (0.32 – 0.06 = 0.26) in the survival between control animals (32%) and the treated animals (6%) can be explained by lung tumor mortality. The animal

data was adjusted for continuous lifetime exposure [(979 $\mu g/m^3$)(6/24 hr)(5/7 day)(78/110) = 122.8 $\mu g/m^3$]. This was used to calculate the human equivalent exposure level using an inspiration rate of 20 m^3/day and a 70 kg body weight. The CDHS staff (CDHS, 1991) used a multistage model (GLOBAL86), fitted to adjusted data from this inhalation bioassay to yield a maximum likelihood estimate of carcinogenic potency of 2×10^{-4} $(\mu g/m^3)^{-1}$) nickel subsulfide (or 28×10^{-4} $(\mu g\ Ni/m^3)^{-1}$). The upper 95% confidence limit of the estimated carcinogenic potency is 28×10^{-4} $(\mu g/m^3)^{-1}$ nickel subsulfide [or 38×10^{-4} $(\mu g\ Ni/m^3)^{-1}$].

The risk quantification was also conducted using epidemiological data from worker studies. The Ontario cohort study (Chovil *et al.,* 1981; Roberts *et al.,* 1984; Muir *et al.,* 1985; ICNCM, 1990) was determined to be the most appropriate for quantitative cancer risk assessment due primarily to the fact that it was the only cohort study with exposure measurements available for a sufficiently early time period. The West Virginia cohort (Enterline and Marsh 1982; ICNCM, 1990) was rejected for use in the quantitative risk assessment due to the imprecision associated with the low SMR reported, which could have been due to confounding factors. The Norwegian cohort (Magnus *et al.,* 1982; Pedersen *et al.,* 1973) was deemed unsuitable for risk assessment due to the absence of nickel exposure data from the refinery. The Welsh cohort (Doll *et al.,* 1977; Peto *et al.,* 1984; Breslow and Day, 1987; Kaldor *et al.,* 1986; ICNCM, 1990) was also not used in the quantitative risk assessment because exposure measurements were not available for a relevant time period.

A relative risk model was chosen as the most appropriate method for linear extrapolation to low dose lifetime exposure. The excess risk from nickel exposure among smokers was assumed to be the same as among non-smokers. SMR values were plotted against cumulative exposure, and the slope of the linear regression of the data was 9.22. The 95% confidence limit of the slope was 11.26. This upper limit was corrected to 11.85 for the fraction of the study group lost to follow-up. The exposure was adjusted for an equivalent lifetime exposure [(8 hr/24 hr) × (5 days/7 days) × (48 weeks/52 weeks)]. The excess relative risk estimate for lifetime exposure at 1 mg/m^3 was 5.04. Considering the background lifetime mortality risk of 0.051 for Ontario at the time of the cohort study follow-up, the upper bound for lifetime added risk for exposure to 1 mg/m^3 was 2.57×10^{-1} (or 2.57×10^{-4} $(\mu g/m^3)^{-1}$). The average of the unit risk is 2.1×10^{-4} $(\mu g/m^3)^{-1}$ (257 × 9.22/11.26) using the actual SMR rather the upper confidence limit. Therefore, based on the human studies the range of unit risk is approximately 2.1 - 2.6×10^{-4} $(\mu g/m^3)^{-1}$. Using the human and animal data, the range of cancer risks is from 2.1 to 37×10^{-4} $(\mu g/m^3)^{-1}$. The best value chosen for the upper bound of risk was 2.6×10^{-4} $(\mu g/m^3)^{-1}$, derived from the human lung cancer incidence data. CDHS (1991) noted that the epidemiological studies indicate both soluble and insoluble nickel compounds are carcinogenic. However, the available epidemiologic data were inadequate to develop separate unit risk factors for different nickel compounds.

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N-NITROSODI-N-BUTYLAMINE

CAS No: 424-16-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	158.2
Boiling point	116° C @ 14 mm Hg
Melting point	0.5° C
Vapor pressure	Not found
Air concentration conversion	1 ppm = 6.46 mg/m^3 @ 25° C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.1 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 1.1 E+1 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There is no direct evidence that links nitrosamines, including N-Nitrosodi-n-butylamine (NDBA), to human cancer. The US EPA (1980) and IARC (1978) concluded that the epidemiological studies to date were inadequate to establish a valid causal relationship between nitrosamine exposure and human cancer. The US EPA (1980) also concluded that it was highly improbable that humans are refractory to the carcinogenic effects of nitrosamines considering the number of animal species that show increased tumor incidence following nitrosamine exposure. IARC (1978) concluded: "Although no epidemiological data were available, N-nitrosodi-n-butyl amine should be regarded, for practical purposes, as if it were carcinogenic to humans."

Animal Studies

Groups of DB rats were exposed to NDBA in the drinking water for an unspecified duration (Druckrey *et al*., 1967). The rats were exposed to 10, 20, 37, and 75 mg/kg-day NDBA. The incidence of liver carcinomas and adenomas was 2/10, 4/10, 13/16, and 4/4, respectively. No data on control rats were reported. Median time-to-tumor decreased from 540 days at 10 mg/kg-day, to 150 days at 75 mg/kg- day.

Male Wistar rats (15 total) were exposed for 24 weeks to 0.05% NDBA in drinking water (Okajima *et al*., 1971). Nine animals served as controls. At the end of this period, the 12 remaining animals were necropsied and found to have papillomas of the bladder. Eleven of the 12 animals had bladder carcinomas, 4 had hepatocellular carcinomas, and all had papillomas or carcinomas of the esophagus. The increased incidence of bladder carcinomas and esophageal tumors was statistically significant compared to the control group ($p < 0.001$). The incidence of liver carcinomas was not statistically different from controls ($p < 0.083$). A group of 20 male Fischer-F344 rats was exposed

to 5.4 mg NDBA by gavage twice per week for 30 weeks (Lijinsky and Reuber, 1983). Six animals survived to 100 weeks. Three animals survived to the end of the 108-week experiment. All treated animals were necropsied and examined for tumors. Of the 20 treated animals, liver carcinomas were observed in 12, lung carcinomas and adenomas in 9 and 4, respectively, forestomach cancer in 10, and bladder cancer in 7. In the control group of 20 male rats, one animal had a lung carcinoma, but no carcinomas of the esophagus, liver, or bladder were observed. The incidences of liver, lung, forestomach, and bladder carcinomas were significantly increased over controls ($p < 0.001$, 0.004, 0.001, and 0.004, respectively.).

A group of 42 male Fischer F344 rats were exposed to 0.005% (50 ppm) NDBA for 4 weeks (Imaida and Wang, 1986). The rats were followed for 100 weeks post-exposure and the median survival was 93 weeks. Esophageal cancer (unspecified type) was found in 26 of the 42 animals and esophageal papillomas in 7 of 42. In addition, liver nodules and carcinomas were found in 8/42 and 3/42 treated animals, respectively, and forestomach papillomas and carcinomas occurred in 6/42 and 2/42 treated animals, respectively. Bladder papillomas and carcinomas were found in 5/42 and 2/42 treated animals, respectively. In the control group of 39 animals, 2 animals had liver nodules, but no other tumors were detected.

Tsuda *et al*. (1987) exposed groups of 20 male F344 rats to 650, 1250, and 2500 ppm NDBA in the diet for 2 weeks. The rats were then fed an untreated diet for 50 weeks, at which time the animals were killed and necropsied. The incidence of bladder papillomas and hepatocellular carcinomas are shown in Table 1.

Table 1. Tumor incidence in male F344 rats exposed to diet containing N-nitrosodi-n-butylamine (NDBA) (Tsuda *et al*., 1987)

NDEA Treatment Group (ppm in diet)	Bladder papillomas	Hepatocellular carcinomas
650	2/20	0/20
1250	2/20	2/20
2500	4/20	4/20

Male ICR mice (39 total) were exposed to 50 ppm NDBA in the diet for 12 months (Takayama and Imaizumi, 1969). Of the surviving 33 mice at the end of 12 months, 27/33 had squamous cell carcinomas of the forestomach, 15/33 developed liver tumors (5 trabecular hepatomas and 10 adenomas), 8/33 developed lung adenomas, and 4/33 developed esophageal papillomas. Examination of the 28 surviving control animals revealed that 2 had lung adenomas, but no other tumors were reported in the controls.

Male or female C57Bl/6 mice (50/sex/group) were exposed to 60 or 240 ppm NDBA in their drinking water from age 10-12 weeks until moribund or dead (Bertram and Craig, 1970). The incidence of bladder carcinomas in males was 17/47 and 36/45 at the 60 and 240 ppm concentrations, respectively. Females developed bladder carcinomas with an incidence of 2/42 and 8/45 for the 60 and 240 ppm groups, respectively. Esophageal papillomas were found in 45/47 and 40/42 for males and 40/42 and 45/45 for females at the 60 and 240 ppm groups, respectively. No data on unexposed controls were presented.

Male and female Syrian Golden Hamsters (5/sex/group) were given single doses of 400, 800, or 1600 mg/kg NDBA by gavage; groups of 20 males or females served as controls (Althoff *et al*., 1973). Animals were observed for their lifespan and were killed when moribund. Mean survival times were affected in a dose-dependent manner; controls survived 63.5 weeks, and low-, medium- and high-dose groups survived for 59.6, 54.5, and 49.3 weeks, respectively. Respiratory neoplasms (unspecified type) were found in 0/40, 3/10, 5/10 and 7/10 hamsters of the control, low-, medium-, and high-dose groups, respectively. In a later study, Althoff *et al*. (1974) exposed groups of 20 (10/sex/group) male and female Syrian Golden hamsters to 0, 29, 58, 116, 232, or 464 mg/kg NDBA once pre week for life. In this study, the incidences of respiratory neoplasms were 0/20, 0/20, 0/19, 2/16, 12/20, and 8/16 for the groups exposed to 0, 29, 58, 116, 232, or 464 mg/kg NDBA, respectively.

Several studies in mice, rabbits and hamsters have shown NDBA to be carcinogenic following subcutaneous injection (Fuji *et al*., 1977; Flaks *et al*., 1973; Althoff *et al*., 1973 & 1974; Reznik *et al*., 1976; Cohen *et al*., 1975).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The study by Bertram and Craig (1970) was used by CDHS (1988) to derive the cancer potency for NDBA. The upper bound estimate of cancer potency from these data is the most reliable upper bound from dose-response data in sensitive species.

The upper 95% bound on the multistage polynomial could not be determined from the tumor incidence data in two other studies: Althoff *et al*. (1974) and Okajima *et al*. (1971). The potency estimates from the studies by Lijinsky and Reuber (1983), and Takayama and Imaizumi (1971) both rely on assumptions about the time of sacrifice and corrections for less than lifetime dosing.

Methodology

The study by Bertram and Craig (1970) showed that several organ sites developed tumors in both sexes of mice exposed to NDBA. The combined incidence of bladder and esophageal neoplasms in male mice was used for the potency estimate. These data depict the most reliable dose-response for the most sensitive site and species.

A linearized multistage procedure was used to estimate the cancer potency of NDBA from the Bertram and Craig. (1970) data in male C57Bl/6 mice (Crump *et al*., 1982). The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. In this case, the scaling factor was equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 10.8 $[mg/kg\text{-}day]^{-1}$ was calculated for NDBA (CDHS, 1988). An airborne unit risk factor of 3.1E-3 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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N-NITROSO-N-METHYLETHYLAMINE

CAS No: 10595-95-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	88.13
Boiling point	163ºC
Melting point	not available
Vapor pressure	not available
Conversion factor	1 ppm = 3.61 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.3 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 2.2 E+1 $(mg/kg\text{-}day)^{-1}$
[Female rat hepatocellular carcinoma data (Druckrey *et al*., 1967), one hit model, time to tumor incidence (US EPA, 1993), cross-route extrapolation]

III. CARCINOGENIC EFFECTS

Human Studies

No human carcinogenicity data on specific exposure to N-nitroso-N-methylethylamine (NMEA) have been reported. Human exposure to nitrosamines is usually the result of exposure to complex mixtures containing these compounds (e.g. cutting oils, tobacco products). Carcinogenicity data on these mixtures are of limited use in evaluating the carcinogenicity of individual nitrosamines because of the presence of other potentially confounding substances.

Animal Studies

Fifteen female BD rats were exposed to N-nitroso-N-methylethylamine (NMEA) in drinking water at doses of approximately 1 mg/kg/day (4 rats) or 2 mg/kg/day (11 rats). Exposure was continuous for the lifetime of the animals. Nine of 15 animals developed hepatocellular carcinomas and one developed a fibrosarcoma of the vagina. Average tumor induction times and total doses to produce tumors in 50% of the animals were 500 days and 0.42 g/kg for the low dose group and 360 days and 0.75 g/kg for the high-dose group. No control group was included in this study (Druckrey *et al*., 1967; reviewed in IARC, 1974 and US EPA, 1993).

DMEA also induced hepatocellular carcinomas (19/20 animals), hemangiosarcomas (17/20) and cholangiocarcinomas (3/20) with accompanying lung metastases and esophageal papillomas and carcinomas in male and female Fisher 344 (F344) rats (20/group) (Lijinsky and Reuber, 1981). Study animals received drinking water (20 ml/day/rat) containing 150 mg/l DMEA 5 days/week (tap water provided on the untreated days) for 30 weeks (total dose 450 mg) with lifetime observation. Untreated control groups were not included in this study. In a similar study, male F344 rats dosed with 600 µg or 3000 µg DMEA/week (6 or 30 mg/l in drinking water 5 days/week)

for 30 weeks developed tumors. Three of 20 animals in the low-dose group developed hepatocellular carcinomas; 12 of 20 animals in the high-dose group developed hepatocellular carcinomas, nasal tumors and esophageal papillomas (Lijinsky and Reuber, 1980). This study also did not include an untreated control group. Liver (hepatocellular carcinoma; 9/20 animals) and nasal cavity (4/20 animals) tumors were also observed in male F344 rats exposed to drinking water containing 30 mg/l NMEA 5 days/week for 30 weeks (total dose 90 mg) (Lijinsky *et al.*, 1982). In contrast, the only possibly exposure-related increase in tumor incidence seen in female F344 rats receiving drinking water containing 6 mg/l NMEA was an increased leukemia incidence (18/20 treated compared to 12/20 controls) (Lijinsky *et al.*, 1983).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The study by Druckrey *et al*. (1967) in which 9 of 15 female BD rats exposed to 1 mg/kg/day (4 rats) or 2 mg/kg/day (11 rats) DMEA in drinking water over their lifetime developed hepatocellular carcinomas was chosen as the basis of a cancer potency factor for NMEA. This study used lifetime exposure to NMEA in a sensitive species and sex.

Methodology

A one-hit model was fitted to time-to-tumor data from the study by Druckrey *et al*. (1967). The dose associated with a lifetime risk of 0.5 was calculated as follows:

$$d = Ck/(t_{50})^n = \frac{88.1\ mg/mmol * 0.81 \times 10^4\ mmol/kg/day}{(728)^{2.3}}$$

where C is the conversion between mmol and mg, k is an empirically derived constant (carcinogenicity index) (Druckrey *et al*., 1967), t_{50} is the median time of tumor induction in days, and n is an empirically generated representative value for dialkylnitrosamines (Druckrey *et al*., 1967). This relationship was derived from experimental data from studies on a number of different N-nitroso compounds. The one-hit model was used to derive a cancer potency factor of 3.72 $(mg/kg/day)^{-1}$. Adjusting this factor by the cube root of the human body weight/assumed rat body weight ratio $[(70\ kg/0.35\ kg)^{1/3}]$ results in a human cancer potency factor of 2.2 E+1 $(mg/kg/day)^{-1}$. A unit risk of 6.3 E-3 $(\mu g/m^3)^{-1}$ was then calculated by OEHHA/ATES from the cancer potency factor (20 m^3/day inspiration rate).

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U.S. Environmental Protection Agency 1993. Integrated Risk Assessment System: N-Nitroso-N-methylethylamine. Office of Health and Environmental Assessment, Washington, DC.

N-NITROSODI-N-PROPYLAMINE

CAS No: 621-64-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	130.12
Boiling point	not available
Melting point	not available
Vapor pressure	0.086 mm Hg @ 20°C
Air concentration conversion	1 ppm = 5.3 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.0 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 7.0 E+0 $(mg/kg\text{-}day)^{-1}$
[calculated from a cancer slope factor derived by US EPA (1986)]

III. CARCINOGENIC EFFECTS

Human Studies

No studies addressing the carcinogenicity of N-nitrosodi-n-propylamine to humans have been conducted.

Animal Studies

Druckrey *et al.* (1967) treated a total of 48 BD rats (sex unspecified) orally with N-nitrosodi-n-propylamine at concentrations of 4, 8, 15, or 30 mg/kg body weight 7 days per week for life (16, 16, 15, and 1 animal, respectively). An untreated control group was not included in the study, although background tumor incidence was reported to be negligible. Liver carcinoma incidence was 14/16, 15/16, 15/15, and 1/1 in the four dose groups, respectively. Tumor induction time was dose-related. The authors also note tumors of the esophagus (8/48) and tongue (6/48).

Lijinsky and Taylor (1978, 1979) exposed 15 male Sprague-Dawley rats to N-nitrosodi-n-propylamine in drinking water 5 days/week for 30 weeks at 1.8 mg/day resulting in a daily dose of 5.1 mg/kg-day. No control group was included. Liver carcinomas (9/15), esophageal papillomas (6/15) and carcinomas (8/15), and nasal adenocarcinomas (8/15) were observed among exposed rats.

Lijinsky and Reuber (1981) exposed 20 Fischer 344 rats (sex unspecified) to N-nitrosodi-n-propylamine in drinking water at 0.9 mg/day for 5 days/week for 30 weeks resulting in a daily dose of 2.6 mg/kg-day. No control group was included. Esophageal carcinomas (20/20) and forestomach tumors (12/20) developed in exposed animals.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

US EPA (1986) based its selection of a cancer potency on a study which demonstrates induction of liver tumors by N-nitrosodi-n-propylamine. US EPA (1986) used the data from Druckrey *et al.*(1967) in the induction of hepatocellular carcinoma in BD rats exposed to N-nitrosodi-n-propylamine in drinking water to calculate a cancer potency value.

Methodology

The high tumor incidence in all the N-nitrosodi-n-propylamine treated animals suggests time-dependent analysis is more appropriate than multistage analysis in the derivation of a cancer potency value. A dosage estimate for use in deriving the cancer potency value was based on the following relationship, where d is the daily dose, C is the mmol to mg conversion factor (130.2 mg/mmol), k is an empirically derived constant estimated from a plot of k versus the number of carbon atoms for lower di-N-alkylnitrosamines ($k=1.7 \times 10^4$ mmol/kg-day), t_{50} is the median time of tumor induction, and n is a representative value for dialkylnitrosamines (n=2.3; Druckrey *et al.*, 1967):

$$\frac{\quad}{\quad}$$

The resulting daily dose estimate was 0.578 mg/kg-day. Applying this estimate to a rearrangement of the one-hit model gave an animal cancer potency value (q_{animal}) of 1.2 $(mg/kg\text{-}day)^{-1}$.

$$q_{animal} = -\ln(0.5/day) / d$$

Conversion of the q_{animal} to a human cancer potency estimate (q_{human}) was made based on the following relationship, where bw_h is the assumed human body weight (70 kg) and bw_a is the assumed experimental animal body weight (0.35 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting estimate of q_{human} was 7.0 $(mg/kg\text{-}day)^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.0 E-3 $(\mu g/m^3)^{-1}$.

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N-NITROSODIETHYLAMINE

CAS No: 55-18-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	102.1
Boiling point	175-177° C
Melting point	Not found
Vapor pressure	0.86 mm Hg @ 20° C
Air concentration conversion	1 ppm = 4.2 mg/m^3 @ 25° C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.0 E-2 $(\mu g/m^3)^{-1}$
Slope Factor: 3.6 E+1 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There is no direct evidence that links nitrosamines, including N-nitrosodiethylamine (NDEA), to human cancer. The US EPA (1980) concluded that the epidemiological studies to date were inadequate to establish a valid causal relationship between nitrosamine exposure and human cancer. The US EPA (1980) also concluded that it was highly improbable that humans are refractory to the carcinogenic effects of nitrosamines considering the number of animal species that show increased tumor incidence following nitrosamine exposure.

Animal Studies

A number of qualitative studies were conducted in a range of species, including rats, mice, hamsters, guinea pigs, rabbits, dogs, and monkeys (Yamamoto *et al*., 1972; Druckrey *et al*., 1967; Magee *et al*., 1976; Rajewski *et al*., 1966; Tomatis, 1973). In addition to these studies, a number of later studies show evidence of quantitative dose-response relationships.

Drinking water containing a range of concentrations from 0.033 to 16.896 ppm NDEA was administered to male and female Colworth rats (60/sex/group) for their natural lifespan (Peto *et al*., 1982; 1984). The control groups consisted of 240 rats/sex. Nearly all animals exposed to the high dose of NDEA died from tumors of the liver or esophagus (Table 1). Other sites showing an increase in tumors included the lower jaw, stomach, kidney, ovaries, seminal vesicles, and nasopharynx.

Table 1. Liver tumors in Colworth male and female rats exposed to drinking water containing N-nitrosodiethylamine (NDEA) (Peto *et al*., 1982)

NDEA concentration (ppm)	Observed deaths from liver tumors	
	males	females
0	1/240	1/240
0.033	1/60	0/60
0.066	0/60	0/60
0.132	5/60	1/60
0.264	2/60	1/60
0.528	4/60	3/60
1.056	8/60	23/60
1.584	14/60	37/60
2.112	7/60	38/60
2.640	17/60	47/60
3.168	17/60	42/60
4.224	26/60	42/60
5.280	26/60	43/60
6.336	30/60	47/60
8.448	25/60	55/60
16.896	44/60	49/60

A later analysis by Peto *et al*. (1984) showed that, in rats, the initial age of contact with NDEA was important in determining the probability of liver cancer. Young rats were much more susceptible than adults to NDEA-induced liver neoplasia than adults exposed for an equal amount of time.

Lijinsky *et al*. (1981) administered NDEA in the drinking water to 11 groups of female Fisher-344 rats (20 per group) for varying durations, up to 104 weeks. The animals were observed for their lifespan. The treatment groups are shown in Table 2.

Table 2. Treatment groups, concentrations, and durations of N-nitrosodiethylamine (NDEA) exposures in female Fisher 344 rats (Lijinsky *et al*., 1981).

Treatment Group	NDEA concentration(mg/l)	Treatment duration (weeks)
Control	0	104
1	113	17
2	45	22
3	18	30
4	7	30
5	2.8	30
6	1.1	30
7	1.1	60
8	0.45	30
9	0.45	60
10	0.45	104

Treatment related increases in the incidence of tumors were observed in the liver, forestomach, esophagus and tongue. The incidence of tumors in the animals exposed to the lowest concentration are shown in Table 3.

Table 3. Tumor incidence in female rats exposed to 0.45 mg/l N-nitrosodiethylamine (NDEA) in drinking water for 0, 30, 60, or 104 weeks (Lijinsky *et al*., 1981).

Treatment duration (weeks)	Total dose (mg) of NDEA	Esophageal carcinoma or papilloma	Forestomach papilloma	Tongue carcinoma	Liver carcinoma	Liver carcinoma or hyperplastic nodule
0	0	0/20	0/20	0/20	0/20	1/20
30	1.35	1/20	1/20	1/20	1/20	6/20
60	2.70	3/20	2/20	2/20	6/20	11/20
104	4.68	13/20	5/20	2/20	4/20	7/20

Habs and Schmahl (1980) exposed male Sprague-Dawley rats (90 per group) to 0 or 0.1 mg/kg/day NDEA in the drinking water 5 times weekly until natural death of the animals. Another group of rats received NDEA followed by a 25% solution of ethanol. Liver tumors (histological type unspecified) were observed in 0/82 controls and 36/82 NDEA-treated rats, respectively. The rats receiving ethanol in addition to NDEA showed a liver tumor incidence of 4/59. A similar pattern was seen for the development of esophageal tumors. Rats exposed to NDEA alone developed esophageal tumors (type unspecified) at a rate of 33/82. Rats exposed to NDEA and ethanol developed esophageal tumors in 18/59 cases, and controls had a tumor incidence of 0/82.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The studies by Peto *et al*. (1982; 1984) were used by CDHS (1988) to derive the cancer potency for NDEA. These studies utilized relatively large numbers of animals (60-240 per group) over a wide dose range. The Peto *et al*. (1982) study contained more information about the dose-response at the low range of experimental doses than the other studies described. Therefore, the cancer potency for NDEA was calculated from the Peto *et al*. (1982) study even though the calculated value is lower than other potency estimates from Lijinsky *et al*. (1981) or Habs and Schmahl (1980).

Methodology

The study by Peto *et al*. (1982) showed that several organ sites developed tumors in both sexes of rats exposed to NDEA. The incidence of hepatocellular neoplasms (histological designation unknown) in males resulted in the highest potency value when only the 6 lowest doses were considered. Water consumption by male rats was reported by Peto *et al*. (1984) to be 41 mL/kg/day. Low-dose group mortality did not differ significantly from that observed in the control group, therefore no time corrections were applied to the calculation.

A linearized multistage procedure was used to estimate the cancer potency of NDEA from the Peto *et al*. (1982) data in male Colworth rats (Crump *et al*., 1982). The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. In this case, the scaling factor was equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the body weight of human or animal, in this case, 450 grams for male rats.

Using these relationships, a human cancer potency (q_{human}) of 36 $[mg/kg\text{-}day]^{-1}$ was calculated for NDEA (CDHS, 1988). An airborne unit risk factor of 1.0E-2 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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N-NITROSODIMETHYLAMINE

CAS No: 62-75-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	74.1
Boiling point	151°C
Melting point	unknown
Vapor pressure	2.7 mm Hg @ 20°C
Air concentration conversion	1 ppm = 3.08 mg/m^3 @ 20°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 1.6 E+1 $(mg/kg\text{-}day)^{-1}$
[calculated from a cancer potency value derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Epidemiological studies correlating exposure to N-nitrosodimethylamine (NDMA) and human cancers are inadequate to establish a causal relationship.

Animal Studies

Terracini *et al* .(1967) exposed male and female MRC Porton rats to feed containing 0, 2, 5, 10, 20 or 50 ppm for up to 120 weeks. Daily dose rates were calculated based upon observed food consumption rates of 15 g/day. Most survivors were sacrificed at 104 weeks, with the exception of an unspecified number of animals which were sacrificed at 120 weeks. Liver tumor incidence data were grouped into those which occured among animals surviving greater than or less than 60 weeks. No liver tumors were reported among 29 untreated animals, four of which died before 60 weeks. Combined incidence data of liver tumors among female rats dying at any time during the course of the experiment were 0/18, 4/62, 2/5, 15/23, and 10/12 for the 2, 5, 10, 20, and 50 ppm dose groups, respectively. Significant dose-related increase in incidence of liver tumors and mortality in female rats was reported (level of significance not stated).

Terracini *et al.* (1973) exposed 4-5 week old female BALB/c mice to 3 ppm NDMA in drinking water for up to 80 weeks in a two generation study. The first generation treated group consisted of 62 animals and the second generation treated group consisted of 66 animals. Among first and second generation animals, an increased incidence of lung tumors was found (first generation:

44/62 treated vs. 20/62 control, $p = 10^{-5}$; second generation: 44/66 treated vs. 15/69 control, $p = 10^{-8}$).

Terao *et al.* (1978) exposed 4 week old male Wistar rats to feed containing NDMA and/or sterigmatocystin (STG) for 54 weeks. Five exposure groups included 10 ppm STG alone, 10 ppm STG and 1 ppm NDMA, 1 ppm STG and 10 ppm NDMA, 10 ppm NDMA, and a group receiving basal diet alone. Animals were sacrificed at 69 weeks with the exception of one animal from each group sacrificed after 5 weeks of exposure. Rats in all groups exposed to NDMA showed an increased incidence of Leydig-cell tumors ($p = 0.002$). Liver tumors were not observed in the group receiving NDMA alone; however, liver tumor incidence was elevated in the group receiving STG alone and in the group receiving 10 ppm STG and 1 ppm NDMA.

Arai *et al.* (1979) exposed 6 week old male and female Wistar rats (7 to 17/sex/group) to feed containing 0, 0.1, 1 or 10 ppm NDMA for 96 weeks. Food intake was monitored. Treated female animals were found to have a higher incidence of nodular hyperplastic liver lesions ($p < 0.05$, Fisher's exact test).

Griciute *et al.* (1981) treated 8 week old male and female C57BL mice with NDMA (0.03 mg) and/or ethanol (0.8 ml) in 0.2 ml water by intragastric intubation for 50 weeks. Control animals received only water. Survivors were sacrificed at 80 weeks. No liver tumors developed in animals receiving ethanol alone. Among animals receiving NDMA alone, the incidence of malignant liver tumors was increased over controls (14/37 treated males, $p = 10^{-5}$; 16/29 treated females, $p < 10^{-6}$). Among animals receiving both NDMA and ethanol, the incidence of forebrain olfactory neuroepithelioma was increased (24/66 treated vs. 0/66 control; $p < 0.001$). No tumors of this type were observed in animals receiving NDMA or ethanol alone.

Peto *et al.* (1982, 1984) exposed Colworth rats (60/sex/group) to NDMA in drinking water at 15 concentrations ranging from 0.033 to 16.896 ppm for life. A group of 240 animals receiving only drinking water served as controls. Additional treatment groups of 6 animals/group were sacrificed at 6 and 12 months. Water consumption for male and female rats was 41 ml/kg and 72 ml/kg, respectively. Among exposed animals, the incidence of fatal liver neoplasms (see Table 1) was significantly increased over controls ($p \leq 0.005$) and the increase was found to be dose-related. Other tumors with trends toward increased incidence include tumors of the lung ($p = 0.004$), skin ($p = 0.001$), lymphatic/hematopoietic tissues ($p = 0.032$), and seminal vesicles ($p = 0.004$).

Lijinski and Reuber (1984) exposed 7-8 week old female Fischer 344 rats (20/group) to NDMA in drinking water at concentrations of 13 and 5.5 mg/l for 5 days/week for 30 weeks. Animals were observed for life. Hepatocellular carcinomas, hemangiosarcomas, and neoplastic nodules were observed in treated animals. Significantly increased incidence of liver tumors of all types was observed in both low-dose (14/20 treated vs. 2/20 controls; $p = 10^{-4}$) and high-dose (19/20 treated vs. 2/20 controls; $p < 10^{-5}$) animals.

Table 1. Liver tumor incidence data in Colworth rats exposed to NDMA in drinking water (Peto *et al.*, 1982).

dose level (ppm)*	fatal liver tumor incidence	
	male	female
0	1/240	1/240
0.033	1/60	1/60
0.066	3/60	0/60
0.132	3/60	2/60
0.264	3/60	3/60
0.528	3/60	5/60
1.056	5/60	5/60
1.584	3/60	27/60
2.112	13/60	33/60
2.640	27/60	44/60
3.168	33/60	48/60
4.224	36/60	53/60
5.280	46/60	52/60
6.336	49/60	51/60
8.448	55/60	55/60
16.896	59/60	58/60

*Colworth rats (48/sex/group) were exposed to NDMA in drinking water for life.

Druckrey *et al.*(1967) exposed BD rats (sex unspecified) to NDMA by inhalation twice per week for 30 minutes. One group of 6 rats received 100 ppm NDMA and a group of 12 rats received 50 ppm NDMA. No information on a control group was reported. Tumors of the nasal turbinates were reported at the time of death in 4/6 and 8/12 of the high- and low-dose groups, respectively. Three animals in the low-dose group died prematurely (time unspecified). No liver tumors were reported in either group.

Moiseev and Benemansky (1975; reviewed in IARC, 1978) exposed Balb/c mice and Wistar rats to NDMA by inhalation at concentrations of 0.005 and 0.2 mg/m^3. Exposure duration was 17 months for mice and 25 months for rats. At 0.2 mg/m^3 NDMA, tumors of the lung, liver, and kidney were reported to arise earlier and in greater numbers than in control animals (IARC, 1978). Exposures to the lower concentration did not result in significantly increased incidence in tumors over controls.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Five studies showing tumor induction in animals by NDMA have been deemed appropriate by CDHS (1988) for the development of cancer potency values. The values derived from the studies are presented in Table 2. The methodologies used to derive the values are described below as well as the rationale for selection of the OEHHA unit risk value for NDMA.

Methodologies

Peto *et al* .(1982, 1984) derived potency values from the incidence data of fatal liver tumors in male and female Colworth rats. The cumulative risk was calculated based on the assumption that the risk increases with the seventh power of exposure duration and the observation that a dose of 1.0 μg/kg-day results in a 0.03-0.04% incidence of liver tumors at two years. Estimated cancer potency at low doses (q_{animal}) was found to be 0.29 and 0.4 $(mg/kg\text{-}day)^{-1}$ for male and female rats, respectively. Peto *et al.* (1982,1984) also scaled these potencies up by a factor of 7 to account for calculated increased risk from the observation that median experimental animal lifespan was beyond 2 years in this study. Conversion to human potency values (q_{human}) was based on the body weight scaling relationship described below, with an assumed human body weight (bw_h) of 70 kg and experimental animal body weights (bw_a) of 450 and 250 g for male and female rats:

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting q_{human} values were 12 and 16 $(mg/kg\text{-}day)^{-1}$ from the male and female rat data, respectively.

Dose rate estimates of 0.82 mg/kg-day for female BALB/c mice receiving NDMA in drinking water in the study by Terracini *et al.* (1973) were based on a US EPA (1988) reference animal body weight value and water consumption rate (CDHS, 1988). Using a multistage procedure, experimental potencies (q_1^*) derived from this dose rate using the incidence of lung tumors in F_0 and F_1 generation animals were 1.5 and 1.6 $(mg/kg\text{-}day)^{-1}$, respectively. Potency in animals (q_{animal}) was estimated assuming cancer incidence increases with the third power of age, with T_e the experimental duration and T the natural lifespan of the animals (104 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

Further conversion to human cancer potencies with a body weight scaling factor were made as described for Peto *et al.*(1982,1984) resulting in human potency estimates (q_{human}) of 49 and 53 $(mg/kg\text{-}day)^{-1}$ from the F_0 and F_1 generation mouse tumor incidence data, respectively.

High- and low-dose rates estimates of 0.80 and 0.35 mg/kg-day in the study by Lijinsky and Reuber (1984) were based on US EPA (1988) animal body weight reference values in the induction of liver tumors in Fischer 344 rats (CDHS, 1988). Using the Crouch (1983) correction for variable dosing and a multistage procedure, the animal cancer potency estimate (q_{animal}) was 5.8 $(mg/kg\text{-}day)^{-1}$. Using the body weight conversion factor as described in the Peto *et al.* (1982, 1984) potency derivation (bw_a=0.229 kg; US EPA, 1988), the resulting q_{human} was 39 $(mg/kg\text{-}day)^{-1}$.

Dose rate estimates to MRC Porton rats exposed to NDMA in diet in the study by Terracini *et al.* (1967) were made by the method of Crouch (1983) to account for variable dosing during the course of the experiment (CDHS, 1988). Using liver tumor incidence among female rats surviving less than 60 weeks, a q_{animal} value of 5.8 $(mg/kg\text{-}day)^{-1}$ was derived from a multistage procedure. Conversion to q_{human} based on a body weight scaling factor resulted in a potency value of 34 $(mg/kg\text{-}day)^{-1}$. Using liver tumor incidence of animals surviving more than 60 weeks resulted in a q_{human} value of 7.6 $(mg/kg\text{-}day)^{-1}$; however, this value may be an underestimate because of early mortality in exposed animals.

Arai *et al.* (1979) estimated an NDMA dose rate of 0.018 and 0.033 mg/kg-day for male and female Wistar rats, respectively, based on experimentally reported food consumption rates and animal body weights. Applying a multistage procedure to the incidence of liver fibrosarcoma in male rats resulted in an estimated q_{animal} of 5.0 $(mg/kg\text{-}day)^{-1}$. Similarly, a q_{animal} for incidence of liver cancer in female rats was found to be 3.8 $(mg/kg\text{-}day)^{-1}$. The resulting q_{human} values from each of these tumor types were 29 and 25 $(mg/kg\text{-}day)^{-1}$, respectively.

Terao *et al.* (1978) demonstrated induction of Leydig-cell tumors in male Wistar rats fed diet containing NDMA. Dose rate calculations of 0.736 mg/kg-day were based on US EPA (1988) reference food intake and body weight values (CDHS, 1988). The dose correction method of Crouch (1983) was applied to account for variable dosing during the course of the experiment. Applying a multistage procedure to the tumor incidence data resulted in a q_{animal} value of 5.8 $(mg/kg\text{-}day)^{-1}$. The corresponding q_{human} value based on the body weight conversion factor was 31 $(mg/kg\text{-}day)^{-1}$.

Table 2. Cancer potencies derived from animal studies.

Study	Tumor type	Sex	q_{human} $(mg/kg\text{-}day)^{-1}$
Peto *et al.*(1982,1984)	fatal liver tumor	male	12
		female	16
Terracini *et al.*(1973)	lung tumor	F_0 female	49
		F_1 female	53
Lijinsky and Reuber (1984)	liver tumor	female	39
Terracini *et al.*(1973)	liver tumor	female	34
Arai *et al.* (1979)	liver fibrosarcoma	male	29
	liver cancer	female	25
Terao *et al.*(1978)	Leydig cell tumor	male	31

Cancer potency estimates from these studies range from 12 to 53 $(mg/kg\text{-}day)^{-1}$. Of these, the q_{human} values from the Peto *et al.* (1982,1984) study were derived from the experiment with the lowest daily dose rate and the data, therefore, are most appropriate for performing a low-dose risk extrapolation. Although the q_{human} values from Peto *et al.* (1982,1984) are lower than those derived from other studies, the fact that this study was conducted at low-doses and demonstrated sensitive and significant induction of liver tumors indicates it is useful for estimation of the cancer potency of NDMA. Furthermore, the other studies were neither as large in scale nor as long in duration, suggesting potency estimates from these studies may be overly conservative and not as representative of the true value. The most sensitive q_{human} value of 16 $(mg/kg\text{-}day)^{-1}$ derived from Peto *et al.* (1982,1984) was therefore adopted as a cancer potency value.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 4.6 E-3 $(\mu g/m^3)^{-1}$.

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N-NITROSODIPHENYLAMINE

CAS No: 86-30-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	198.2
Boiling point	66.5°C
Melting point	unknown
Vapor pressure	0.1 mm Hg @ 25°C
Air concentration conversion	1 ppm = 8.1 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 9.0 E-3 $(mg/kg\text{-}day)^{-1}$
[calculated from a cancer potency value derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no human carcinogenicity studies available for N-nitrosodiphenylamine (NDPA).

Animal Studies

Seven day-old $B6C3F_1$ and $B6AKF_1$ mice (18/sex/group) were treated with 1000 mg NDPA in dimethyl sulfoxide per kg body weight by oral gavage for 4 weeks (initial dose was not adjusted) (NTIS, 1968; Innes *et al.*, 1969). Mice were then exposed to 3769 ppm NDPA in feed to 79 weeks of age. Animals were observed for a total of 18 months. Among male $B6C3F_1$ mice, 6/15 surviving animals developed hepatomas versus 1/17 matched controls. Among female $B6AKF_1$ mice, 3/18 developed lung adenomas versus 0/17 matched controls. No statistically significant increases in tumor incidence were reported by NTIS (1968). However, a re-analysis of incidence data by current methodology showed significant increases in hepatoma incidence among male $B6C3F_1$ mice (p =0.027 by Fisher's exact test) and borderline significant increase in lung adenoma incidence among female $B6AKF_1$ mice (p =0.07) (CDHS, 1988).

$B6C3F_1$ mice (50/sex/group) were fed diet containing NDPA at two dose levels (NCI, 1979; Cardy *et al.*, 1979). Male mice received either 10000 or 20000 ppm NDPA in their diet for 101 weeks. The low- and high-dose groups of female mice received 5000 or 10000 ppm NDPA , respectively, for 38 weeks, no NDPA for 3 weeks, then 1000 or 4000 ppm NDPA for 60 weeks. Groups of 20 mice/sex fed only standard diet served as controls. No statistically significant increases in tumor incidence were observed over controls. Some incidence of epithelial hyperplasia of the urinary bladder was noted which was not seen in control animals.

Six-week old Fischer 344 rats (50/sex/group) were exposed to diet containing 1000 or 4000 ppm NDPA for 100 weeks, with groups of 20 rats/sex serving as controls (NCI, 1979; Cardy *et al.*, 1979). No dose-related increase in mortality was observed in male mice; however, a dose-related increase in mortality was observed in females (p =0.024). Among male rats, incidence of transitional-cell carcinoma of the urinary bladder was 16/45 in the high-dose group, 0/46 in the low-dose group, and 0/19 in the control animals (p =0.001). Among female rats, incidence of transitional-cell carcinoma of the bladder was 40/49 in the high-dose group, 0/46 in the low-dose group, and 0/18 in the control animals ($p < 0.001$). Among male mice, a dose-related trend in increased incidence of fibroma of the subcutis and skin was observed (p =0.003).

Argus and Hoch-Ligeti (1961) treated 25 male Wistar rats (92 g average body weight) with 1070 μg NDPA in 1 ml of 1.1% aqueous methylcellulose by oral gavage for 45 weeks, 5 days per week. At 53 weeks, all rats were alive and upon autopsy, no tumors were observed.

Druckrey *et al.* (1967) exposed 20 BD rats (sex unspecified) to NDPA in drinking water at a daily dose of 120 mg/kg body weight. No tumors were observed within 700 days.

Iverson (1980) applied 0.1 ml of 1% NDPA in acetone weekly for 20 weeks to the interscapular skin of 16 male and 24 female hairless hr/hr Oslo mice. Appropriate control mice were not included. Upon necropsy at 80 weeks, lung adenomas were observed in three of the 14 male survivors.

Boyland *et al.* (1968) injected 6-7 week old male CB rats (24/group) intraperitoneally with 2.5 mg NDPA in polyethylene glycol 400 once per week for six months. Control animals were injected with vehicle alone. After 2 yrs of observation, one of five treated and one of ten control rats which survived the treatment had hepatomas. One treated rat also had a pituitary adenoma.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Two animal studies described above are adequate for the derivation of cancer potency values for N-nitrosodiphenylamine. The studies initiated by Cardy *et al.* (1979) and Innes *et al.* (1969) were conducted with adequate numbers of animals and with appropriate controls such that statistically significant increases in tumor incidence were established. Cardy *et al.* (1979) report increased incidence of transitional-cell carcinomas of the bladder in male and female Fischer 344 rats. Innes *et al.*(1969) report increased incidence of hepatomas in male $B6C3F_1$ mice. The derivation of cancer potency values from these studies and the selection of a reference unit risk value are described below.

Methodology

Dosage estimates of NDPA from the Cardy *et al.* (1979) study were made based on reference body weights of 0.380 and 0.229 kg and daily food consumption rates of 0.030 and 0.021 kg for male and female mice, respectively. The resulting daily dosage calculations are 79 and 92 mg/kg-day for males and females, respectively, for the groups fed 1000 ppm in their diet, and 316 and 368 mg/kg-day for males and females, respectively, for the groups fed 4000 ppm in their diet. Fitting a multistage procedure to the incidence data for transitional-cell carcinoma of the bladder gives upper 95% confidence bounds on the cancer potency (q_1^*) of 0.00050 and 0.00048 $(mg/kg\text{-}day)^{-1}$ for male and female rats, respectively (Crump and Howe (1984)).

Calculation of the cancer potency for animals (q_{animal}) can be made using q_1^* and the following relationship, where T is the natural lifespan of the animal (104 weeks) and T_e is the experimental duration (100 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

The resulting q_{animal} values of 0.00056 and 0.00050 $(mg/kg\text{-}day)^{-1}$ for male and female rats, respectively, can be converted to human cancer potency values (q_{human}) based on the following relationship, where bw_{animal} is the assumed body weight for the test species and bw_{human} is the assumed human body weight (reference values from US EPA (1986)):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting estimates of q_{human} are 0.0032 and 0.0034 $(mg/kg\text{-}day)^{-1}$.

Daily dosage estimates for animals from the Innes *et al.*(1969) study were made with estimates of food consumption rates of 12% and 13% for male and female mice, respectively, based on Gold *et al.* (1984). During the oral gavage dosing period (days 7 to 28) it is assumed that a linear threefold increase in body weight occurs. The method of Crouch (1983) was used to account for variable dosing during the study period. Calculations of daily dosage are 444 and 476 mg/kg-day for male and female mice, respectively. Fitting the linear model below to the significant tumor incidence data for hepatomas in male $B6C3F_1$ mice results in a cancer potency estimate (q_{animal}) of 0.0046 $(mg/kg\text{-}day)^{-1}$. In this relationship, D is the estimated daily dose, $p(T_e)$ is the probability of dying with a tumor at time T_e, and A is the background (control) tumor incidence.

$$P_{animal}$$

Conversion of the q_{animal} to q_{human} is achieved as described for the Cardy *et al.* (1979) data, with an assumed experimental animal body weight (bw_{animal}) of 0.03 kg. The resulting q_{human} for this study is 0.061 $(mg/kg\text{-}day)^{-1}$.

Selection of a reference cancer potency value comes from identification of the most sensitive site, species, sex and study, in the absence of evidence that the data are not representative. The Innes *et al.*(1969) study presents the highest, and thus most sensitive, cancer potency value of 0.061 $(mg/kg\text{-}day)^{-1}$. The lower 95% confidence bound on the Innes *et al.* (1969) potency value

also exceeds the potency values derived from Cardy *et al.* (1979) indicating the mouse strain used by Innes *et al.* (1969) may be more sensitive. The small number of animals used in this preliminary study, however, suggests the possibility this value may be overly conservative. The two q_{human} values for NDPA in male and female rats derived from Cardy *et al.* (1979) are close, 0.0032 and 0.0034 $(mg/kg\text{-}day)^{-1}$, respectively. Since these data were derived from a large, thorough study, the development of a reference cancer potency value should include these values. The potency estimate was therefore derived from the geometric mean of the three q_{human} values described above according to the approach of Anderson *et al.* (1983). The resulting reference q_{human} is 0.009 $(mg/kg\text{-}day)^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.6 E-6 $(\mu g/m^3)^{-1}$.

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p-NITROSODIPHENYLAMINE

CAS No: 156-10-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	198.24
Boiling point	not available
Melting point	144-145 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 8.1 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.3 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 2.2 E-2 $(mg/kg\text{-}day)^{-1}$
[Male rat liver tumor data (NCI, 1979), contained in Gold *et al.* (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *p*-nitrosodiphenylamine in humans are known to exist.

Animal Studies

Male and female Fischer 344 rats and $B6C3F_1$ mice were fed diets containing technical grade *p*-nitrosodiphenylamine (73% active material, 25% water, unspecified impurities). Rats were fed diets containing 2500 or 5000 mg/kg diet *p*-nitrosodiphenylamine for 78 weeks, followed by a 27 week observation period. Mice were fed diets containing either 5000 mg/kg diet *p*-nitrosodiphenylamine for 40 weeks, then 2500 mg/kg diet for 17 weeks, or 10000 mg/kg diet for 40 weeks, followed by control diet for 7 weeks, then 5000 mg/kg for 10 weeks. Both dose groups were then maintained on control diet for an additional 35 weeks. Treatment groups consisted of 50 animals/sex/species/group; matched control groups consisted of 20 animals/sex/species and were kept under observation for 105 and 92 weeks for rats and mice, respectively. Rat survival was 90, 86 and 92% for males and 85, 84 and 92% for females in the control, low-dose and high-dose groups, respectively. Mouse survival was 85, 88 and 60% for males and 90, 84 and 52% for females in the control, low-dose and high-dose groups, respectively. Significant increases in the incidence of liver tumors (neoplastic nodules, hepatocellular adenomas and carcinomas) was noted in treated male mice and rats. Tumor incidence data is listed in Table 1.

Table 1. *P*-Nitrosodiphenylamine-induced liver tumor incidence in male Fischer 344 rats and B6C3F$_1$ mice (NCI, 1979)

Species	Dose group	Average dose[1] (mg/kg-day)	Tumor incidence[2]
rat	control	0	0/20
	low dose	74.3	10/50
	high dose	149	19/50
mouse	control	0	2/20
	low dose	316	22/50
	high dose	587	12/50

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The results of NCI (1979) feeding studies of *p*-nitrosodiphenylamine in male and female F344 rats and B6C3F$_1$ mice are listed by Gold *et al.* (1984). NTP (1991) characterizes the studies in male rats and male mice as positive. Significant increases in malignant liver tumors were observed in males of both species, with rats displaying greater sensitivity to the compound. However, survival was significantly reduced in the study in male mice, so the apparently lower sensitivity of these animals may have been due to the fact that they were at risk for a shorter time period than the rats. Cancer potency is based on the dose-response data for liver tumors in male rats as seen in Table 1 (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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National Cancer Institute (NCI) 1979. Bioassay of *p*-Nitrosodiphenylamine for Possible Carcinogenicity. CAS No. 156-10-5. Carcinogenesis Technical Report Series No. 190. NCI-CG-TR-190 DHEW Publication No. (NIH) 79-1746. U.S. Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

N-NITROSOMORPHOLINE

CAS No: 59-89-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	116.11
Boiling point	224-225 °C (@ 747 mm Hg)
Melting point	29 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.75 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.9 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 6.7 E+0 $(mg/kg\text{-}day)^{-1}$
[Female hamster respiratory tract tumor data (Ketkar *et al*., 1983), contained in Gold *et al.* (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of N-nitrosomorpholine in humans are known to exist.

Animal Studies

IARC (1978) reviewed a study in which 58 male NMRI mice were exposed to N-nitrosomorpholine in drinking water at a concentration of 100 mg/l for the life of the animals (Bannasch and Müller, 1964; Müller, 1964). Increases in liver tumor incidence were noted; 16/58 animals developed hepatocellular adenomas. Treated animals also developed "numerous" lung adenomas and one lung squamous cell carcinoma was observed. Only 1/17 controls developed lung adenomas.

Male and female MRC rats (15 animals/sex) were exposed to *N*-nitrosomorpholine in drinking water (100 mg/l; total dose 500 mg) for 50 weeks, then observed for the life of the animal (Garcia and Lijinsky, 1972). Male and females displayed increased incidences of liver tumors (hepatocellular carcinomas and hemangioendotheliomias; 13/15 and 13/14 in males and females, respectively) and nasal cavity tumors (9/15 and 5/14 in males and females, respectively). The study did not report that a control group was included.

Male and female Syrian golden hamsters (20/sex/group) were given weekly subcutaneous injections of *N*-nitrosomorpholine, which were one-fifth, one-tenth or one-twentieth of the LD50 of *N*-nitrosomorpholine, for life (Haas *et al*., 1973). Males received 24.6, 49.2 or 98.4 mg/kg body

weight; females recieved 28.1, 56.2 or 112.4 mg/kg body weight. Treatment-related increases in the incidence of respiratory tract tumors (primarily in the nasal cavity and trachea) were observed.

Lijinsky *et al*. (1976) exposed male Sprague-Dawley rats (30/exposure group) to *N*-nitrosomorpholine in drinking water (8 or 40 mg/l, 5 days/week; total dose 0.21 and 1.05 mM, respectively) for 30 weeks. The animals were then observed for the remainder of their lifetime. Hepatocellular (benign or malignant) tumors were reported in 11/30 and 16/30 low- and high-dose animals, respectively. Hemangioendothelial tumors were reported in 1/30 and 2/30 low- and high-dose animals, respectively. The authors did not report the inclusion of a control group in this study.

Ketkar *et al*. (1983) exposed male and female Syrian golden hamsters (30/sex/group) to 0.001, 0.005 or 0.01% *N*-nitrosomorpholine in the drinking water for life; untreated control groups (50 animals/sex) were also included. Increased incidences of benign and malignant tumors of the respiratory tract (primarily papillary polyps, papillomas and epidermoid carcinomas of the larynx and trachea) and the gastrointestinal tract (primarily liver tumors, including hepatocellular adenomas and carcinomas) were observed in both males and females. No corresponding tumors were observed in the control groups. Tumor incidence data is listed in Table 1.

Table 1. *N*-nitrosomorpholine-induced tumor incidence in male and female Syrian golden hamsters (Ketkar *et al*., 1983)

Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male controls	0	respiratory tract	0/50
male low dose	1.2		8/29
male mid dose	6		13/29
male high dose	12		21/30
male controls	0	liver tumors	0/50
male low dose	1.2		4/29
male mid dose	6		9/29
male high dose	12		18/30
female controls	0	respiratory tract	0/50
female low dose	1.36		14/28
female mid dose	6.82		16/30
female high dose	13.6		22/30
female controls	0	liver tumors	0/50
female low dose	1.36		0/28
female mid dose	6.82		2/30
female high dose	13.6		6/30

1. Doses as reported by Gold *et al.* (1987).
2. Tumor incidences as reported by Gold *et al*. (1987).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al*. (1987) list results from a drinking water study in male and female Syrian Golden hamsters (Ketkar *et al.*, 1983). Tumors of the respiratory system and liver were observed at significant levels in both sexes; females were slightly more sensitive than males. Cancer potency for N-nitrosomorpholine is based on tumors of the respiratory system, the more sensitive site, in female hamsters (see Table 1) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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N-NITROSOPIPERIDINE

CAS No: 100-75-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	114.15
Boiling point	217 °C (@ 721 mmHg)
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.7 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.7 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 9.4 E+0 $(mg/kg\text{-}day)^{-1}$
[Rat liver tumors (Eisenbrand *et al*., 1980), contained in Gold *et* al. (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *N*-nitrosopiperidine in humans are known to exist.

Animal Studies

Takayama (1969) fed 33 male ICR mice diets containing 50 mg/kg *N*-nitrosopiperidine for a period of 12 months; a 30 animal untreated control group was included. An increased incidence of forestomach (squamous cell carcinoma), liver and lung (adenomas) tumors were observed in treated animals when compared to controls. Tumor incidence data is listed in Table 1.

Table 1. *N*-nitrosopiperidine-induced tumor incidence in male ICR mice (Takayama, 1969)

Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
controls	0	forestomach liver lung	0/30 0/30 2/30
treated	6	forestomach liver lung	18/33 6/33 10/33

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

Male and female Sprague-Dawley rats were exposed to *N*-nitrosopiperidine in the drinking water 5 days/week for the life of the animals at exposure levels of 0, 0.024, 0.12, 0.6 and 3 mg/kg body

weight (group sizes were 40, 78, 75, 34 and 34 animals, respectively) (Eisenbrand *et al*., 1980). Significant increases were noted in the incidence of esophageal squamous cell carcinomas and liver tumors (hemangioendotheliomas, and hepatocellular adenomas and carcinomas). Tumor incidence data is listed in Table 2.

Table 2. Induction of liver tumors in male and female Sprague-Dawley rats by *N*-nitrosopiperidine (Eisenbrand *et al*., 1980)

Dose group $(mg/kg/day)^{-1}$	Average dose[1] $(mg/kg/day)^{-1}$	Tumor incidence[2]
0	0	0/40
0.024	0.0171	3/78
0.12	0.0857	5/75
0.6	0.429	16/34
3.0	2.14	11/34

1. Doses as reported by Gold *et al.* (1987).
2. Tumor incidences (males and females combined) as reported by Gold *et al*. (1987).

Adamson and Sieber (1982) exposed male and female rhesus and cynomolgus monkeys to *N*-nitrosopiperidine by gavage (400 mg/kg body weight, 5 days/week; average dose 279 and 280 mg/kg-day for cynomolgus and rhesus monkeys, respectively); male and female rhesus monkeys were also exposed to *N*-nitrosopiperidine by intraperitoneal injection (40 mg/kg body weight; average dose 5.59 mg/kg). Exposure and total experimental (exposure and untreated observation period) durations were 90 and 92 months, respectively for cynomolgus monkeys, 8 and 9 years, respectively for rhesus monkeys exposed by gavage, and 91 and 93 months, respectively, for rhesus monkeys exposed by intraperitoneal injection. Increased incidences of hepatocellular carcinomas were found in treated cynomolgus monkeys (5/5 compared to 0/38 in controls), rhesus monkeys exposed by gavage (6/7 compared to 0/32 in controls) and in rhesus monkeys exposed by intraperitoneal injection (3/5 compared to 0/32 in controls).

Ketkar *et al*. (1983) exposed male and female Syrian golden hamsters (30/sex/treatment group; 50/sex for controls) to 0, 0.006, 0.025 or 0.05% *N*-nitrosopiperidine in drinking water for the life of the animals. Increased incidences were noted for respiratory tract tumors (papillary polyps, papillomas and epidermoid carcinomas of the larynx, pharynx and trachea), liver tumors (hepatocellular adenomas and carcinomas, cholangiomas and cholangiocarcinomas) and digestive tract tumors (forestomach and colon adenocarcinomas). Tumor incidence data is listed in Table 3.

Table 3. *N*-Nitrosopiperidine-induced tumor induction in male and female Syrian golden hamsters (Ketkar *et al*., 1983)

Dose group (% *N*-nitrosopiperidine)	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male		respiratory tract	
0	0		0/50
0.006	7.2		5/30
0.025	30		10/30
0.05	60		15/30
female		respiratory tract	
0	0		0/50
0.006	8.18		4/30
0.025	34.1		6/30
0.05	68.2		10/30
male		liver tumors	
0	0		0/50
0.006	7.2		1/30
0.025	30		2/30
0.05	60		10/30
female		liver tumors	
0	0		0/50
0.006	8.18		1/30
0.025	34.1		2/30
0.05	68.2		4/30
male		digestive tract	
0	0		0/50
0.006	7.2		0/30
0.025	30		4/30
0.05	60		13/30
female		digestive tract	
0	0		0/50
0.006	8.18		4/30
0.025	34.1		5/30
0.05	68.2		7/30

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al.* (1984, 1987) list results from drinking water studies in male and female Syrian Golden hamsters, feeding studies in male ICR mice, feeding studies in rhesus and cynomolgus monkeys, intraperitoneal studies in rhesus monkeys (combined data for males and females), and drinking water studies in Sprague-Dawley rats (combined data for males and females). N-Nitrosopiperidine induced liver tumors in all species and strains. Hamsters are the least sensitive of the species tested. The majority of treated primates developed liver tumors, including all cynomolgus monkeys given the compound in feed. Rats and mice exhibit sensitivity similar to primates. Because treatment groups in the primate studies are small and incidences observed are high, accurate estimates of cancer potency cannot be obtained from these studies. Of the dose-response data available for rats and mice, the highest quality data set is reported by Eisenbrand *et al.* (1980) for liver tumors in Sprague-Dawley rats. Cancer potency is derived from this data set (Table 2) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Analysis of the data set using the computer program TOX_RISK (Crump *et al*., 1991) indicated that inclusion of the high dose group resulted in a *p*-value of 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor of 6.0 E-6 $(\mu g/m^3)^{-1}$ was derived by OEHHA/ATES from the human q_1^* using an inspiration rate of 20 m^3/day.

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N-NITROSOPYRROLIDINE

CAS No: 930-55-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	100.1
Boiling point	214°C
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.10 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.0 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 2.1 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by US EPA/IRIS (1994) from rat liver tumor data (Preussmann *et al*. 1977) using a linearized multistage procedure]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *N*-nitrosopyrrolidine in humans are known to exist. Human exposure to nitrosamines occurs through contact with complex mixtures (e.g., metal cutting fluids) containing these compounds. US EPA (1994) states that data from such exposures are of limited use in evaluating the carcinogenicity of individual nitrosamines due to potential confounding by other substances present in the mixtures.

Animal Studies

Druckrey (1967) (reviewed by IARC, 1978) exposed 25 BD rats to drinking water containing *N*-nitrosopyrrolidine; average doses were 5 or 10 mg/kg body weight-day. After 150 days of treatment, the doses were increased to 10 or 20 mg/kg-day. Hepatocellular carcinomas were noted in 23/25 animals; the average induction time for the low- and high-dose animals was 470 and 290 days, respectively.

Male and female MRC rats (15/sex) were exposed to *N*-nitrosopyrrolidine in drinking water 5 days/week at a concentration of 200 mg/l for 67 weeks (mean total dose 1340 mg/animal, mean daily intake 16 mg/kg) (Greenblatt and Lijinsky, 1972a). After treatment, animals were observed for an additional 105 weeks. An untreated control group of 35 animals/sex was also included. An increased incidence of liver tumors (primarily hepatocellular carcinomas) were observed in both males (12/12) and females (13/13); 7/12 male rats also developed papillary mesotheliomas of the testes. No liver or testicular tumors were noted in the corresponding controls.

Greenblatt and Lijinsky (1972b) exposed male and female (30/sex/group) Swiss mice to 0 or 0.01% *N*-nitrosopyrrolidine in drinking water 5 days/week for 26 weeks (average dose 7-8 mg/kg-day). All surviving animals were killed after 38 weeks. Animals were only histopathologically evaluated for lung adenomas. Lung tumor incidence in treated mice was not significantly increased when compared to controls; however, the duration of treatment was short and the mean survival time of the treated animals was only 12 weeks, with the primary cause of mortality being liver necrosis.

Male and female Sprague-Dawley rats (14 males, 15 females) were exposed to 200 mg/l *N*-nitrosopyrrolidine in drinking water 5 days/week for 50 weeks (total dose 1000 mg/animal), then observed for the remainder of their lifetime (Lijinsky and Taylor, 1976). An increased incidence of hepatocellular tumors was noted in both males (12/14) and females (13/15). No liver tumors were reported in the control group (group size not reported).

Exposure of male and female Sprague-Dawley rats to N-nitrosopyrrolidine in drinking water at levels of 0, 0.3, 1, 3 or 10 mg/kg body weight for the life of the animals resulted in significant increases in the incidence of hepatocellular tumors (adenomas and carcinomas) (Preussmann *et al*., 1977). Tumor incidence data is listed in Table 1. Equal numbers of male and female animals were used.

Table 1: Incidence of hepatocellular carcinomas and adenomas in male and female Sprague-Dawley rats treated with *N*-nitrosopyrrolidine via drinking water (Preussmann *et al*., 1977)

Number of animals/ group[1]	*N*-nitrosopyrrolidine exposure level (mg/kg-day)	Human equivalent dose[2] (mg/kg-day)	Hepatocellular tumor incidence[1]
61	0	0	0/61
60	0.3	0.051	3/60
62	1.0	0.17	17/62
38	3.0	0.51	31/38
24	10	1.70	14/24

1. Males and females combined.
2. Calculated by US EPA (1994).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Tumor incidence data from the study by Preussmann *et al*. (1977) were the basis of cancer potency factor derivation. There were significant increases in the incidence of hepatocellular carcinomas and adenomas (see Table 1). Overall, there appeared to be dose-related increases in hepatocellular tumors, as well as shorter latency periods with increasing dose.

Methodology

Cancer potency values are based on the most sensitive site, species and study, in the absence of other evidence indicating that such a value is not appropriate (CDHS, 1985). Based on the dose-response data for hepatocellular tumors in male and female Sprague-Dawley rats, the cancer potency factor for *N*-nitrosopyrrolidine was calculated to be 2.1 $(mg/kg\text{-}day)^{-1}$ using a linearized multistage procedure with surface area scaling for conversion of the rat administered dose to a human equivalent dose (US EPA, 1994). A unit risk factor was calculated from the cancer potency factor by OEHHA/ATES using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day. US EPA has stated that the unit risk should not be used if air concentrations exceed 20 $\mu g/m^3$, since above this concentration the unit risk may not be appropriate.

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PARTICULATE MATTER FROM DIESEL-FUELED ENGINES

CAS No: not available

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	not applicable
Boiling point	not applicable
Melting point	not applicable
Vapor pressure	not applicable
Air concentration conversion	not applicable

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-4 - 1.5 E-3 $(\mu g/m^3)^{-1}$ (measured as particulate matter)[Scientific Review Panel unit risk "reasonable estimate" = 3.0 E-4 $(\mu g/m^3)^{-1}$.]
Slope Factor: 1.1 E+0 $(mg/kg\text{-}day)^{-1}$
[Human occupational exposure lung tumor incidence (Garshick *et al*. (1987a, 1988), estimated exposure concentrations (Woskie *et al*., 1988a,b), relative risk model (OEHHA, 1998); human occupational exposure lung tumor incidence, meta-analysis (OEHHA, 1998).]

III. CARCINOGENIC EFFECTS

Human Studies

The epidemiological evidence concerning the carcinogenicity of diesel exhaust primarily involves cancers of the lung and bladder. The review of human diesel exhaust-exposure cancer studies in the document entitled *Health Risk Assessment For Diesel Exhaust* written for the Toxic Air Contaminant (TAC) program (OEHHA, 1998) focuses first on studies of lung cancer (Sections 6.2.1 and 6.2.2) and then turns to those of bladder cancer (Section 6.2.3). The evidence for causation of lung cancer was then assessed using criteria for causal inference from epidemiological studies (Section 6.2.4). The evidence linking diesel exposure and bladder cancer was not as extensive or compelling, and is discussed in the diesel exhaust TAC document but not in this summary. Because there are no epidemiological studies involving industrial hygiene measurements concurrent with the exposures of the study populations, exposure has typically been defined by the surrogate measures of usual occupation or job classification within an industry.

Review Of Lung Cancer Studies

The question of whether diesel exhaust causes lung cancer has been addressed by both industry-based cohort and case-control studies as well as population-based studies of lung cancer. In Section 6 of the diesel exhaust TAC document (OEHHA, 1998), the review of the lung cancer studies was divided into five parts focusing on studies of: (1) truck drivers, (2) transport and equipment workers, (3) dock workers, (4) railway workers, and (5) other miscellaneous occupations involving diesel exhaust exposure. This summary will focus on the railway workers studies, which were

used to derive the range of human cancer risks associated with diesel exhaust exposure. A summary of all occupational studies evaluating the relationship between diesel exhaust exposure and lung cancer is provided in Table 1.

Studies Of Lung Cancer Among Railway Workers

In 1959, Kaplan studied lung cancer mortality among employees of the Baltimore and Ohio Railroad. This railroad initiated locomotive dieselization in 1935, completing this process by 1958. Workers employed at any time between 1953 and 1958 were eligible for entry into the cohort; 154 deaths from primary cancers of the lung or bronchus were identified. Exposure was categorized into three groups by job type. The lung cancer SMR for the most exposed group, relative to the general population, was 0.875. The limited number of years of exposure to diesel exhaust for some members of the cohort and the abbreviated follow-up time do not allow for sufficient latency to be informative regarding the relationship of diesel exhaust exposure to lung cancer. In addition, no data on smoking were available.

In the Third National Cancer Survey discussed above, Williams *et al*. (1977) found a nonsignificant increased risk for railroad workers among lung cancer patients, OR = 1.40, based on 12 cases (no confidence intervals reported).

Howe *et al*. (1983) carried out a mortality study of 43,826 male pensioners of the Canadian National Railroad. The cohort consisted of all male pensioners who were alive at the beginning of 1965. Subjects were followed until 1977, by which time 933 deaths from respiratory cancer (trachea, bronchus and lung) had been recorded. Occupations at the time of retirement were classified as "nonexposed", "possibly exposed" or "probably exposed". Analysis restricted to individuals retiring after 1950 (n = 897 cases) yielded relative risks of 1.00, 1.20 ($p = 0.013$), and 1.35 ($p < 0.001$) for the three exposure groups, respectively (test for trend: $p < 0.00l$). There was little change in these effect estimates when individuals involved in locomotive maintenance (and who therefore may have been exposed to asbestos) were excluded from the analysis (n = 69).

This study also found coal dust to be associated with lung cancer, with a similar increasing trend with degree of exposure. Because of a high degree of overlap between exposures to coal dust and to diesel exhaust, the authors could not separate the effects of the two. However, since there is evidence from animal and human studies for the carcinogenicity of diesel exhaust, but such evidence does not exist for coal dust, the apparent effect of coal dust was more likely to have been due to confounding by diesel exhaust, rather than vice versa. No smoking information was available for this study, although there were increasing trends with degree of diesel exposure for mortality from emphysema (SMRs = 1.00, 1.35, and 1.44) and other smoking-related cancers combined (SMRs = 1.00, 1.08, and 1.16). The authors suggested that since the results were based on internal comparisons little variation in smoking would be expected among the different diesel exposure groups.

Garshick *et al*. (1987a) carried out a case-control study of lung cancer in U.S. railroad workers. Cases comprised 1,256 lung cancer deaths occurring between 1981 and 1982 in the population of active or retired railroad workers who had had 10 years or more of railroad service and were born in 1900 or later. Two controls who had died of causes other than cancer, suicide or accident were

matched to each case by dates of birth and death. Next of kin were interviewed to obtain information about the decedents, including their smoking habits. Job codes were obtained from the Railroad Retirement Board, and an industrial hygiene survey was used to classify the degree of diesel exposure for each job type. Jobs were dichotomously categorized as exposed or not exposed to diesel exhaust.

Garshick *et al*. considered exposure to diesel exhaust to have begun in 1959, since the transition from steam to diesel-powered locomotives took place mainly in the 1950s, and was nearly complete in 1959. Years of diesel exhaust exposure to death or retirement were totaled for each worker. The analysis separated those workers who died at age 65 (retirement age) or older (921 cases and 1,748 controls) from those workers <64 years at death (335 cases and 637 controls). Analysis by logistic regression showed no effect of diesel exhaust in the workers in the older age category, who had substantially less diesel exposure than those in the younger category. For example, 36% of cases and 43% of controls had no exposure in the younger group, while 52% of cases and 53% of controls had no exposure in the older group. Furthermore, 35% of cases and 26% of controls had more than 19 years of diesel exposure in the younger group, while only 3% of cases and controls had more than 19 years of diesel exposure in the older group.

In the group whose members were younger than 64 years old at time of death, the analysis by Garshick *et al*. showed evidence of an exposure-response relationship with an OR of 1.41 (95% C.I. = 1.06-1.88) for 20 or more years of exposure (diesel-years) after adjusting for smoking and asbestos exposure. Excluding exposure occurring within five years of death, the OR for 15 or more years of cumulative diesel exposure was 1.43 (95% C.I. = 1.06-1.94). For workers with 5 to 14 years of cumulative exposure, the OR was 1.07 (95% C.I. = 0.69-1.66) relative to a reference category of 0 to 4 diesel exposure years.

Garshick *et al*. (1988) also conducted a retrospective cohort study of U.S. railroad workers. Eligible for inclusion in the cohort were white males aged 40 to 64 years, who started work between 1939 and 1949 and were still employed in 1959 in designated jobs. Follow-up extended through 1980. Jobs with recognized asbestos exposure were not included in the job codes selected for study, although some of the selected occupations had at least some potential for asbestos exposure. The cohort consisted of 55,407 men, among whom there were 19,396 deaths, including 1,694 attributable to lung cancer. Diesel exhaust exposure was characterized based on their 1959 job group. Career paths were found to be very stable in the railways, such that a worker aged 40-44 with a diesel-exposed job in 1959 was likely to have a diesel-exposed job 20 years later; similarly a nonexposed person in 1959 was likely to have a nonexposed job 20 years later.

The youngest workers in 1959 had the longest potential duration of diesel exposure in the cohort. In a proportional-hazards model these workers had the highest estimated relative risks for lung cancer associated with diesel exhaust exposure: the relative risk for the group aged 40-44 in 1959 was 1.45 (95% C.I. = 1.11-1.89); for the group aged 45-49 the relative risk was 1.33 (95% C.I. = 1.03-1.73); for the group aged 50-54, 1.12 (95% C.I. = 0.88-1.42); for the group aged 55-59, 1.18 (95% C.I. = 0.94-1.50); and for the group aged 60-64, 0.99 (95% C.I. = 0.74-1.33). Though the results were statistically significant only for the two youngest groups, there was a decreasing trend with increasing age in 1959 (except for the 55-59 year age group), implying declining risk with decreasing duration of exposure.

When exposure to diesel over the last five years before death was excluded, a relationship was apparent between lung cancer risk and duration of exposure. The group with greater than 15 years of cumulative exposure had a RR for lung cancer of 1.72 (95% C.I. = 1.27-2.33); for those with 10 to 14 years of exposure the RR was 1.32 (95% C.I. = 1.13-1.56); for 5 to 9 years, 1.24 (95% C.I. = 1.06-1.44); and for 1-4 years, 1.20 (95% C.I. = 1.01-1.44). All of these results are statistically significant.

Although no smoking information was available for the cohort, the previous case-control study of railway workers by the same group (Garshick *et al*., 1987a) reported that little change occurred in the estimates of diesel exhaust effect due to adjustment for smoking habits and asbestos exposure (unadjusted OR = 1.39, 95% C.I. = 1.05-1.83; adjusted OR = 1.41, 95% C.I. = 1.06-1.88). In this analysis, the larger percentage of workers whose pack-year history was unknown (23% of cases and 22% of controls) was treated as a separate category of smoking. In additional analyses using only those workers for whom the investigators had detailed smoking data (n = 758), the ORs for 20 years of diesel exposure ranged from 1.50-1.53, adjusted for asbestos exposure and several specifications of cigarette smoking history. These models included pack-years as a single continuous variable, as two independent variables (cigarettes per day and years of smoking), or as a categorical variable classified in terms of the number of years the study subject had stopped smoking prior to death. These analyses suggested that the diesel exhaust-lung cancer odds ratios were not confounded by cigarette smoking in this population. Moreover, in a group of railroad workers previously surveyed for asbestos exposure (Garshick *et al*., 1987b) there was no difference in smoking prevalence between workers with and without diesel exhaust exposure (data not presented).

It should be noted that the case-control and the cohort studies by Garshick *et al*. involved different study populations: The case-control study (Garshick *et al*. 1987a) contained cases and controls who had died in 1981 and 1982, whereas the cohort study (Garshick *et al*., 1988) involved deaths occurring up to 1980. Thus, they may be considered different tests of the hypothesis of an association between lung cancer and diesel exhaust exposure, although this does not exclude the possibility of a common bias shared by the two studies, such as exposure to chemicals transported by rail or to suspended dusts and debris.

In the American Cancer Society prospective mortality study mentioned above (see Section 6.2.1.1, OEHHA, 1998), Boffetta *et al*. (1988) found an age- and smoking-adjusted RR of 1.59 (95% C.I. = 0.94-2.69) for lung cancer mortality in railroad workers. This estimate was based on only 14 lung cancer deaths.

Swanson *et al*. (1993) also examined the industrial category of railroad workers in their case-control study of lung cancer. The smoking-adjusted odds ratios for white males (67 cases) were 1.2 (95% C.I. = 0.5-2.7) for 1-9 years of employment and 2.4 (95% C.I. = 1.1-5.1) for more than 10 years of employment (χ^2 test for trend: $p < 0.05$). Elevated, but nonsignificant, smoking-adjusted ORs were also associated with the 31 lung cancer cases occurring in African-American railroad workers, OR = 2.6 (95% C.I. = 0.8-7.9) for 1-9 years and OR = 2.7 for $\geq$ 10 years of employment (95% C.I. = 0.6-12.1).

Nokso-Koivisto and Pukkala (1994) compared the incidence of lung cancer among locomotive drivers to the total Finnish population. The retrospective cohort consisted of the 8,391 members of the Finnish Locomotive Drivers' Association from 1953 until 1991 (retired drivers remain members until death). After excluding 302 members for lack of personal identification information, an overall standardized incidence ratio (SIR) of 0.86 (95% C.I. = 0.75-0.97) was found (236 cases). The overall incidence for all cancer sites was also lower than expected, SIR 0.95 (95% C.I. = 0.89-1.01) but the incidence of mesothelioma (SIR 4.05, 95% C.I. = 1.75-7.97) and oral cavity/pharyngeal cancers (SIR 1.75, 95% C.I. = 1.02-2.80) were significantly increased. Prior to the 1970s Finnish drivers trained for 2 years in railroad workshops, where significant exposure to asbestos occurred routinely during steam engine maintenance, with little, if any, diesel exposure. Only drivers working after this period had the potential for substantial exposure to diesel exhaust, and the electrification of the railroad in the 1970s and 1980s may also have reduced the proportion of the cohort's person-years that truly reflect exposure to diesel exhaust. No data on smoking within the cohort were available, though a cross-sectional study of locomotive drivers in 1976 showed that the prevalences of current smokers (40%), ex-smokers (34%), and never-smokers (26%) were similar to those in the Finnish population as a whole.

All three population-based case-control studies found elevated risks for lung cancer in railroad workers (Williams *et al*., 1977; Boffetta *et al*., 1988; Swanson *et al*., 1993); however, only the study by Swanson *et al*. (1993) found a statistically significant increase, with a smoking-adjusted OR of 2.4 (95% C.I. = 1.1-5.1) for workers with ten or more years of employment. This study also found evidence of a significant exposure-response relationship for the 67 cases observed in white railroad workers. Williams *et al.* (1977) and Boffetta *et al*. (1988) had relatively fewer railroad workers (12 and 14 cases respectively) and no information on duration of exposure.

In the railroad industry-based studies, three of the larger studies identified statistically significant increases in relative risk (Howe *et al*., 1983; Garshick *et al*., 1987a; Garshick *et al*., 1988). The large cohort reported on by Howe *et al.* (1983) found elevated risks for individuals categorized as "probably" and "possibly" exposed to diesel exhaust, but without adjustment for smoking or duration of employment, the underlying risk is uncertain. In both the case-control and cohort studies by Garshick *et al*., 1987a, 1988), significantly increased risks were associated with long-term employment in diesel-related railroad jobs. Both studies had substantial exposure assessment, sufficient latency, and duration of employment data, and the case-control investigation also controlled for potential confounding by smoking and by asbestos exposure. In contrast, the study by Nokso-Koivisto *et al*. (1994), found no increase in lung cancer risk among Finnish locomotive engineers, though the description of the cohort indicates the earlier cases were unlikely to have experienced any diesel exposure.

Studies Of Lung Cancer Among Truck Drivers

The studies that have examined the lung cancer risk to truck drivers are summarized in Table 1. These studies have consistently reported small increases in lung cancer relative risk. However, the studies suffer from various deficiencies, including small numbers of subjects, inadequate adjustment for confounding, and crude exposure assessments, usually based on occupational classification. Most of the earlier studies did not adjust for smoking. Because of evidence that truck drivers have a higher smoking prevalence (Wynder and Higgins, 1986), individual studies that do not account for smoking generally provide limited evidence regarding carcinogenicity. Before 1988, the two studies that took smoking into account, Williams *et al*. (1977) and Hall & Wynder (1984), had ORs of 1.4 - 1.5, which were not statistically significant. The third study that accounted for smoking (Damber and Larsson, 1985, 1987), only found significantly elevated risks in truck drivers who smoked after stratifying on age (i.e., only for those > 70 years old at diagnosis). However, in the follow-up study, after analyzing for duration of employment (20 or more years), elevated but nonsignificant risks were observed for all professional drivers combined (Damber and Larsson, 1987).

By comparison, the majority of studies published since 1988 have adjusted for smoking to varying degrees. Of the smoking-adjusted population based studies, two of four found statistically significant increases in the relative risk for lung cancer associated with occupation as a truck driver, especially in individuals employed for 10 or more years (Hayes *et al*. 1989; Swanson *et al*. 1993). In addition, both studies reported some evidence of a positive trend between increased duration of employment and risk for lung cancer. Although both found statistically significant trends ($p <$ 0.05), the only stratum with statistically significant relative risk estimates was that including 20 or more years' employment as a truck driver, with ORs of 1.5 (95% C.I. = 1.0-2.3) and 2.5 (95% C.I. = 1.1-4.4), reported by Hayes *et al*. (1989) and Swanson *et al*. (1993), respectively.

Three of the six more recent industry-specific studies adjusted for smoking, at either the individual (Benhamou *et al*. (1988) and Steenland *et al*. (1990)) or group level (Pfluger and Minder 1994). The two studies of professional drivers, a portion of which included truck drivers, found significantly elevated estimates of relative risk with smoking-adjusted ORs of 1.42 (95% C.I. = 1.07-1.89) and 1.48 (95% C.I. = 1.30-1.68) (Benhamou *et al*., 1988 and Pfluger and Minder, 1994, respectively). The one smoking-adjusted study focusing on trucking, Steenland *et al*. (1990), found elevated relative risk estimates for several occupational and duration of employment categories; however, the only statistically significant risk estimate found was for diesel truck drivers with greater than 34 years of exposure, (OR = 1.89; 95% C.I. = 1.04-3.42).

While several population-based studies enrolled a large number of subjects overall (Williams *et al*. 1977; Milne *et al*., 1983; Hall and Wynder, 1984; Damber and Larsson, 1987; Boffetta *et al*. 1988), the actual numbers of subjects occupationally exposed to diesel exhaust (considered here as truck drivers) were small. Of the larger, general population studies (Hayes *et al*., 1989; Benhamou *et al*., 1988; Boffetta *et al*., 1990; Swanson *et al*., 1993) and industry- or occupation-specific studies (Ahlberg *et al*., 1981; Rafnsson and Gunnarsdottir, 1991; Guberan *et al*., 1992; Hansen *et al*., 1993; Pfluger and Minder, 1994; Steenland *et al*., 1990) with greater numbers of truck drivers, significantly elevated smoking-adjusted risk estimates were limited mainly to the case-control studies described above (Hayes *et al*., 1989; Benhamou *et al*., 1988; Steenland *et al*.,

1990; Swanson *et al*., 1993; Pfluger and Minder, 1994). Although several industry-specific cohort studies found significantly elevated risks associated with truck or professional driving, with SMRs ranging between 1.33 and 2.14, all lacked smoking data.

Studies Of Lung Cancer Among Transport Workers

Table 1 summarizes the studies that have examined the lung cancer risk to truck drivers. Most studies of transportation workers are limited by small sample size, lack of smoking data, or limited follow-up. None of the three studies of London transportation workers, drivers or garage workers, (Raffle, 1957; Waller, 1981; Rushton *et al*., 1983) obtained information on smoking. In addition, two lacked sufficient follow-up (Raffle, 1957; Rushton *et al*., 1983), excluded retirees, or suffered from small sample size (Raffle, 1957; Waller, 1981). Of the other European studies focusing on bus company employees (Edling *et al*., 1987; Netterström, 1988; Gustavsson *et al*., 1990), only Gustavsson *et al*. (1990) found an elevated risk for lung cancer, with an overall SMR of 1.22 (95% C.I. = 0.71-1.96). However, in the more detailed nested case-control analysis using conditional logistic regression, estimated RRs increased with the cumulative diesel-exhaust exposure index, as noted above.

Of the three studies reporting increased risks for heavy equipment operators (Wong *et al*., 1985; Boffetta *et al*., 1988; Hayes *et al*., 1989), only the RR reported by Boffetta *et al*. (1988) was statistically significant (RR = 2.6; 95% C.I. = 1.12-6.06). However, this estimate was based on only five lung cancer deaths. The large industry-specific cohort study of Wong *et al*. (1985) did not find an elevated risk for lung cancer among unionized heavy equipment operators (SMR = 0.99; 95% C.I. = 0.88-1.10). A subset of individuals retiring at age 65 did have a significantly elevated risk, but a group excess in emphysema deaths (SMR = 2.75; 95% C.I. = 2.09-3.55) and the absence of smoking data suggest that the increased risk may have been related more to tobacco use than to diesel exhaust exposure.

Table 1: Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Truck Drivers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Menck and Henderson, 1976 USA	Cohort Truck drivers	109	SMR 1.65	$p < 0.01$	Included 2,161 lung cancer cases identified from death certificates in white males, aged 20 to 64, from 1968 through 1970, and 1777 incident cases of lung cancer reported to LA County Cancer Surveillance Program for 1972 - 73. Occupational information obtained from death certificates or hospital admission sheets/medical records represented the last occupation and industry of employment. No data on smoking.
Decoufle *et al*. 1977 USA	Case-control Truck or tractor driver ≥ 5 years as truck, bus or taxi driver	 56 50	OR 1.07 0.89	 N.S. N.S.	Hospital-based study of 6,434 cancers cases admitted to Roswell Park Memorial Institute between 1956 and 1965. Controls were patients admitted with non-neoplastic disease. Occupation and smoking data obtained by questionnaire. Crude adjustment for smoking. Inadequate latency.
Williams *et al*. 1977 USA	Case-control Transportation Industry Truck drivers Railroad workers Truck Industry	 38 22 12 13	RR 1.17 1.52 1.40 1.34	 N.S. N.S. N.S. N.S.	Study examined cancer incidence and its relation to occupation and industry based on the U.S. 3rd National Cancer Survey. The number of cases of cancer at various sites were compared with that of cases at all other sites combined. Occupational history (main and recent employment) and data on smoking were obtained by interview (n = 7,518). IARC noted the potential bias in this study due to the relatively low level of response to the questionnaire (57%). Results were controlled for tobacco use, alcohol consumption, race, education and geographic location.
Leupker and Smith, 1978 USA	Cohort Total cohort Age 50-59	 34 not given	SMR 1.21 1.37	 N.S. $p < 0.001$	Death certificates for a 3-month period in 1976 in the Central States Teamster population were examined. Comparison group was the US male population and was not adjusted for race. No data on smoking. Authors noted the follow-up was short. Retirees and members with lapsed benefits were excluded. 48,358 members were eligible in the 50-59 age group.
Ahlberg *et al*. 1981 Sweden	Cohort All truck drivers* Stockholm truck drivers#	 161	RR 1.33 1.62	 1.13-1.56 1.15-2.28	Cohort consisted of 34,027 Swedish drivers considered to be exposed to diesel exhaust identified from the 1960 national census. Reference population consisted of blue-collar workers from the same census thought to have had no exposure to petroleum products or chemicals (n=686,708). No data on smoking; however, a study of 470 professional drivers in Stockholm found that 78% of fuel truck drivers and 31% of other truck drivers smoked compared to 40% in the Swedish population (citing unpublished study). # Subset of all non-fuel tank drivers. *Does not include fuel tank drivers.

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust. OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Truck Drivers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Milne *et al*. 1983 USA	Case-control Occupational groups: All transport operatives Bus drivers Truck drivers Other transport Industry groups: Railroad	 36 4 23 7 34	OR 1.3 (1.1)* 3.5 (2.8)* 1.6 (1.3)* 0.7 (0.6)* 0.8 (0.8)*	 N.S. $p < 0.05$* $p < 0.05$* N.S. N.S.	Study compared lung cancer deaths with mortality from all other cancers in Alameda County between 1958 and 1962 to investigate possible associations between lung cancer and occupation. Data on cause of death and occupation were obtained from death certificates. No data on smoking or the types of vehicle engines. Results reported are for males. *Results in parentheses are ORs with potential occupationally related cancer removed from the control population. Significant risk estimates only observed when compared with control group before such cancers removed.
Hall and Wynder, 1984 USA	Case-control <u>Usual employment:</u> Total diesel-exposed - adjusted for smoking <u>Selected occupations:</u> Truck drivers Railroad workers Heavy equipment repairmen & operators - adjusted for smoking <u>Smoking & DE exposure:</u> Non & ex-smokers ≤ 20 cigarettes/day > 20 cigerettes/day	 45 22 5 10 10 10 7	OR 2.0 1.4 1.4 2.6 3.5 1.9 1.46* 0.82* 1.30*	 1.2-3.2 0.8-2.4 0.7-2.6 0.5-12.8 1.0-11.8 0.6-5.5 0.9-2.3 0.5-1.4 0.8-2.1	Study consisted of 502 men with histologically confirmed primary lung cancer (20 to 80 years old) and matched control patients in 18 hospitals in six cities. Controls with tobacco-related diseases were excluded. Patients were interviewed between December 1980 and November 1982. Smoking data were obtained. Occupations were grouped either dichotomously as exposed to diesel exhaust (warehousemen, bus drivers, truck drivers, railroad workers, heavy equipment operators) or unexposed. Exposure categorization also conducted by NIOSH-based occupational classifications with job title classified as having "probable" exposure to diesel exhaust as either "high" (10 cases), "moderate" (16 cases) or "little or none" (476 cases). No significantly elevated risks were reported in this latter analysis (data not shown here). See also Boffetta *et al*., 1990. *Compared DE exposed to unexposed within each smoking category.

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust. OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Truck Drivers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Boffetta *et al.*, 1990 USA	Exposure by occupation:		OR		Study consisted of 2584 histologically confirmed lung cancer cases and 5009 controls derived from 18 hospitals in six cities. Controls were patients with current non-tobacco-related diseases matched by age, hospital and year of interview. Exposure was assessed by occupational titles and self-reported exposure to diesel exhaust. Results were adjusted for smoking, education and asbestos exposure by logistic regression. Occupations were classified as having probable, possible or no diesel exhaust exposure. Exposure prevalence was low. Only 15.6% of the controls were ever in an exposed job and 6.4% were considered probably exposed. Self-reported exposure to diesel exhaust had consistently higher point estimates of risk than those based on occupational classification, suggesting the possibility of recall bias. See also Hall and Wynder, 1984. *Duration of employment data only available for 23 cases and 27 controls of all patients classified as truck drivers (114 cases and 176 controls).
	"Possible" exposure	240	0.92	0.76-1.10	
	"Probable" exposure	210	0.95	0.78-1.16	
	By duration:				
	"Probable" DE				
	1-15 years	4	0.52	0.15-1.86	
	16-30 years	15	0.70	0.34-1.44	
	31+ years	17	1.49	0.72-3.11	
	Truck driver*				
	1-15 years	4	1.83	0.31-10.73	
	16-30 years	12	0.94	0.41-2.15	
	30+ years	7	1.17	0.40-3.41	
	Self-reported exposure:		1.21	0.73-2.02	
	By duration				
	1-15 years	11	0.90	0.40-1.99	
	16-30 years	12	1.04	0.44-2.48	
	31+ years	12	2.39	0.87-6.57	
Damber and Larsson, 1985 Sweden	Case-control		OR		Study included 604 male patients with lung cancer from the 3 most northern counties in Sweden (all new cases reported to the Swedish Cancer Registry in 1972 to 77 who had died at least one year before the start of the study in 1979). Matched controls were drawn from the national registry for causes of death. Living controls were also used. Data on occupational and smoking habits were obtained by questionnaire. Study focused on professional drivers, most of whose vehicles had diesel engines. Investigators noted that drivers had considerably higher average tobacco consumption than nondrivers. Authors stated that the study suggests a synergistic interaction between smoking and occupational exposure. See also Damber and Larsson 1987. Risk estimates presented for portion of cohort with date of birth after 1900. [#] Subset of all drivers. * Compared to nondrivers. ** Compared to nondrivers/nonsmokers, where "nonsmokers" included ex-smokers who had quit for at least 10 years.
	By age of diagnosis:				
	Professional drivers				
	<70 years	40	1.00*	0.66-1.50	
	≥70 years	23	3.15*	1.66-6.00	
	Truck drivers[#]				
	<70 years	22	0.83*	0.50-1.40	
	≥70 years	13	5.70*	2.22-14.67	
	By age & smoking status:				
	Drivers/ Nonsmokers**				
	<70 years	NG	1.9	0.5-5.5	
	≥70 years	NG	4.5	1.1-16.4	
	Drivers/Smokers**				
	<70 years	NG	6.0	3.5-10.3	
	≥70 years	NG	20.8	9.4-46.0	

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust. OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Truck Drivers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Damber and Larsson, 1987 Sweden	Case-control Professional drivers Years worked ≥1 ≥20 Adjusted for smoking ≥1 ≥20	 72 37 72 37	OR 1.3 1.5 1.0 1.2	 0.9-1.9 0.9-2.6 0.7-1.5 0.6-2.2	Study consisted of 600 men with lung cancer in northern Sweden reported to the Swedish Cancer Registry from 1972 through 1977 and dead before the start of the study (1979). Cases were matched with both dead and living controls. Results reported here are for comparisons with dead controls. Results with living controls were in good agreement. See Damber and Larsson (1985) for study focused on professional drivers only.
Boffetta *et al*. 1988 USA	Prospective Cohort Self-reported as DE: All DE exposed By duration exposure: 1-15 years 16+ years DE & smoking status*: nonsmokers ex-smokers current smokers Occupation: Railroad worker Truck driver Heavy equipment By occupation & DE: Truck/exposed Truck/nonexposed	 174 7 85 78 14 48 5 18** 18**	RR 1.18 1.05 1.21 1.73 11.06 19.82 1.59 1.24 2.60 1.22 1.19	 0.97-1.44 0.80-1.39 0.94-1.56[#] 0.60-4.95 6.27-19.53 11.20-35.07 0.94-2.69 0.93-1.66 1.12-6.06 0.77-1.95 0.74-1.89	Included 461,981 males, aged 40 to 79, participating in the American Cancer Society's Prospective Mortality Study in 1982. Follow-up for two years. Exposure assessment was based on self-reported (questionnaire) occupation and diesel exhaust exposure. Investigators stated that, although the sample was large, it was comprised of volunteers, who were healthier and were less frequently exposed to important risk factors such as smoking and alcohol. Reference population included men with no reported exposure or likely occupational exposure to diesel exhaust. Results were adjusted for smoking and other occupational exposures (asbestos, coal and stone dust, coal tar pitch, and gas exhaust). See Hall and Wynder, 1984. *Smoking data not available for all subjects. **Diesel exhaust exposure data not available for all truck drivers. [#]Test for trend reported by investigators as $0.05 < p < 0.10$.
Benhamou *et al*. 1988 France	Case-control Motor vehicle mechanic Transport equipment operators Professional drivers	 65 157 128	RR 1.06 1.35 1.42	 0.73-1.54 1.05-1.75 1.07-1.89	Study consisted of 1,334 histologically confirmed lung cancer cases and 2,409 controls matched on sex, age, hospital admission and interviewer. Study was conducted between 1976 and 1980. Results were adjusted for smoking and are limited to males. Occupation was determined by questionnaire (interview). The types of motor vehicle engines worked with were not specified. No evidence of increased risk with increased duration of exposure (years employed).

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust. OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Truck Drivers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Hayes *et al*. 1989 USA	Case-control Pooled Analysis Truck Drivers		OR		The study is a pooled analysis of three case-control studies conducted between 1976 and 1983 in Florida, New Jersey, and Louisiana. Total
	< 10 yrs employed	161	1.0	0.8-1.3	eligible cases = 2,291 and controls = 2,570. All occupational
	≥ 10 yrs employed	112	1.5	1.1-2.0	data were recoded from original interviews. No specific information regarding
	Heavy Equipment				
	< 10 yrs employed	7	1.5	0.4-5.3	diesel exposure or engine type. ORs were adjusted for birth
	≥ 10 yrs employed	10	2.1	0.6-7.1	cohort(<1910, 1910-19, 1920-29, 1930+), usual daily cigarette use, and state.
	Bus Drivers				
	< 10 yrs employed	23	1.1	0.6-2.1	
	≥ 10 yrs employed	24	1.7	0.8-3.4	
Steenland *et al*. 1990 USA	Case-control Occupation data: 1) Teamster records data		OR		Study consisted of 1,086 lung cancer cases and 1,085 controls among truck drivers in the Central States Teamsters Union. Information on work history was obtained from next of kin and union records.
	Long-haul driver		1.27	0.83-1.93	Subjects died in 1982-83 after applying for pensions, which
	Short-haul driver		1.31	0.81-2.11	required at least 20 years of union membership. Subjects
	2) Next-of-kin data				were classified according to the job category in which they
	Truck driver, diesel		1.42	0.89-2.26	worked the longest. Union data provided no information on
	Truck driver, gasoline		1.22	0.79-1.88	the type of truck driven. 90% of union long-haul drivers were also identified as diesel truck drivers by next of kin.
	Truck driver, both		1.25	0.81-1.95	Results were adjusted for smoking and asbestos exposure. Smoking data obtained by next-of-kin interview used in both types of exposure classification. Steenland *et al*. (1992) summarized results from a recent industrial hygiene survey of exposure to diesel exhaust in the trucking industry, and found that elemental carbon measurements were generally consistent with the results; i.e., mechanics had the highest exposure and the highest risks, followed by long-haul and local drivers. Authors noted that exposure to asbestos may account for some of the observed effects in mechanics, but its confounding effect was probably small. Study results for truck mechanics and dock workers were elevated but not significant. *Study also presented risk estimates for duration of employment inclusive of the pre-1959 work era for both job ascertainment categories and for majority of job classifications.
	Duration employment after 1959*: 1) Teamster records data				
	Long-haul driver				
	1-11 years	162	1.08	0.68-1.70	
	12-17 years	228	1.41	0.90-2.21	
	≥18 years	213	1.55	0.97-2.47	
	2) Next-of-kin data				
	Diesel truck driver				
	1-24 years	48	1.27	0.70-2.27	
	25-34 years	72	1.26	0.74-2.16	
	≥35 years	56	1.89	1.04-3.42	

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust. OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Truck Drivers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Burns and Swanson 1991 USA	Case-control		OR		Occupational and smoking histories were obtained by telephone interview for 5,935 incident lung cancer cases and 3,956 incident colon and rectal cancer controls diagnosed between 1984 and 1987 and reported to the Detroit cancer registry. The smoking- and race-adjusted OR for all drivers (238 cases, 86 controls) was 1.88 (95% C.I. = 1.37-2.58), while drivers of "heavy trucks" (166 cases, 48 controls), maintained a higher risk even after adjustment for smoking, OR = 2.31 (95% C.I. = 1.56-3.42). Mechanics also had a significantly elevated OR for lung cancer (OR = 1.72, 95% C.I. = 1.15-2.59). The types of the vehicle engines were not specified. Results were adjusted for smoking. See Swanson *et al*. 1993.
	Drivers (white)	187	2.40	1.65-3.48	
	All drivers (race adj.)	238	1.88	1.37-2.58	
	Railroad workers	14	1.27	0.45-3.53	
Swanson *et al*. 1993 USA	Case-control Occupation and duration: 1) White males		OR		Cases and controls were from OCISS (see Burns and Swanson, 1991 for description of subjects). Incident lung cancer cases among black and white males, aged 40 to 84, from 1984 through 1987 are included in this report. Controls were colon and rectal cancer cases. Information on occupation, smoking, medical history were obtained by telephone interview. Results were adjusted for age at diagnosis, race and smoking. *Test for trend $p \leq 0.05$.
	Heavy truck drivers				
	0 years	88	1.0	Reference	
	1-9 years	78	1.4	0.8-2.4*	
	10-19 years	38	1.6	0.8-3.5*	
	20+ years	121	2.5	1.1-4.4*	
	Light truck drivers				
	0 years	88	1.0	Reference	
	1-9 years	46	1.7	0.9-3.3	
	10+ years	36	2.1	0.9-4.6	
	Railroad workers				
	0 years	73	1.0	Reference	
	1-9 years	27	1.2	0.5-2.7	
	10+ years	40	2.4	1.1-5.1	
	2) Black males				
	Heavy truck drivers				
	0 years	12	1.0	Reference	
	1-9 years	27	2.7	0.8-9.2	
	10-19 years	16	1.9	0.5-7.2	
	20+ years	16	2.1	0.5-9.2	
	Railroad workers				
	0 years	15	1.0	Reference	
	1-9 years	22	2.6	0.8-7.9	
	10+ years	9	2.7	0.6-12.1	

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust. OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Truck Drivers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Rafnsson and Gunnarsdottir 1991 Iceland	Cohort Truck drivers Duration employment: <2 years 2-10 years 11-30 years >30 years	24	SMR 2.14 2.70 2.46 0.68 2.32	1.37-3.18 0.74-6.92 0.99-5.08 0.01-3.76 0.85-5.04	Cohort consisted of truck and taxi drivers in Reykjavik followed from 1951 to 1988. National mortality rates were used as for comparison. Information on truck drivers was obtained from their union. No data on smoking or type of vehicle engines used. No trend of increased risk with increased follow-up time was observed.
Guberan *et al*. 1992 Switzerland	Cohort Professional drivers	77	SMR 1.50	1.23-1.81	Cohort identified from vehicle license records of professional drivers required to obtain special license during the period from 1949 to 1961. Excluding individuals born prior to 1900, 1,726 drivers were eligible. Lung cancer cases identified from death and tumor registries through 1986. No smoking data obtained. Approximately 1/3 to 1/4 of professional drivers were reported to be long-haul truck drivers. Death rates compared to regional mortality rates. A significant ($p < 0.02$) upward trend in lung cancer mortality with time from first exposure was also observed: SMRs = 0.67, 1.18, 1.30, 1.35, and 2.59 for 0-14, 15-24, 25-34, 35-44, and ≥ 45 years, respectively (no confidence intervals reported).
Hansen 1993 Denmark	Cohort Age on Nov. 9, 1970 15-29 30-39 40-44 45-49 50-54 55-59 60-64 65-74 Total	 0 3 3 11 12 19 22 6 76	SMR 1.96 0.56 1.17 1.10 2.29 2.27 2.60 1.60	 0.40-5.73 0.12-1.64 0.58-2.09 0.57-1.93 1.38-3.58 1.42-3.44 0.95-5.65 1.26-2.00	Cohort consisted of 14,225 truck drivers followed for a 10-year period. Comparisons were made with another cohort of unskilled laborers. Members of the cohort were identified from the file of a nationwide census conducted in 1970. Self-reported occupation, trade, industry and employment on the day of the census were recorded. The study was comprised of unskilled male laborers 15 to 74 years old who were occupationally active on the day of the census. 627 truck drivers and 3,811 members of the control cohort died within the 10 years. No data on smoking. Diesel engines have comprised most of Danish fleet of trucks since the late 1940s.
Pfluger and Minder, 1994 Switzerland	Case-control Professional drivers - smoking adjusted	284	OR 2.27 1.48	1.99-2.58 1.30-1.68	Mortality of Swiss professional drivers (truck, bus and taxi drivers) was determined from death certificates and compared to census data to obtain occupation and age-specific death rates. No individual smoking data were available, but an indirect adjustment was conducted based on occupation specific mortality rates.

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust. OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Transport (i.e., bus) and Equipment Workers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Raffle 1957 England	Cohort Overall Bus & trolley drivers Age 55-64	 96 30	SMR 1.4	 N.S.	Cohort consisted of deaths, retirements and transfers due to lung cancer in London transport employees (bus and trolley workers, bus engineers), aged 45 to 64 years, in jobs with presumably different exposures to exhaust fumes in 1950 to 1954. Only cases arising during exposure employment were considered. Rates were compared to lung cancer mortality in other company employees. Diesel buses had been gradually introduced since the 1930s. At the end of WWII only 15% of the buses still used petrol. All had been replaced by 1950. Consequently, the duration of exposure of some workers to DE might have been short. No data on smoking. See also Waller 1981.
Waller 1981 England	Cohort All workers Bus drivers Bus conductors Engineers, garages Engineers, central works Motormen and guards	 667 259 130 177 42 59	SMR 0.79 0.75 0.75 0.90 0.66 0.87	 NP NP NP NP NP NP	Cohort consisted of lung cancer deaths and retirements or transfers due to lung cancer in men, aged 45 to 64, employed within five categories of London Transport employees. Mortality was compared to men in Greater London. The study covered 25 years ending in 1974, thus including some of the data described by Raffle (1957). No data on smoking. Those who retired at age 65 or left earlier were not followed up, thus limiting the extent of case ascertainment.
Rushton *et al.* 1983 England	Cohort	 102	SMR 1.01	 $p = 0.94$	Cohort consisted of 8,684 men employed as maintenance workers in 71 bus garages in London for at least one year from 1967 to 1975. Follow-up through 1975. No data on smoking. Authors noted short follow-up period (average of 6 years). Lung cancer mortality was compared with the male population of England and Wales. The all-cause mortality was significantly lower than expected based on London residence.
Buiatti *et al.* 1985 Italy	Case-control Transportation Taxi driving Train conductors	 45 20 7	OR 1.1 1.8 1.4	 0.7-1.6 1.0-3.4 0.5-3.9	Study consisted of 340 confirmed cases in males (and 817 controls) in Florence, diagnosed from 1981 through 1983 in the regional general hospital and a referral center for lung cancer. Controls were matched on sex, age, date of admission and smoking, and were from the same hospital. Diesel exhaust exposure was assessed by questionnaire for all jobs held for more than one year.

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust, OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio, NP = not presented.

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Transport (i.e. bus) and Equipment Workers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Wong *et al*. 1985 USA	Cohort Total By Duration <5 years 5-9 years 10-14 years 15-19 years ≥20 years All retired members Normal retired members	 309 10 25 53 58 163 155 86	SMR 0.99 0.45 0.75 1.08 1.02 1.07 1.64* 1.30**	 0.88-1.10 N.S. N.S. N.S. N.S. $p = 0.05$ $p < 0.01$ $p < 0.05$	Cohort consisted of 34,156 male members of a heavy construction equipment operators union for at least one year from 1964 through 1978. Mortality experience was compared with that of the US white male population. Partial work history was available for some cohort members through the union. A random sample of union members was surveyed to determine smoking habits, and no significant difference between members and the general population was found. Work groups evaluated were considered to have high exposure to diesel exhaust (scraper operator, bulldozer operator, backhoe operator and loader operator) or low exposure (mechanical maintenance workers and engineers). Overall mortality in the cohort was less than that in the U.S. male population (SMR 0.81, 95% C.I. 0.79-0.84). Workers were also categorized by job title and potential exposure, but no significant risks were observed. Analysis of retirees found an excess risk for lung cancer* and emphysema. *Includes also retirements due to ill health. *Normal retirees are those workers retired at or over 65 and early retirees who reached 65.
Edling *et al*. 1987 Sweden	Cohort Bus company employees Bus drivers Bus garage workers Clerks	 6 5 1 0	SMR 0.67 0.69	Not presented	Cohort consisted of 694 bus garage employees followed from 1951 through 1983. Men were divided into three exposure categories (clerks, bus drivers and bus garage workers). Clerks were assumed to have had the lowest exposure to diesel exhaust and bus garage workers the highest. Authors stated that the power of the study to detect specific cancers was limited. No data on smoking.
Netterstrom 1988 Denmark	Cohort Bus drivers	 15	SMR 0.87	 0.48-1.43	Cohort of 2,465 Danish bus drivers from three companies during the period 1978 to 1984. Cases were identified through death and cancer registries. Death rates were compared with national rates. No data on smoking were available. Mean value for employment duration among the lung cancer cases was 30 years

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust, OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Transport (i.e. bus) and Equipment Workers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Gustavsson *et al*. 1990 Sweden	Cohort Total (deaths) DE exposure index: 0-10* 10-30 >30 Nested case-control (20 incident cases) 0-10* 10-20 20-30 >30	 17 5 5 7 5 2 3 10	SMR 1.22 0.97 1.52 1.27 RR 1.0 1.34 1.81 2.43	 0.71-1.96 Reference 1.09-1.64 1.20-2.71 1.32-4.47	Cohort consisted of 695 bus garage workers employed as mechanics, servicemen or hostlers for at least six months in five bus garages in Stockholm between 1945 and 1970. A nested case-control study was performed within the cohort. Follow-up was through 1986. No data on smoking although no large variation in smoking habits was expected within the cohort. Exposure to diesel exhaust and asbestos were assessed based on time period-specific data on job tasks. Lung cancer cases were identified through tumor and death registries. In the cohort analysis regional rates were used for comparison. *Cumulative exposure index values (unitless).
Gustafsson *et al*. 1986 Sweden	Cohort Deaths Incident cases	 71 89	SMR 1.29 SIR 1.53	 1.02-1.63 1.24-1.80	Cohort consisted of 6,071 Swedish dockworkers first employed before 1974 for at least six months. The group was followed from January 1961 through January 1981. Cancer morbidity was determined among 6,071 dockworkers who had been alive and without cancer in January 1961. Comparison group was Swedish male population. Diesel trucks were introduced into Swedish ports in the late 1950s and became prevalent during the 1960s. No data on smoking. See Emmelin *et al*. (1993) for results from the follow-up study. Employment as a dockworker was the only information on diesel exhaust exposure used in the analysis.

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust, OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Transport (i.e. bus) and Equipment Workers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Emmelin *et al*. 1993 Sweden	Case-control Exposure variable: Machine time high* Fuel consumption high* Exposed time high* Exposure & Smoking: Machine time medium high smoker Fuel consumption medium high smoker Exposed time medium high smoker	 14 15 19 	OR 1.3 1.7 2.9 1.8 2.9 5.7 1.5 2.9 5.5 2.7 6.8 6.2	 0.3-5.6** 0.5-5.9** 0.8-10.7** 0.5-6.6** 0.6-14.4** 2.4-13.3** 0.5-4.8** 0.7-11.5** 2.4-12.7** 0.6-11.3** 1.3-34.9** 2.6-14.6**	Study was a nested case-control of lung cancer among Swedish male dockworkers in the cohort studied by Gustafsson *et al*. (1986). 154 referents were matched to 50 cases on port and date of birth. Indices of exposure to diesel exposure were derived from employment records and records of annual fuel consumption by diesel vehicles. Three different exposure classifications were created: "machine time", "fuel consumption" and "exposed time". Information on smoking was obtained from questionnaires and interviews with foremen or workers who had worked with subjects. Response rate for mailed questionnaires was low (67%) but information from the interviews was available for 95% of the subjects. Some ex-smokers were classified as never smokers. No exposure level ("low", "medium", or "high") was significant for any DE exposure scheme (only "high" strata reported here). Comparisons based on exposure and smoking tended to find more elevated risks. Investigators noted that the increase in the OR for both smoking and exhaust exposure indicate that smoking does not explain the results from the exposure-only models, and that there may be an interaction between smoking and exhaust exposure. No information on asbestos exposure, which was said to have decreased by the 1970s. See also Gustafsson *et al*. (1986). * "Low" exposure category used for reference comparison. **Note: authors reported confidence intervals at 90% level.
Kaplan 1959 USA	Cohort Total Most likely exposed	 154 49	SMR 0.80 0.875	 0.68-0.94 N.S.	Cohort consisted of 6,506 deaths among railroad workers from the Baltimore and Ohio Railroad Relief Department between 1953 and 1958. Subjects were categorized into 3 groups by exposed to diesel exhaust and compared with national lung cancer mortality rates. IARC noted that since the changeover to diesel engines began in 1935 and was 95% completed by 1959 (Garshick *et al*. 1988), few, if any, of the lung cancer deaths could have occurred in workers with more than 10 years of exposure to diesel exhaust. No data on smoking.

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust, OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Railroad Workers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence Interval[a] or *P*-Value	Comments
Howe *et al*. 1983 Canada	Cohort		SMR		Study consisted of 43,826 males of the Canadian National Railway Co. retired and alive in 1965 and followed until 1977. No data on smoking. However, authors note that this may not be crucial since conclusions were based on internal comparisons where no large variation in smoking habits was likely. It was also noted that certain smoking-related deaths were elevated. The results remained unchanged when individuals likely to have been exposed to asbestos were excluded from the analysis.
	Entire cohort	933	1.06	0.99-1.13	
	Retired after 1950	897			
	Exposure to DE				
	"nonexposed"	239	1.00		
	"possibly" exposed	407	1.20	$p = 0.13$	
	"probably" exposed	279	1.35	$p < 0.001$	
Garshick *et al*. 1987a USA	Case-control	1256	OR		Study consisted of Railroad Retirement Board registrants (1,256 cases and 2,385 matched controls) who died between March 1981 and February 1982. Subjects were active and retired workers with at least 10 years work experience. Persons who died from cancer, suicide, accidents or unknown causes were excluded as controls. Results were adjusted for smoking and asbestos exposure. The baseline study year was 1959, when diesel engines had nearly replaced all steam engines. Consequently, few of these workers were exposed to asbestos. Personal exposure was assessed by industrial hygiene sampling in 39 job categories. Job titles were used to dichotomize subjects into exposed and unexposed groups (Woskie *et al*., 1988a,b). See also Garshick *et al*. (1988). *Shopworkers had the highest levels of asbestos exposure. **These results excluded exposure occurring within 5 years before death. The shortest exposure category, 0 to 4 years, was used as a reference group.
	Age (years)				
	≤64	335	1.41	1.06-1.88	
	≥65	921	0.91	0.71-1.17	
	DE Exposure:				
	Diesel-years ≤ 64 worker				
	5-19		1.02	0.72-1.4	
	≥20		1.64	1.18-2.2	
	Diesel-years > 65 worker				
	5-19		0.95	0.79-1.13	
	≥20		0.94	0.56-1.59	
	Minus shopworkers*				
	≥20 years of exposure		1.55	1.09-2.21	
	Years of cumulative DE exposure:**				
	5-14		1.07	0.69-1.66	
	≥15		1.43	1.06-1.94	

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust, OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer Studies Among Railroad Workers

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence[a] Interval or *P*-Value	Comments
Garshick *et al*. 1988 USA	Cohort	1694	RR		Cohort consisted of 55,407 white male railroad workers aged 40-64 exposed to little or no asbestos who had started work between 1939 and 1949 and had worked 10 to 20 years after 1959. Follow-up through 1980. Industrial hygiene data were used to categorize jobs as exposed or unexposed. No data on smoking; however, authors noted that there was no difference in smoking habits by job title in comparison studies of current workers (see Garshick *et al*. 1987). Diesel exhaust exposure in the US railroad industry occurred after WWII. The approximate midpoint of dieselization was in 1952 and by 1959, 95% of the locomotives were diesel-powered. Workers aged 40 to 44 in 1959 were the group with the longest possible duration of exposure. Most workers with potential asbestos exposure were excluded, though some did have potential exposure to asbestos (shopworkers and hostlers). Analyses were done with and without these groups. Exposure was assessed from samples of respirable dust taken in 1980s (Woskie *et al*. 1988a). Mean exposure levels suggested a five-fold range of exposure between clerks and shopworkers (Woskie *et al*. 1988b). These values confirmed the assignment of categories of diesel exhaust exposure in the present study and Garshick *et al*. 1987. * Excluding exposure to diesel exhaust over the 4 years preceding the year of death
	By Age in 1959 w/ DE:				
	40-44		1.45	1.11-1.89	
	45-49		1.33	1.03-1.73	
	50-54		1.12	0.88-1.42	
	55-59		1.18	0.94-1.50	
	60-64		0.99	0.74-1.33	
	Minus those w/ asbestos exposure				
	40-44		1.57	1.19-2.06	
	45-49		1.34	1.02-1.76	
	By Years DE Exposure:*				
	1-4 years		1.20	1.01-1.44	
	5-9 years		1.24	1.06-1.44	
	10-14 years		1.32	1.13-1.56	
	≥ 15 years		1.72	1.27-2.33	
	Minus those w/ asbestos exposure				
	1-4 years		1.34	1.08-1.65	
	5-9 years		1.33	1.12-1.58	
	10-14 years		1.33	1.10-1.60	
	≥ 15 years		1.82	1.30-2.55	
Nokso-Koivisto and Pukkula, 1994 Finland	Cohort		SIR		Cohort consisted of 8,391 members of the Finnish Locomotive Drivers' Association from 1953 to 1991 (including retirees). Information was not available for 302 members. No smoking data were available. The overall incidence for all cancer sites was lower than expected when compared to national rates (SIR = 0.95).
	Total	236	0.86	0.75 – 0.97	

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. DE = Diesel Exhaust, OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer (Additional Studies Other Than Those Listed In Above Categories)

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence[a] Interval or *P*-Value	Comments
Wegman and Peters, 1978 USA	Case-control Total study Transportation equipment operatives - Registry derived - Combination w/ registry data	91 8 5	OR 8.67 1.26	 NP NP	Tumor registry-based study of oat cell carcinoma during 1965 to 1972. Cancer controls identified from same registry. Smoking data collected but not used in analysis (94% cases and 78% controls smoked). Two methods used to classify occupation, registry-derived or combination of registry and next-of-kin questionnaire data. Number of cases classified as transportation equipment operatives decreased from 8 to 5 between two methods.
Coggon *et al*. 1984 England	Case-control Total DE exposed High DE exposure	 172 32	RR 1.3 1.1	 1.0-1.6 0.7-1.8	Study included all men 40 years of age in England and Wales who had died of tracheobronchial cancer from 1975 through 1979. A job exposure matrix was constructed in which occupations were grouped according to likely exposure to each of nine known or putative carcinogens. Occupational information abstracted from the death certificates. No information on smoking. IARC noted the limitations of information on death certificates, the young age of the subjects, short exposure and latency times, and the lack of data on smoking and other potential confounders.
Lerchen *et al*. 1987 USA	Case-control Diesel exhaust fumes - adjusted for smoking Diesel engine mechanics - adjusted for smoking	 7 5	OR 0.6 1.0	 0.2 – 1.6 0.2 – 2.0	Population-based case-control study of 506 patients diagnosed between January 1980 and December 31, 1982, and reported to the New Mexico tumor registry (333 males and 173 females). Data on lifetime occupation and smoking were obtained by personal interview and self-reported history of exposure to specific agents. Matched controls were selected randomly from the telephone directory or for persons over 65 from the roster of participants in a health insurance plan. Only seven males reported exposure to diesel exhaust.
Magnani *et al*. 1988 England	Cohort All DE exposure	 NP	SMR 1.07	 1.04 – 1.10	General population-based cohort analysis of death certificate and census survey information on 31,925 men with lung cancer between 1970-72. No smoking data were available. A job-exposure matrix was developed for several potential carcinogens, including diesel exhaust.

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. NP = not presented. DE = Diesel Exhaust, OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Table 1 (continued): Epidemiological Studies of Exposure to Diesel Exhaust and Lung Cancer (Additional Studies Other Than Those Listed In Above Categories).

Reference	Study Design, Population, and Exposures	Cases or deaths	Effect Measure	Confidence[a] Interval or *P*-Value	Comments
Siemiatycki *et al*. 1988 Canada	Case-control Lung cell types among DE exposed: Oat cell Squamous cell Adenocarcinoma Other Total DE-exposed occupations minus mining:	 34 81 28 34 177 70	OR 1.1	 0.8-1.5** 1.0-1.5** 0.6-1.2** 0.8-1.4** 0.8-1.5**	This population-based case-control study provided information on the association between several cancer types and 10 types of exhaust and combustion products. Interviews were carried out for 3,726 cancer patients, aged 35 to 70, diagnosed in any of 19 participating Montreal area hospitals. Each type of cancer was a case series; reference groups were selected from among the other cancer patients interviewed. Results reported are adjusted for smoking, socioeconomic status, ethnic group and several other potential confounders. Authors noted that the excess lung cancers were concentrated among mine and quarry workers. **Authors reported 90% confidence intervals.
Bender *et al*. 1989 USA	Cohort State highway workers	 NP	SMR 0.69	 0.52 – 0.90	Cohort consisted of Minnesota highway workers employed for a minimum of one year and working at least one day after January 1, 1945. Mortality was compared to state rates. No data were available on smoking. Overall mortality was significantly lower than the expected, SMR = 0.83 (95% C.I. = 0.73-0.94).
Kauppinen *et al*., 1993 Finland	Case-control Engine exhaust exposure: Any exposure ≥ 1 month 1 month - 5 years > 5 years	 8 5 3	OR 1.7 0.39 2.21	 0.55-5.20** 0.05-2.94** 0.65-7.48**	Nested case-control study of woodworkers in Finland consisted of 136 lung cancer cases diagnosed between 1957 to 1982 and 408 matched controls. Original cohort consisted of 7,307 workers from 35 factories. Multiple chemical exposures were analyzed for, including engine exhaust (combination of diesel and gasoline engines). Smoking, age, and other chemical exposures were adjusted for; however, only a small number of individuals were categorized as having been exposed to engine exhaust. **Authors reported 90% confidence intervals.

[a] 95% Confidence intervals unless noted. N.S.= Not significant. No confidence intervals or *p*-values reported in original study. NP = not presented. DE = Diesel Exhaust, OR = Odds Ratio, RR = Relative Risk, SIR = Standardized Incidence Ratio, SMR = Standardized Mortality Ratio

Animal Studies

Section 6.1 (Animal Studies) of the diesel exhaust TAC document (OEHHA, 1998) describes the results of diesel exhaust inhalation carcinogenicity bioassays performed using mice, rats, hamsters and monkeys. The studies in rats provided the only clear and unequivocal evidence of diesel exhaust-induced carcinogenicity in animals.

The results of eleven animal cancer bioassays of inhalation of diesel exhaust alone were available at the time the document entitled *Health Risk Assessment For Diesel Exhaust* was written for the Toxic Air Contaminant (TAC) program (OEHHA, 1998). None of the four studies with either (a) exposure periods of less than 7 hours/day, 5 days/week for 24 months or (b) particulate exposure concentrations of less than 2.2 mg/m^3 (Karagianes *et al*., 1981; White *et al*., 1983; Lewis *et al*., 1986, 1989; Takemoto *et al*., 1986) gave positive results for carcinogenesis of diesel exhaust. The seven studies that presented positive results are as follows: Brightwell *et al*., 1986, 1989; Heinrich *et al*., 1986; Ishinishi *et al*., 1986a; Iwai 1986; Mauderly *et al.*, 1987a; Heinrich *et al*., 1995; Nikula *et al*., 1995. Results of these studies are described in detail in the diesel exhaust TAC document (OEHHA, 1998).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The diesel exhaust TAC document (OEHHA, 1998) stated that the results of the epidemiological analyses described above are consistent with a positive association between occupational exposure to diesel exhaust and an increased risk of developing lung cancer. The diesel exhaust TAC document reviewed the evidence for causality in the association between diesel exhaust and cancer of the lung. The following criteria for causal inference were considered: (1) the consistency of the findings; (2) the strength of the associations; (3) the possibility that findings are due to bias; (4) the likelihood that findings are due to chance; (5) evidence for exposure-response relationships; (6) temporality of the associations; and (7) biological plausibility of a causal association.

Chapter 6 of the diesel exhaust TAC document provided evidence consistent with a causal relationship between occupational diesel exhaust exposure and lung cancer. A lengthy discussion of causal inference, including the strengths and limitations of the underlying data, can be found in Section 6.2.4 of that document. The key findings relating lung cancer and occupational exposure to diesel exhaust are as follows: the majority of studies examining the diesel exhaust-lung cancer association have reported elevated estimates of relative risk, many of which are statistically significant. The consistency of these findings is unlikely to be due to chance. Moreover, with the possible exception of some studies that did not take smoking into account, the results are unlikely to be explained by confounding or bias. This is reinforced by the results of a meta-analysis undertaken by OEHHA staff (summarized below, and presented in detail in Appendix C of the diesel TAC document (OEHHA, 1998)), in which statistically significant pooled estimates of relative risk persisted through numerous subset and sensitivity analyses. The most important potential confounder is cigarette smoking, which was measured and controlled for in multiple studies: in the meta-analysis the pooled relative risk estimate for studies that adjusted for smoking

was 1.43 (95% C.I. = 1.31-1.57). In addition, several studies provide evidence of exposure-response relationships. The strength of the associations reported is typically within the range considered "weak" in epidemiology (i.e., estimates of relative risk between 1 and 2); nonetheless, this is not a bar to causal inference as long as other criteria are met, as discussed in Section 6.2.4 of the diesel exhaust TAC document. The temporal relationship between exposures and lung cancer is consistent with a causal relationship.

Additionally, the basic hypothesis -- that occupational exposure to diesel exhaust causes human lung cancer -- is highly plausible biologically. The evidence can be briefly summarized as follows: (1) Diesel exhaust has been shown to induce lung and other cancers in laboratory animal studies (Brightwell *et al*. 1989; Heinrich *et al*. 1986a; Iwai *et al*. 1986; Mauderly *et al*. 1987a); (2) Diesel exhaust has been shown to contain highly mutagenic substances, including polycyclic aromatic hydrocarbons and nitroaromatic compounds (Ball *et al*., 1990; Gallagher *et al*., 1993; Nielsen *et al*., 1996; Sera *et al*., 1994); (3) Diesel exhaust contains many substances which occur in recognized complex mixtures of human respiratory carcinogens, including cigarette smoke and coke oven emissions (IARC, 1989); and (4) Diesel exhaust contains known and probable human carcinogens.

Therefore, a reasonable and very likely explanation for the increased risks of lung cancer observed in the occupational epidemiological studies is a causal association between diesel exhaust exposure and lung cancer.

Results based on the human data and those based on the animal data are both subject to uncertainty. The principal uncertainties in using the rat data are their application to humans in terms of response, the choice of dose-response model to extrapolate the risk to environmental concentrations, the presence or absence of a threshold for response, and the range of dose extrapolation involved. While there are issues surrounding the quantitation of worker exposure to diesel exhaust, the uncertainty of extrapolating from one species (rat) to another (human) is avoided by using the epidemiological data to estimate risk to humans from diesel exhaust exposure. OEHHA preferred, on balance, to use the epidemiological data in order to estimate risk to humans from diesel exhaust exposure. Therefore, only the unit risk estimates based on human data were included in the final range of cancer unit risks associated with exposure to particulate matter from diesel-fueled engines in the diesel exhaust TAC document (OEHHA, 1998). OEHHA included quantitative risk assessment data based on rat studies in Appendix G of the diesel exhaust TAC document (OEHHA, 1998) for informational purposes.

<u>Quantitative Meta-Analysis on the Relationship of Occupational Exposure to Diesel Exhaust and Lung Cancer</u>

A meta-analysis was conducted to summarize and help interpret the published reports examining the relationship of lung cancer and exposure to diesel exhaust (OEHHA, 1998). A meta-analysis systematically combines the results of previous studies in order to generate a quantitative summary of a body of research and to examine the sources of variability among studies (for review see Petitti, 1994). The variability, or heterogeneity, of results among studies may exist due to numerous factors, including differences in study design, exposures experienced by study subjects,

methods and accuracy of exposure ascertainment, length of follow-up, and control of confounders (such as smoking).

As described in OEHHA (1998), 30 studies, contributing a total of 39 effect estimates, were utilized in the meta-analysis. The pooled relative risks for lung cancer from all 39 risk estimates combined varied with the statistical model used, 1.04 (95% C.I. = 1.02-1.06) under the fixed-effects model and 1.33 (95% C.I. = 1.21-1.46) with the random-effects model. However, significant evidence of heterogeneity was found (DerSimonian and Laird Q-statistic = 214.59, 38 d.f., $p < 0.001$). Heterogeneity in this context refers to large between-study variability. The presence of heterogeneity undermines the validity of the pooled estimates, and suggests the need for additional analysis to identify the sources of heterogeneity. As discussed in detail in Appendix C of OEHHA (1998), this involved deriving pooled estimates for a variety of subsets of the reports.

Through subset analysis, several factors were identified which strongly influenced both the magnitude and the degree of heterogeneity of the pooled risk estimates: (1) whether or not a study adjusted for smoking, (2) study design (3) the exposure assessment, as developed from occupational categories, (4) the presence of selection bias, as manifested by an observed "healthy worker effect", and other study characteristics (See Appendix C of OEHHA (1998)). By stratifying the meta-analysis on whether the risk estimates accounted for smoking, the effect of failure to control for this exposure on the pooled estimate became readily apparent. Not only did the positive association between diesel-exhaust exposure and lung cancer persist, but the pooled risk estimate increased to 1.43 (95% C.I. = 1.31-1.57, random-effects model) with little evidence of heterogeneity among the 12 studies controlling for smoking.

The case-control studies (15 included in the meta-analysis) gave a summary estimate of 1.44 (95% C.I. = 1.33-1.56), again with little evidence of heterogeneity, while the estimate based on the results of the cohort studies remained heterogeneous. The lower pooled RR estimate and substantial heterogeneity obtained from the cohort subanalysis was probably due at least in part to failure to adjust for smoking, as only one of sixteen cohort studies controlled for this confounder, while most case-control studies did (11 of 14 studies, accounting for 17 of the 20 case-control risk estimates).

The "healthy worker effect" (HWE - here based on significantly lower than expected all-cause mortality) is a manifestation of selection bias related to hiring and retention of workers who are typically healthier than the general population, resulting in spuriously lower risk estimates for a variety of illnesses, including those potentially related to occupational exposures. Subsetting the cohort studies into those with and those without an obvious healthy worker effect markedly reduced the degree of heterogeneity in the group without the HWE (Q-statistic = 11.190, 9 d.f., $p = 0.27$), and produced an increase in the magnitude of the pooled relative risk (RR = 1.52, 95% C.I. = 1.36-1.71-1.78, random-effects model). In contrast, those studies whose results were characterized by the presence of a HWE continued to show substantial heterogeneity, and the pooled risk estimates declined. Thus, selection bias is likely to have played a role in the heterogeneity observed among the cohort studies. Selection bias results from choosing a study sample that is not representative of the entire population that could have been studied, and can distort the measure of effect (e.g., relative risk or odds ratio) (Rothman, 1986). With respect to exposure assessment, statistically significant pooled estimates of elevated risk lacking evidence of

heterogeneity were identified in several occupational subgroup analyses, both with and without additional stratification for smoking. Prior to stratifying by adjustment for smoking, the occupational subgroups involving trucking (pooled RR = 1.47, 95% C.I. = 1.33-1.63), the railroad industry (random-effects pooled RR = 1.45, 95% C.I. = 1.08-1.93), mechanics and garage workers (random-effects pooled RR = 1.35 (95% C.I. = 1.03-1.78), general transportation and professional drivers (random-effects pooled RR = 1.45, 95% C.I. = 1.31-1.60) gave risk estimates greater than the overall pooled risk estimate. The pooled RR estimates for trucking and general transportation and professional drivers showed little to no evidence of heterogeneity; however, estimates for the railroad industry demonstrated considerable heterogeneity (Q statistic = 30.90, $p < 0.001$).

Further stratification of the occupational subgroup analysis by adjustment for smoking produced a large impact on the pooled risk estimates, with all smoking-adjusted subgroup estimates displaying little evidence of heterogeneity and leading to increased risk estimates in all but one of the occupational categories. Pooled risk estimates by occupation in smoking-adjusted studies showed little evidence of heterogeneity for several occupations under both models, including truck drivers (random-effects pooled RR = 1.53, 95% C.I. = 1.20-1.94), railroad workers (random-effects pooled RR = 1.68, 95% C.I. = 1.28-2.19), and diesel mechanics and garage workers (random-effects pooled RR = 1.25, 95% C.I. = 0.87-1.80). The pooled estimates for the heavy equipment operators and dock workers and for the railroad industry studies adjusting for smoking displayed the most dramatic changes relative to the occupational analysis without smoking stratification. Among the former subgroup, the pooled risk estimate changed from 1.28 (random-effects model, 95% C.I. = 0.99-1.66) to 2.43 (95% C.I. = 1.21-4.88). Among the railroad industry studies, the pooled risk estimate also increased substantially (from 1.45 to 1.68, 95% C.I. = 1.28-2.19). In both subgroups, the pooled smoking-adjusted estimates showed little evidence of heterogeneity, though these estimates were based on two studies in the former instance and three in the latter. However, the other two heavy equipment operator and dock worker studies and the other three railroad industry studies that were not adjusted for smoking still displayed evidence of heterogeneity (Q-statistics = 2.933, 1 d.f., $p = 0.09$, and 21.517, 2 d.f., $p < 0.001$, respectively).

The meta-analysis also identified evidence of exposure-response relationships in the subgroup analyses based on duration of employment. However, as noted in OEHHA (1998), this analysis was hampered by the absence of duration-specific risk estimates in approximately one-half the studies. While the initial analysis conducted on all the included studies resulted in elevated pooled risk estimates for strata in which exposure durations were greater than 10 years relative to those with less than 10 years of exposure or for which the exposure durations were not clear from the published reports, there was still significant evidence of heterogeneity for several of the duration strata. In contrast, the analysis utilizing only estimates from the smoking-adjusted studies showed some evidence of an exposure-response gradient without evidence of statistical heterogeneity. The summary risks for all three exposure-duration strata were: RR = 1.39 (95% C.I. 1.19-1.63) for $<$ 10 years (based on three estimates from two studies), RR = 1.64 (95% C.I. = 1.40-1.93) for 10 $\leq$ to $<$ 20 years (11 estimates from 6 studies), and RR = 1.64 (95% C.I. = 1.26-2.14) for $\geq$ 20 years (four estimates from four studies). The pooled risk estimate for those studies for which the exposure duration was not clear in the published reports was 1.24 (95% C.I. = 1.00-1.54) (six estimates from four studies) (see Table C-4 in Appendix C of OEHHA (1998)).

These results were robust to a variety of sensitivity analyses. In an analysis of potential publication bias, however, there appeared to be a modest increase in the RR estimates with increasing sample size (reflected in a decreased standard error of the estimates). Publication bias, or the increased likelihood or preference for the publication of statistically significant results compared to nonsignificant or null results, may potentially distort pooled risk estimates. Publication bias is generally attributed to journal editorial policies that prefer "positive" results, so that small, statistically nonsignificant studies are less likely to be published than large, statistically nonsignificant studies (Greenland, 1994). However, it should be noted that the studies with the smallest standard errors were almost exclusively cohort studies that did not adjust for smoking and which also had a clear HWE, suggesting that other significant biases are likely to have played a role in creating an appearance of publication bias. Therefore, although publication bias cannot be ruled out, the inclusion of numerous studies of varying sample sizes and statistically insignificant findings, as well as the uncontrolled confounding and likely selection bias affecting many of the larger cohort studies, make it unlikely that the result of this meta-analysis can be completely explained by publication bias.

In summary, the meta-analysis indicated a consistent positive association between occupations involving diesel exhaust exposure and the development of lung cancer. Although substantial heterogeneity existed in the initial pooled analysis, stratification on several factors identified a persistent positive relationship. The major sources of heterogeneity included: (1) whether or not a study adjusted for smoking, (2) study design (3) the exposure assessment, as developed from occupational categories, (4) and the presence of selection bias, as manifested by an observed healthy worker effect. Taking these factors into account tended to increase the estimates of relative risks of lung cancer from occupational exposure to diesel exhaust.

Another independently conducted meta-analysis of diesel exhaust exposure and lung cancer produced remarkably similar results, with an overall pooled relative risk estimate of 1.33 (95% C.I. = 1.24-1.44) (Bhatia *et al*., 1998). In that analysis, the study inclusion and exclusion criteria were somewhat different than those used by OEHHA staff, so that 23 studies were included. Consequently, the results of some of their subset analyses differed from those described in OEHHA (1998). In addition, those authors used only a fixed-effects model to derive pooled risk estimates, and did not focus on explorations of sources of heterogeneity. Nevertheless, Bhatia and co-workers also found a persistent positive relationship between diesel exhaust exposure and lung cancer that could not be attributed to potential confounding by cigarette smoking. Moreover, in the narrower group of studies in their report, they identified a positive exposure-response relationship in studies stratified by exposure duration.

Table 2. Studies Included in Meta-analysis of Diesel Exhaust Exposure and Lung Cancer

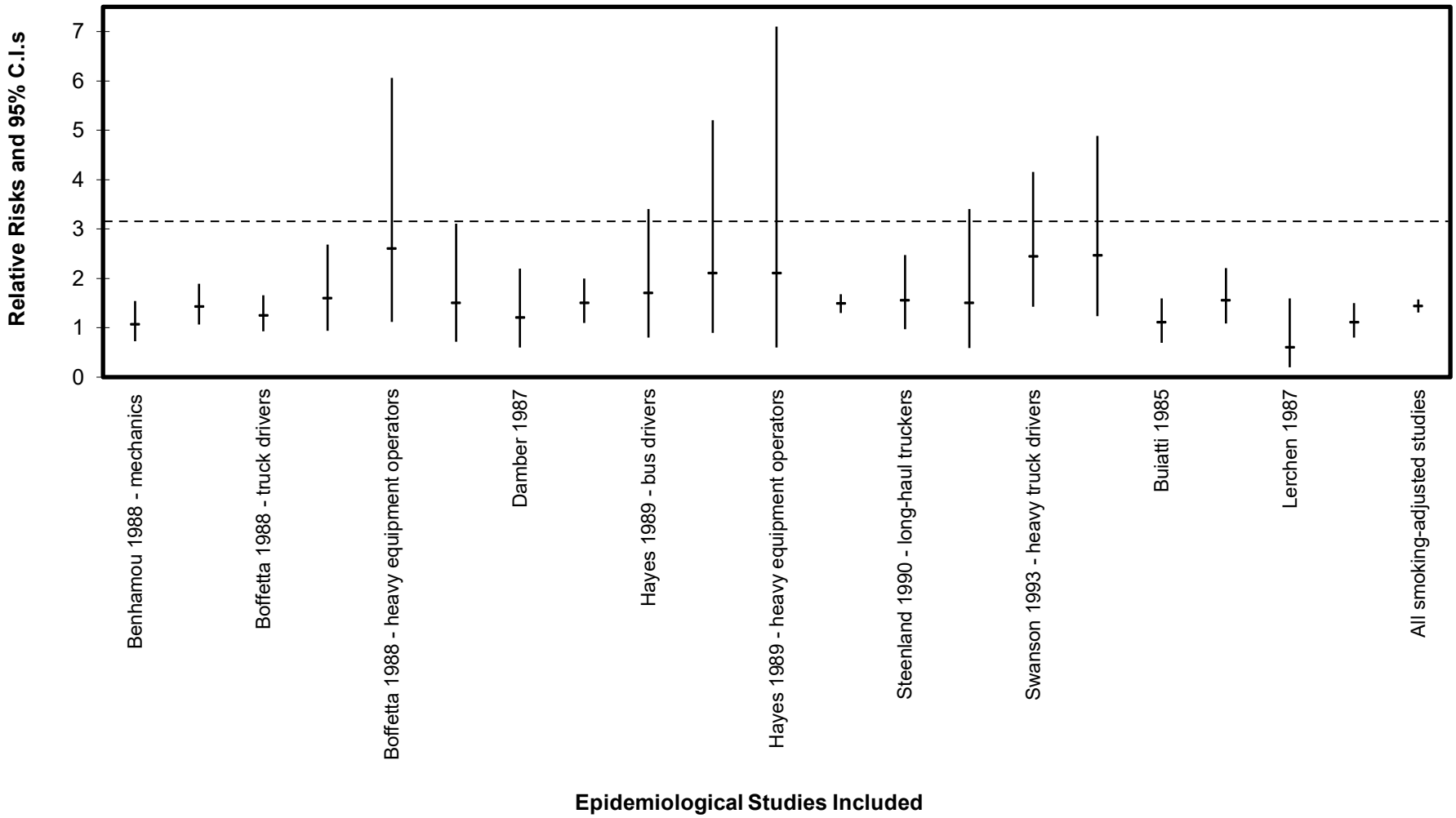
Study (year)	Design (Location)*	Occupation or Exposure Group	Smoking Adjusted	RR	C.I.
Ahlberg *et al*. (1981)	Cohort (†)	Truck drivers	no	1.33	1.13-1.56
Balarajan & McDowall (1988)	Cohort (†)	Truck drivers	no	1.59	1.00-2.53[a]
Bender *et al*. (1989)	Cohort (‡)	Highway maintenance	no	0.69	0.52-0.90
Benhamou *et al*. (1988)	Case-control (†)	Professional drivers	yes	1.42	1.07-1.89
Buiatti *et al*. (1985)	Case-control (†)	Transportation general	yes	1.1	0.7-1.6
Benhamou *et al*. (1988)	Case-control (†)	Mechanics	yes	1.06	0.73-1.54
Boffetta *et al*. (1988)	Cohort (‡)	Truck drivers	yes	1.24	0.93-1.66
	Cohort (‡)	Railroad workers	yes	1.59	0.94-2.69
	Cohort (‡)	Heavy equipment operators	yes	2.60	1.12-6.06
Boffetta *et al*. (1990)	Case-control (‡)	Probable DE $\geq$ 30 yr	yes	1.49	0.72-3.11
Coggon *et al*. (1984)	Case-control (†)	Diesel exhaust exposed group	no	1.1	0.7-1.8
Damber & Larsson (1987)	Case-control (†)	Professional drivers	yes	1.2	0.6-2.2
Edling *et al*. (1987)	Cohort (†)	Bus drivers	no	0.69[b]	0.2-1.6[b]
Garshick *et al*. (1987)	Case-control (‡)	Railroad workers $\geq$ 20 yrs[c]	yes	1.55	1.09-2.21
Garshick *et al*. (1988)	Cohort (‡)	Railroad workers $\geq$ 15 yrs[c]	no	1.82	1.30-2.55
Guberan *et al*. (1992)	Cohort (†)	Professional drivers	no	1.50	1.23-1.81[e]
Gustafsson *et al*. (1986)	Cohort (†)	Dock workers	no	1.32	1.05-1.66
Gustvasson *et al*. (1990)	Nested case-control (†)	Bus garage workers > 20 yr[d]	no	1.49[d]	1.25-1.77[d]
Hansen (1993)	Cohort (†)	Truck drivers	no	1.6	1.26-2.0
Hayes *et al*. (1989)	Case-control (‡)	Truck drivers $\geq$ 10 yr	yes	1.5	1.1-2.0
	Case-control (‡)	Bus drivers $\geq$ 10 yr	yes	1.7	0.8-3.4
	Case-control (‡)	Mechanic (excl auto) $\geq$ 10 yr	yes	2.1	0.9-5.2
	Case-control (‡)	Heavy equip. operators $\geq$ 10 yr	yes	2.1	0.6-7.1
Howe *et al*. (1983)	Cohort (‡)	Railroad workers probably exposed	no	1.35	1.13-1.61[a]
Lerchen *et al*. (1987)	Case-control (‡)	Diesel exhaust grouped	yes	0.6	0.2-1.6
Magnani *et al*. (1988)	Death certificate study (†)	Diesel exhaust grouped	no	0.97	0.95-1.00
Menck & Henderson (1976)	Cohort (‡)	Truck drivers	no	1.65	1.13-2.40[a]
	Cohort (‡)	Mechanic (excl auto)	no	3.32	1.35-8.18[a]
Nokso-Koivisto & Pukkala(1994)	Cohort (†)	Railroad workers	no	0.90[d]	0.79-1.04[d]
Pfluger & Minder (1994)	Case-control (†)	Professional drivers	yes	1.48	1.30-1.68
Rafnsson & Gunnarsdottir (1991)	Cohort (†)	Truck drivers $\geq$ 30 yr	no	2.32	0.85-5.04
Rushton *et al*. (1983)	Cohort (†)	Bus garage workers/mechanics	no	1.01	0.82-1.22
Siemiatycki *et al*. (1988)	Case-control (‡)	Diesel exhaust grouped	yes	1.1	0.8-1.5[e]
Steenland *et al*. (1990)	Case-control (‡)	Truck drivers $\geq$ 18 yr	yes	1.55	0.97-2.47
	Case-control (‡)	Truck mechanic $\geq$ 18 yr	yes	1.50	0.59-3.40
Swanson *et al*. (1993)	Case-control (‡)	Heavy truck drivers $\geq$ 20 yr	yes	2.44[d]	1.43-4.16[d]
	Case-control (‡)	Railroad workers $\geq$ 10 yr	yes	2.46[d]	1.24-4.89[a]
Wegman & Peters (1978)	Case-control (‡)	Transportation equip. operators	no	2.39[b]	0.70-8.05[b]
Wong *et al*. (1985)	Cohort (‡)	Heavy equip. operators $\geq$ 20 yr	no	1.07	1.00-1.15[a]

[a] Calculated from p-value.
[b] Calculated from data presented in publication.
[c] Risk estimates excluding shop workers.
[d] Pooled risk estimates from two racial or duration categories.
[e] 90% confidence intervals originally presented within study.

DE = diesel exhaust
RR = risk ratio
C.I.= 95% confidence interval.

* Location: (†)Europe, (‡)North America

Figure 1: Estimates of Relative Risks for Smoking-Adjusted Studies of Diesel Exhaust Exposure and Lung Cancer



Methodology

The complex and potentially variable mix of chemical species in the condensed phase and the vapor phase of diesel exhaust, required the measure of exposure related to carcinogenic risk to be specified. The most commonly used measure of exposure is atmospheric concentration of particles in $\mu g/m^3$. That measure is obtained from the mass of particles collected on a filter per volume of the air that flowed through the filter. On the basis of its relation to health studies and its general practicality, that measure was used in the diesel exhaust TAC document cancer risk assessment (OEHHA, 1998).

OEHHA used two approaches to employing epidemiological studies for diesel exhaust quantitative risk assessment. The first approach used the overall relative risks derived from the meta-analysis along with an overall range of exposure for all the studies. The second approach focused upon the railroad worker studies in developing the range of unit cancer risks.

Meta-analysis-Derived Cancer Unit Risks

The results of the meta-analysis provide information useful in bracketing the broadest likely range of plausible carcinogenic potencies for diesel exhaust. The pooled relative risk values derived from the 12 epidemiological studies in the meta-analysis which adjusted for smoking were 1.44 (95% C.I. 1.32 -1.56) for the fixed effects model and 1.43 (95% C.I. 1.31 -1.57) for the random effects model. The magnitude of these relative risks provide information on the potential magnitude of the cancer risk associated with diesel exhaust exposure. For the random effects model the upper 95% confidence limit on excess relative risk is 0.57.

None of the studies in the meta-analysis provide direct measurements of exposure concentration over the time of their follow up. Therefore, to the extent that the meta-analysis can be used to bracket the carcinogenic potency of diesel exhaust, the exposures of the various study populations need to be reconstructed. Hammond (1998) has reviewed the available industrial hygiene survey literature on the occupations considered in the meta-analysis (bus garage workers, mechanics, truck drivers, heavy equipment operators, railroad workers) and provided estimates of the plausible possible ranges of workplace exposures of diesel exhaust respirable particulate matter for those occupations. Because of the overall limitations in the data, the estimated ranges for each occupational subgroup of interest are particularly broad. The lowest plausible estimate of occupational exposure for any such subgroup is 5 $\mu g/m^3$ (heavy equipment operators). The highest plausible estimate of any occupational subgroup is 500 $\mu g/m^3$ (bus garage workers, railroad workers, mechanics). The total range of plausible exposures for the different populations therefore varies 100-fold. Using these air concentrations and the assumption that workers inhaling $10m^3$ of air per work shift were exposed to them for over 45 year period for a 70 year lifetime, it is possible to characterize a bracket of risks compatible with the results of the meta-analysis:

q_1^* = Excess relative risk × CA lifetime lung cancer risk.
Air concentration × exposure factor × intermittency factors × duration of exposure/lifetime

= 0.57 × 0.025
(5 or 500 μg/m^3) × 10 m^3/shift/20m^3 /d × 5d/7d × 48wk/52wk × 45 yrs/70yrs

Therefore, the results of the meta-analysis bracket lung cancer risks up to approximately 1.3×10^{-4} $(\mu g/m^3)^{-1}$ (assuming all the worker populations in the meta-analysis were exposed to 5 μg/m^3) to 1.3×10^{-2} $(\mu g/m^3)^{-1}$ (assuming all the workers populations in the meta-analysis were exposed to 500 μg/m^3). As these assumptions establish the extreme bounds of probable exposures, and such calculations based upon a meta-analysis are novel and subject to further possible refinements, these results are not incorporated into the range of risks. However, these results do bracket the carcinogenic potencies which would be consistent with the results of the meta-analysis and the broadest range of exposure estimates.

A more plausible range can be estimated by determining the 90% confidence interval (CI) of the range of risks. For the meta-analysis the range of concentrations thought to be plausible by Hammond (personal communication) was 5 to 500 μg/m³ with a mean of about 200 μg/m³, which corresponds to a unit risk of 3.3×10^{-4} $(\mu g/m^3)^{-1}$. Using that concentration range as the 98% CI for a shifted lognormal distribution fixes the geometric standard deviation at 1.22 with a shift of the origin of the distribution by 330 μg/m³. The 90% CI for this distribution of concentration is [52.5 to 356.5 μg/m³], corresponding to a 90% CI for the distribution of unit risk of [1.6×10^{-4} to 1.2×10^{-3} $(\mu g/m^3)^{-1}$].

Railroad Worker Study-Derived Cancer Unit Risks

Quantitative relationships were also developed between lung cancer risk and exposure to diesel exhaust for two nation-wide studies of lung cancer rates in U. S. railroad workers. These relationships provided additional values for the range of risk to the general California population. The first, Garshick *et al*. (1987a), is a case-control study. Using a logistic regression, that study determined the coefficient of the logistic relationship of the odds of lung cancer for duration of the workers' exposure to diesel exhaust. The coefficient determined in that study was used to estimate lifetime unit risks for exposure of the general population. The second study, Garshick *et al*. (1988), is a cohort study. Using a proportional hazards model, that study calculated the relative hazard of lung cancer for increasing duration of worker exposure. However, those numerical results have not been supported by Garshick (1991); so instead of using them to derive lifetime unit risks for the general population, new analyses were performed with the individual data, upon which that study is based, to determine a linear relationship of lung cancer hazard for worker exposure to diesel exhaust.

The term hazard was used for a prediction of incidence (cancers per year per population) resulting from a model. Relative hazard is generally called relative risk in epidemiological model work, and the term, relative risk, was used in the context of the epidemiology results. The lifetime inhalation unit risk, often simply called unit risk, is defined as the probability of contracting lung cancer from a 70-year exposure to a unit concentration (1 μg/m^3) of diesel exhaust.

The unit risks ultimately derived for the general population assume that the mass concentration of particles governs the risk of diesel exhaust, regardless of the particular type of diesel engine or fuel. The resulting estimate of risk entails uncertainties due primarily to the limited exposure information available and to the choice of models and data used in the analysis.

These two studies are among a number of studies establishing excess relative risk of lung cancer among workers exposed to diesel exhaust. These two studies were specifically selected for the quantitative risk assessment because of their general excellence, their apparent finding of a relationship of cancer rate to duration of exposure and because of the availability of measurements of diesel exhaust among such railroad workers from the early 1980's in other studies. The case-control study appears to have an advantage in obtaining direct information on smoking rates, while the cohort study has an advantage of smaller confidence intervals of the risk estimates.

Estimating Cumulative Exposure

The risk relationships developed for the case-control study and the initial analyses for the cohort study used cumulative atmospheric exposure to diesel exhaust particles as the effective dose. The use of cumulative exposure, defined as the area under the curve (AUC) of concentration versus time, required a specification of the temporal pattern of exposure concentration. However, direct measurements of exposure concentration over the time of the follow up were not available.

Therefore, the calculations required reconstruction of the exposure history in order to determine cumulative exposure. The reconstruction was undertaken using (1) personal exposure measurements on railroad workers just after the end of the follow-up period in that study, (2) historical data on the dieselization of locomotives in the United States, and (3) descriptive information. The analysis included workers on trains and excluded shop workers from the original cohort because of mixed exposures, including no exposure to an unknown number in this group.

Exposure Measurements In The Early 1980s

Woskie *et al*. (1988b) estimated national average concentrations of respirable particulate matter (RSP) for 13 job-groups. These concentrations were obtained by temperature correction of measurements of respirable particulate matter (RSP) made in 1982-1983 in the northern region of the United States, as reported in Woskie *et al*. (1988a). The investigators adjusted these concentrations to remove the portion of RSP attributable to environmental tobacco smoke (ETS). The average values of the ETS-adjusted RSP for the principal categories of workers are listed in Table 3 for exposed and unexposed workers.

Table 3: Number of Workers in the Exposure Categories and the Cohort Averages of the Worker Exposure Concentration Following the Garshick *et al.* (1988) Cohort Study.

Exposure status	Career group	Number of workers	Subsequent exposure concentration[a] ($\mu g/m^3$)
Uncertain	Shopworkers	12,092	141(those exposed)
Exposed[b]	Engineers, firemen	11,005	71
	Brakemen, conductors, hostlers	18,285	89
Unexposed[c]	Clerks	10,475	33
	Signalmen	3548	58

[a] Exposures reported by Woskie *et al* (1988b) for these career groups, based on measurements of ETS-adjusted RSP, circa 1982-3.

[b] For all exposed workers in the table, except for those shopworkers who were exposed, the temporal exposure patterns are assumed to be the same, and the concentrations are close to each other; so a simple population-weighted average for the two career groups characterizes the average concentration for the exposed group, train workers, circa 1982-83:

$$(11{,}005 \times 71 + 18285 \times 89) / (11005 + 18285) = 82\ \mu g/m^3$$

[c] For all unexposed workers (background) in the table except for those shopworkers who were unexposed, the concentrations are close to each other; so a simple population-weighted average for the two groups characterizes the average background concentration, circa 1982-83:

$$(10475 \times 33 + 3548 \times 58) / (10475 + 3548) = 39\ \mu g/m^3.$$

Reconstruction Of The Time Course Of Concentration

In order to estimate the time course of the exposure factors for the cohort, it was necessary to make assumptions about time trends of nationwide average concentration breathed by the workers. The exposure measurements made just after the follow-up period constitute a baseline for the reconstruction. The reconstruction of the time course of concentration proceeds by developing an exposure factor to multiply these baseline values. The analyses below explore the effect of alternative patterns of exposure concentration and baseline values.

Dieselization of the U.S. railroads began after the Second World War ended in 1945. The exposure of the railroad workers up until 1981 can be divided into two periods: (1) an initial period of increasing dieselization of U.S. locomotives from 1945 until mostly completed in 1959 and (2) a subsequent period of a moderate rate of addition of locomotives that were less smoky.

Woskie *et al*. (1988b) reported data showing a linear rise of percent dieselization with time in the first period from 1945 to 1959. They reported data from the Bureau of Labor Statistics showing that by 1947 fourteen percent of locomotives were diesel, by 1952 fifty-five percent were diesel, and by 1959 ninety-five percent were diesel. This linear rise of dieselization may be expected to have produced a linear rise of the national average exposure concentration around the trains. This linear rise is used in all the more realistic exposure patterns.

The exposure of workers on trains would then generally have declined as the newer, less smoky locomotives replaced the older, smokier locomotives on the main lines. To quantify the anecdotal information of greater smokiness of locomotives in the period before 1960, the national average exposure concentration was assumed to decline linearly in the second period, 1960-1980, to the baseline measured in 1982-3. The decline assumed from 1959 to 1980 is consistent with the report of sharp decreases of emissions of new engines between the 1970's and the 1980's. Emissions from naturally aspirated four-stroke engines declined from 2.1-3.0 g/kW-hr in the 1970's to 0.25 -0.6 g/kW-hr in the 1980's (Sawyer and Johnson, 1995).

In order to bracket the exposure of the railroad workers to diesel exhaust a variety of patterns of exposure are considered. The patterns are characterized by two components: a) the extent of change from 1959 to 1980 in diesel exhaust exposure, expressed as a ratio, and b) the average exposure concentration for the workers on trains measured in the Woskie *et al*. (1988a) study (i.e., the baseline). The alternate ratios are as follows: a) a ratio of 1 suggested and used in Crump *et al*. (1991) as more realistic than the Garshick *et al*. (1987a, 1988) assumption of constant concentration from 1959-1980 and none before that; b) a ratio of 2 suggested by K. Hammond to allow for a modest peak in 1959; c) a ratio of 3 allowing for more peak, a scaled down version of the exposure factor of 10 that Woskie *et al*. (1988b) reported for exposure concentration of shopworkers to nitrogen dioxide in enclosures including engine test sheds; and d) a ratio of 10, peak of the magnitude of values for the engine test sheds. The alternate baselines of exposure concentrations are as follows: 1) 40 $\mu g/m^3$, obtained by subtracting the background measurement of the unexposed workers from the measurement of the train workers, rounded down; 2) 50 $\mu g/m^3$, which also subtracted background from the train worker measurements but rounded up to allow somewhat for measurements of workers on trains not having as much exposure to non-diesel exhaust background particulate as the clerks; and 3) 80 $\mu g/m^3$, obtained by assuming that the entire ETS-adjusted RSP of the train workers is diesel exhaust while the clerks are considered unexposed to diesel exhaust (0 concentration).

The specific alternative patterns of linear decline (if any) of concentration from 1959 through 1980 are:

1. no decline, constant at the baseline values of 50, a ramp (1,50) pattern suggested and used in Crump *et al*. (1991).
2. declining 3-fold from a peak of 150 to a baseline of 50, a roof (3,50) pattern, the preferred pattern in this report;
3. declining 10-fold from a peak of 500 to a baseline of 50, a roof (10,50) pattern, suggested in information submitted by the Engine Manufacturers Association;
4. declining, 2-fold from a peak of 80 to a baseline of 40, a roof (2,40) pattern suggested by K. Hammond, one of the investigators in the Woskie *et al*. study; and
5. declining 3-fold from a peak of 240 to a baseline of 80, a roof (3,80) pattern, a variant on Pattern 3 for not subtracting background ETS-adjusted RSP in the exposed group while still maintaining
6. unexposed workers at zero concentration.

Calculation Of Cumulative Exposure

The estimate of the time course permits calculation of the overall average cumulative exposure for the cohort for each year of the follow-up period, 1959-1980. The cumulative exposure factor was calculated as the area under the curve (AUC) of the exposure factor (EF, ratio of concentration to baseline concentration) for successive years. Cumulative exposure is the cumulative exposure factor times the baseline value.

Intermittency Correction

The equivalent exposure duration for non-continuous exposure was scaled on the basis of volume of air breathed. Exposure durations are calculated to have the same cumulative yearly intake of the substance as produced by continuous inhalation of 20 m^3/day at the concentration of the substance breathed in. Assuming that the average exposed member of the cohort inhales 10 m^3 during an 8-hour working day implies an adjustment factor of 10/20 to multiply the exposure concentration to account for ventilation rate not equaling the standard human daily inhalation of 20 m^3/day. Adjusting for the discontinuous work week and work year yields additional adjustment factors of 5/7 for exposure days per week and 48/52 for weeks per year, all to multiply the exposure measure. In order to take account of the non-continuous work exposure, the resulting overall multiplicative factor on exposure duration is

$$(10/20)(5/7)(48/52) = 0.33.$$

Determining Lifetime Unit Risk From The Relative-Risk Slope

The analyses below calculate the relationship between relative risk (relative hazard) and duration of exposure. The relative risk is the prediction of the ratio: incidence (yearly death rate per population) of lung cancer due to diesel exhaust divided by the background incidence of lung cancer. In the principal modeling of both sets of epidemiological data, reported below in this chapter, relative risks are fitted linearly to duration of exposure. From that slope, an estimate of the slope with respect to cumulative exposure for the specific alternative patterns of occupational exposure considered is obtained by modifying the duration scale for the slope. The approximation for this modification is simply to multiply the duration scale by the overall area under the curve (AUC) of the desired pattern and to divide by the total duration of exposure in the analysis.

Approximations may often be used to determine lifetime unit risk from this slope, but the present work will, for consistency and accuracy, use life-table calculations for that determination. This calculation starts with a background life table for lung cancer in California. For each unit risk to be calculated, a modification of that table is constructed in a way that includes the predicted effect of a lifetime exposure to 1 unit of concentration, 1 $\mu g/m^3$ in the present calculations. The predicted effect is incorporated by multiplying the background lung cancer incidence for each age interval in the table by the relative risk (relative hazard) for that age interval. The relative risk is (1+ excess relative risk due to exposure). The excess relative risk due to exposure for unit concentration is the slope of relative risk with concentration, obtained from the epidemiological analyses. Using the general model based on cumulative exposure, as in the present calculations, the excess relative risk requires the slope coefficient per concentration-year to be multiplied by the age in years for

each age group in the table and to be divided by the intermittency factor. Any ages that fall within the number of years of detection lag prior to the target age have zero excess relative hazard. The modified table is completed in the manner of the original table. The lifetime unit risk is then the following difference: the probability of lung cancer at the target age in the table modified by exposure less the probability at the same age in the original table.

Use of the Garshick *et al*. (1987a) Case-Control Study to Estimate Unit Risk

The first study used to estimate lung cancer risk due to diesel exhaust exposure is the case-control study of U.S. railroad workers by Garshick *et al*. (1987a). For this case-control study Garshick *et al*. (1987a) collected 15,059 US railroad worker death records for 1981. They matched each of 1256 lung-cancer cases with 2 other deaths, each of those having nearly the same date of birth and death. For each of the controls, death was due to a specified natural cause with no mention of cancer on the death certificate. For each subject, Garshick *et al*. (1987a) determined years in a job with diesel exposure, asbestos exposure and smoking history. Taking into account the effect of age, their analysis used multivariate conditional logistic regression to determine the relationship between lung cancer and duration of exposure to diesel exhaust. For workers with more than 20 years exposure and for exclusion of shopworkers, they calculated the odds ratio was 1.55 (95% CI = 1.09, 2.21) with a referent category of 0 to 4 years work in a job exposed to diesel exhaust.

From the odds ratio for a 20 year duration of exposure, the coefficient of increase with duration of exposure was estimated by assuming a linear rise over the 20 years. Using a calculation similar to that used by Garshick *et al*. with shopworkers included, the slope coefficient for the odds ratio is 0.022 (90% C.I. = 0.0071, 0.037) year^{-1}. Because the odds ratio approximates relative risk (Breslow and Day, 1980, pp. 69-73), this value is approximately the rate of increase of relative risk (relative hazard) and is used in a life table to obtain the lifetime unit risk. The modified life table calculation for unit concentration (1 μg/m^3) for 5-yr. lag from carcinogenesis to death is in Table 7-1 of the diesel exhaust TAC document (OEHHA, 1998). The resulting unit risks are presented in Point I in Table 7-3 of the diesel exhaust TAC document. The highest values in that set are for the assumption that workers on trains have a ramp (1,50) pattern of exposure. The 95% UCL for lifetime unit risk is 2.4×10^{-3} (μg/m^3)$^{-1}$, with an MLE of 1.4×10^{-3} (μg/m^3)$^{-1}$. For the roof (3,50) pattern of exposure, the procedure is similar, but the exposure scale is increased by the ratio 65/22, representing the ratio of area under the EF of the roof to the area under the EF of the block. The resulting 95% UCL for lifetime unit risk is 1.0×10^{-3} (μg/m^3)$^{-1}$, with an MLE of 6.2×10^{-4} (μg/m^3)$^{-1}$. The lowest values in the set are for the roof (10,50) pattern of exposure. Using a similar approach, multiplying the exposure scale by the AUC ratio of 191/22, the 95% UCL for lifetime unit risk is 3.6×10^{-4} (μg/m^3)$^{-1}$, with an MLE of 2.1×10^{-4} (μg/m^3)$^{-1}$.

Using the slope coefficient for the analysis including shopworkers, reported in Garshick *et al*. (1987a), McClellan *et al*.(1989) previously calculated the expected increase in U.S. lung cancer deaths per year for each μg/m^3 of diesel exhaust exposure for two alternative exposure concentrations, 125 μg/m^3 and 500 μg/m^3, constant from 1959-1980. Mauderly (1992a) used these death rates to estimate unit risks, finding expected values of 1.2×10^{-3} (lifetime-μg/m^3)$^{-1}$ and 2.9×10^{-4} (lifetime μg/m^3)$^{-1}$, respectively. These values are close to the higher MLE values just given. Even though the higher concentrations assumed by McClellan *et al*. would tend to produce lower unit risks, the effect of using the more accurate life table method has a counteracting effect.

Use of the Garshick *et al*. (1988) Cohort Study to Estimate Unit Risk

The second study selected to estimate lung cancer risk due to diesel exhaust exposure was the retrospective cohort study of U. S. railroad workers by Garshick *et al*. (1988). The present analysis uses the individual data collected for that study in new calculations to determine slopes for the relationship of incidence to cumulative exposure. The analysis uses reconstructions of exposure, the ramp and the roof exposure patterns, to adjust the slope obtained from the analysis that is implemented with duration of exposure as the measure of exposure.

Further material on the cohort is developed in Appendices D, E, F of the diesel exhaust TAC document (OEHHA, 1998). Appendix E contains references to correspondence cited in this chapter. (The original unpublished documents referred to in Appendix E are available on request from the California Air Resources Board, Stationary Source Division or from the U.S. EPA docket for the Health Assessment Document for Diesel Emissions at the National Center for Environmental Assessment, Washington, DC. 20460 (1997)).

Description of the Original Study

The cohort consisted of 55,407 railroad workers, who were aged 40-64 in 1959 and who had started railroad service 10-20 years earlier; 1694 lung cancers were identified. The unexposed group in the cohort, the clerks and signal tenders, constituted 25.3% of the whole cohort. To develop the original data set, Garshick *et al*. (1988) obtained the following information for each individual in their cohort of railroad workers for the follow-up years of 1959-1980: cause of death by death certificate, the primary job classification for each year, and months worked in that classification in each year. In addition, the investigation obtained the age at the start of follow-up in 1959, total service months and, for those workers who began work after 1946, the date of starting work. From these data Garshick *et al*. calculated the elapsed time of exposure for each individual from 1959 up to each follow-up year or up to the four years before each follow-up year.

Relative Risk Analysis

Because of much uncertainty about the proportion of shop workers exposed to diesel exhaust, OEHHA decided to exclude them from the analysis, as suggested by the study authors and other participants at the Diesel Exhaust Workshop, January, 1996. Garshick (1991) had previously called attention to dilution of the effect of diesel exhaust on the shop workers because of the inclusion of shopworkers in that cohort who had no true exposure. The original study obtained risk estimates both with and without the shop workers, and found the results changed very little. The exclusion of shop workers simplifies the analysis in that lung burden calculations are not needed because the exposures of other exposed workers, namely train workers, are sufficiently low that lung burden may be assumed essentially proportional to atmospheric exposures. Exposure measurements for 1982-83 (Woskie *et al*. 1988a), just after the end of the follow-up period, show that train workers considered here all experienced approximately the same average concentration of diesel exhaust (for example, 50 $\mu g/m^3$, rounded, for use in determining unit risk in this work). The present work uses years with any month of exposure time, excluding the four years previous to each year of observation as the average lag time from carcinogenesis to death. This calculation

of exposure time starts in 1952 and continues yearly through 1980, the end of follow-up. It extends 7 years back from 1959, the start of follow-up, to account on the average for the assumed linear rise of exposure from 1945 to 1959. The unexposed workers are assigned zero exposure time throughout.

The OEHHA analysis uses two programs in the EPICURE software package, which is designed for several standard kinds of epidemiological analysis. The first program, DATAB, reduces the individual data to cells with each desired variable having a single value for the cell. The cells are designated by a set of numbers, one for each categorical variable to determine the category number of that variable. The second program, AMFIT, determines parameters of a model to provide a best fit of the data using Poisson regression, a maximum likelihood procedure (Breslow and Day, 1987). The calculation approach is described in more detail for the closely related calculations using general models, in Appendix D of the diesel exhaust TAC document (OEHHA, 1998).

The assumptions not otherwise specified here are essentially those of Garshick *et al*. (1988). For example, all years of the study are included, and their rather irregular boundary points on years of exposure are used.

The OEHHA analysis explored the fit and other characteristics of a number of forms of a general model. The model that appeared to be most satisfactory is the one with linear and quadratic continuous covariates, age and calendar year. The slope calculated for relative risk (relative hazard) per year of exposure is 0.015 (95% CI: 0.0086 to 0.022) $year^{-1}$. The slope divided by the intermittency correction (0.33) and the assumed constant concentration (e.g., 50 $\mu g/m^3$ for 29 years) and multiplied by attained age provides the excess relative hazard to determine the increase of lung cancer rates for the lifetable calculation of the unit risk. The resulting unit risks are presented in Point II in Table 4, and closely parallel the results for the case-control study (Point I). The highest values in that set are for the assumption that workers on trains have a ramp (1,50) pattern of exposure. For the ramp pattern the result is a 95% UCL of 1.8×10^{-3} $(\mu g/m^3)^{-1}$ and a MLE of 1.3×10^{-3} $(\mu g/m^3)^{-1}$. For the roof (3,50) pattern of exposure, the procedure is similar, but the exposure scale is increased by the ratio 65/29, representing the ratio of area under the EF of the roof to the area under the EF of the ramp. The result is a 95% UCL of 8.2×10^{-4} $(\mu g/m^3)^{-1}$ and a MLE of 5.7×10^{-4} $(\mu g/m^3)^{-1}$. The lowest values in the set are for the roof (10,50) pattern of exposure. Using a similar approach, multiplying the exposure scale by the AUC ratio of 191/29, the 95% UCL for lifetime unit risk is 2.8×10^{-4} $(\mu g/m^3)^{-1}$, with an MLE of, 1.9×10^{-4} $(\mu g/m^3)^{-1}$.

Table 4: Values from Unit Risk for Diesel Exhaust from Using Hazard Slope on Exposure Measure in California Life-Table. Garshick *et al*. (1987a, 1988) Studies of U.S. Railroad Workers.

	q1 $(\mu g/m^3)^{-1}$ MLE	q1 $(\mu g/m^3)^{-1}$ 95% UCL
I. Case-Control study (1987a) using published slope coefficient for hazard on years of exposure to diesel exhaust (Section 7.3.3)		
A. Adapted to ramp (1,50) pattern of exposure	1.4×10^{-3}	2.4×10^{-3}
B. Adapted to roof (2,40) pattern of exposure	1.1×10^{-3}	1.8×10^{-3}
C. Adapted to roof (3,50) pattern of exposure	6.2×10^{-4}	1.0×10^{-3}
D. Adapted to roof (3,80) pattern of exposure	3.9×10^{-4}	6.6×10^{-4}
E. Adapted to roof (10,50) pattern of exposure	2.1×10^{-4}	3.6×10^{-4}
II. Cohort study (1988) using individual data to obtain a slope for hazard on years of exposure to diesel exhaust (Section 7.3.4) Continuous covariates: (attained age and calendar year) or (age-at-start-of study and calendar year)		
A. Adapted to ramp (1,50) pattern of exposure	1.3×10^{-3}	1.8×10^{-3}
B. Adapted to roof (2,40) pattern of exposure	9.9×10^{-4}	1.4×10^{-3}
B. Adapted to roof (3,50) pattern of exposure	5.7×10^{-4}	8.2×10^{-4}
D. Adapted to roof (3,80) pattern of exposure	3.6×10^{-4}	5.1×10^{-4}
E. Adapted to roof (10,50) pattern of exposure	1.9×10^{-4}	2.8×10^{-4}
III. Cohort study (1988) applying time varying concentrations to individual data to obtain a slope of hazard on exposure (from Appendix D)		
A. Ramp (1,50) pattern of exposure		
1. General multiplicative model with age-at-start-of-study and U.S. rates as categorical covariates	1.2×10^{-3}	1.9×10^{-3}
2. 6th/7-stage model with age-at-start-of study as categorical covariate	2.4×10^{-4}	3.8×10^{-4}
B. Roof (3,50) pattern of exposure		
1. General multiplicative model with age-at-start-of-study and U.S. rates as categorical covariates	5.1×10^{-4}	7.2×10^{-4}
2. 6th/7-stage model with age-at-start-of-study as categorical covariate	8.1×10^{-5}	1.3×10^{-4}
3. 7th/7-stage model with age-at-start-of-study as categorical covariate	1.0×10^{-4}	1.5×10^{-4}

Discussion of Results

The investigation of the forms of the model using Poisson regression explored the use of categorical covariates, calendar year and age-at-start-of-follow-up that verified the categorical trend with exposure that Garshick *et al*. (1988) had obtained for relative hazard by using a Cox regression with calendar year as the principal time scale and age-at-start-of-follow-up as a covariate. This result was an elevated relative risk (relative hazard) for the middle durations of exposure and an apparent rise at the highest exposure, albeit with large error bars. Crump (1997) found by direct comparison a close correspondence of results for this Poisson regression and a Cox regression that replicated Garshick *et al*.

The investigation also explored the use of a general model with the categorical covariates, calendar year and attained age, that verified the categorical results for relative risk in Crump *et al*. (1991) and Crump (1997). This result showed a rise and then an apparent fall of relative risk for increasing exposure. Age and calendar year are important determinants of lung cancer rate, and Crump (1997) has argued that this choice should be used for covariates because it is the most accurate in characterizing background rates and, further, that a fall of relative risk at the higher exposure, obtained for this choice of covariates, is not consistent with an exposure response.

It should be kept in mind that the categorical trends of the relative risk with duration of exposure are all used to represent a large cloud of observed points of incidence as a function of duration of exposure. Appendix F of the diesel exhaust TAC document (OEHHA, 1998) indicates that the discrepancy between the results of Garshick *et al*. and of Crump *et al*. may be more apparent that real. The slopes for the relative risk are significant for both these choices of covariate, but the slope for the use of calendar year and age-at-start is about twice that for the use of calendar year and attained age. The latter slope is larger, though less significant, than the identical slope obtained in the present analysis using continuous forms of either pair of covariates. The use of the continuous form of the covariates appears to have a salutary effect on reducing the variance of the slope estimate. This choice allows some flexibility, but not a lot, in describing time trends.

Conclusion

Based on the human data, the principal finding of the diesel exhaust TAC document quantitative risk assessment is a range of lifetime unit risk (95% UCL) as shown in the right-hand column of Table 4 above. The lowest value in the range is 1.3×10^{-4}, and the highest value is 2.4×10^{-3}. The geometric mean unit risk obtained from these end points of the range of values is 6×10^{-4} (lifetime-$\mu g/m^3)^{-1}$. The geometric mean provides information on the central tendency of the range and is not to be confused with a best estimate identified from the available calculations. The lower end of the range is the rounded value for both forms of multistage model using the roof exposure pattern for the data of the Garshick *et al*. (1988) cohort study of U.S. railroad workers. OEHHA concluded that incorporation of the roof exposure pattern and biologically-based analyses improved the unit risk estimates. Consequently, unit risk values incorporating this information, those at the lower end of the range, provide more scientifically defensible values. The upper end of the range is obtained using the published results of the Garshick *et al*. (1987a) case-control study for US railroad workers. The Scientific Review Panel concluded in their findings that a reasonable estimate of the cancer unit risk is 3×10^{-4} $(\mu g/m^3)^{-1}$.

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PENTACHLOROPHENOL

CAS No: 87-86-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	266.35
Boiling point	309°C
Melting point	190°C
Vapor pressure	0.00011 mm Hg @ 25°C
Air concentration conversion	1 ppm = 10.9 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 1.8 E-2 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1991) from male mouse liver tumor data (NTP, 1989) using a linearized multistage procedure.]

III. CARCINOGENIC EFFECTS

Human Studies

No human epidemiological studies were located that were adequate to evaluate a possible association between exposure to pentachlorophenol and cancer.

Animal Studies

The National Toxicology Program (NTP, 1989) conducted 2 studies on the carcinogenic effects of lifetime exposure of mice to pentachlorophenol (PeCP). In these studies, $B6C3F_1$ mice were exposed to dietary PeCP, as either the technical grade or EC-7 grade, for 2 years. The technical grade PeCP contained polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs) as contaminants in significantly higher concentrations than the EC-7 grade. The NTP found dose-related increases in liver and adrenal medullary tumors in male and female mice, and an increase in hemangiosarcomas in the females exposed to the EC-7 grade (Table 1). The incidence of liver neoplasms and hemangiosarcomas was higher in female mice exposed to technical grade PeCP. The incidence of hemoangiosarcomas in female mice was 0/35, 3/50, and 6/50 for the 0, 100, and 200 ppm PeCP groups, respectively.

Table 1. Tumor incidence in male and female B6C3F$_1$ mice exposed to technical or EC-7 grade pentachlorophenol (PeCP) (NTP, 1989).

Grade of PeCP	Sex	Adrenal gland/medullary tumor incidence (benign and malignant pheochromocytomas) Dietary concentration (ppm)[a] 0	100	200	600	Liver tumor incidence (hepatocellular adenomas and carcinomas) Dietary concentration (ppm)[a] 0	100	200	600
EC-7	males	1/34	4/48	21/48	45/49	6/35	19/48	21/48	34/49
	females	0/35	2/49	2/46	38/49	1/34	4/50	6/49	31/48
Technical	males	0/31	10/45	23/45	NT	7/32	26/47	37/48	NT
	females	2/33	2/48	1/49	NT	3/33	9/49	9/50	NT

a) EC-7 dose levels for males and females were 0, 18, 37 and 118 mg/kg-day and 0, 17, 34 and 114 mg/kg-day, respectively.
NT = not tested

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NTP (1989) study in mice was used as the basis for the cancer potency for PeCP. This represents the only adequate, long-term, positive study of the carcinogenic effects of PeCP. The NTP study shows that PeCP exposure in mice results in several types of tumors in males and females. In the NTP (1989) study, mice (35-50 per group) were exposed to 0, 100, 200, or 600 mg/kg diet PeCP (EC-7 grade) for 2 years. In a parallel series of experiments, mice were exposed to 0, 100, or 200 mg/kg diet of technical grade PeCP. Results of these bioassays included a significant incidence of liver and adrenal neoplasms in male and female mice exposed to PeCP. In addition, female mice exhibited a significant increase in hemangiosarcomas. Although there were trace amounts of PCDD's and PCDF's in the EC-7 grade, the amount of these contaminants was determined by CHDS (1991) to be insufficient to result in the observed tumor incidence.

Methodology

A linearized multistage procedure was used to estimate the cancer potency of EC-7 grade PeCP from the NTP (1989) liver tumor (hepatocellular adenomas and carcinomas) data in male B6C3F$_1$ mice (Crump *et al.*, 1982). The concentrations of PeCP given in the feed were 0, 100, 200, or 600 mg/kg diet. The tumor incidence data are shown in Table 1. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for PeCP.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. The default lifespan for mice is 104 weeks. In this case, the lifetime scaling factor is equal to 1. An estimated value for the human cancer potency was determined using the

relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 1.8E-2 $[mg/kg\text{-}day]^{-1}$ was derived (CDHS, 1991). An airborne unit risk factor of 4.6E-6 $(\mu g/m^3)^{-1}$ was calculated from the q_{human} value by OEHHA/ATES using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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PERCHLOROETHYLENE

CAS No: 127-18-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	165.83
Boiling point	121ºC
Melting point	-19 ºC
Vapor pressure	18.47 mm Hg @ 25ºC
Air concentration conversion	1 ppm = 6.78 mg/m^3 @ 25ºC

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 5.9 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 2.1 E-2 $(mg/kg\text{-}day)^{-1}$
[Male mouse hepatocellular adenoma and carcinoma incidence data (NTP, 1986), cancer risk estimate calculated using a linearized multistage procedure and PBPK model dose adjustment (CDHS, 1991).

III. CARCINOGENIC EFFECTS

Human Studies

Epidemiological studies of perchloroethylene (PCE) exposure have been reviewed by Reichert (1983) and by the U.S. EPA (1985). Blair *et al*. (1979) analyzed the death certificates of 330 union laundry and dry-cleaning workers (out of a cohort of 10,000). Of 330 decedents, 279 had worked solely in dry-cleaning establishments. Increased mortality from cancers of the respiratory tract, cervix, and skin was documented, and when all malignancies were evaluated together, the number of observed deaths was significantly greater than expected ($p < 0.05$). Although an excess of liver cancer and leukemia was also observed, these increases were not statistically significant.

In an expanded study, Blair *et al.* (1990) reported on mortality among 5,365 dry cleaning union members. Statistically significant excesses of cancer of the esophagus and cervix and non-significant excesses for cancer of the larynx, lung, bladder, and thyroid were reported. Lack of PCE exposure data and lack of accounting for potential confounding factors, such as economic status, tobacco, or alcohol use, prevents any firm conclusion as to the association of PCE exposure and excess cancer.

Katz and Jowett (1981) analyzed the mortality patterns of 671 white female laundry and dry-cleaning workers. Occupational codes listed on the certificates did not distinguish between the two types of work. Data on the duration of employment were not available, nor were the investigators able to determine to which solvent(s) the individuals were exposed. Smoking history was not known. A significant increase in risk of death from cancer of the kidneys ($p < 0.05$) and genitals ($p < 0.01$) was documented. An excess risk from skin and bladder cancer was also found; however, neither increase was statistically significant.

Other studies of laundry and dry-cleaning workers have also reported an increased risk of death from cervical cancer (Blair *et al.,* 1979; Kaplan, 1980); however, these investigators have not compared mortality data by low-wage occupation. Although not definitive, the findings of Katz and Jowett (1981) suggest that factor(s) other than (or in addition to) solvent exposure are important contributors to cervical cancer.

Kaplan (1980) completed a retrospective mortality study of 1,597 dry-cleaning workers exposed to PCE for at least one year (prior to 1960). The solvent history of approximately half of the dry-cleaning establishments was known. The inability of Kaplan to quantify solvent exposure adds an important confounding variable to the study (Kaplan, 1980). The mean exposure concentration of individuals to PCE was calculated to be 22 ppm for dry-cleaning machine operators and 3.3 ppm for all other jobs. Kaplan found an elevated SMR (182) for malignant neoplasms of the colon (11 observed deaths, 6.77 to 6.98 expected deaths). In addition to colon cancer, malignant neoplasms of the rectum, pancreas, respiratory system, urinary organs, and "other and unspecified sites (major)" were observed (Kaplan, 1980). Although the relatively small cohort in this study limits conclusions about the carcinogenic potential of PCE, the study (Kaplan, 1980) results suggest a relationship between colon cancer and solvent exposure.

A group of Danish laundry and dry-cleaning workers was identified from the Danish Occupational Cancer Register (Lynge *et al.,* 1990). From cancer incidence data for a 10-year period, a significant excess risk was found for primary liver cancer among 8,567 women (standardized incidence ratio 3.4, 95% confidence interval 1.4-7.0). No case of primary liver cancer was observed among 2,033 men, for whom the expected value was 1.1. Excess alcohol consumption did not appear to account for the excess primary liver cancer risk for women. However, no data was available on actual exposures of the study group to PCE or other chemicals.

Duh and Asal (1984) studied the cause(s) of mortality among 440 laundry and dry-cleaning workers from Oklahoma who died during 1975 to 1981. Smoking histories were not available and separation of the two groups by occupation was not possible. NIOSH reported that, although 75% of dry-cleaning establishments in the U.S. use PCE, Oklahoma may be unique in that petroleum solvents account for more that 50% of total solvents used during this period (NIOSH, 1980). Analysis of deaths due to cancer showed an increase for cancers of the respiratory system, lung, and kidney.

Brown and Kaplan (1987) conducted a retrospective, cohort-mortality study of workers employed in the dry-cleaning industry to evaluate the carcinogenic potential from occupational exposure to PCE. The study cohort consisted of 1,690 members of four labor unions (located in Oakland, Detroit, Chicago, and New York City). Individuals selected for the study had been employed for at least one year prior to 1960 in dry-cleaning shops using PCE as the primary solvent. Complete solvent-use histories were not known for about half of the shops included in the study. Because petroleum solvents were widely used by dry cleaners prior to 1960, most of the cohort had known or potential exposure to solvents other than PCE (primary, various types of Stoddard solvents). The investigators also identified a subcohort of 615 workers who had been employed only in establishments where PCE was the primary solvent. The PCE exposure in shops included in the study was evaluated independently (Ludwig *et al.,* 1983). The geometric mean of time-weighted-

average exposures was 22 ppm PCE for machine operators and approximately 3 ppm for other workers.

In summary, a statistically significant excess of deaths from urinary tract cancer was observed in those workers that were potentially exposed to both PCE and petroleum solvents. Individuals employed in shops where PCE was the primary solvent did not have an increased risk of mortality from kidney or bladder cancer. Although these findings do not rule out PCE as the causative agent of urinary tract cancer, the data suggest that other factors or agents may have contributed to the development of neoplastic disease. CDHS stated in the Toxic Air Contaminant document "Health Effects of Tetrachloroethylene" that until studies are completed that include a thorough analysis and quantification of PCE exposures, epidemiological studies will not be useful for the assessment of the human health risks of PCE (CDHS, 1991).

Animal Studies

Two lifetime bioassays have been completed on PCE (NCI, 1977; NTP, 1986). Additionally, three other studies have addressed the question of PCE carcinogenicity (Rampy *et al.,* 1978; Theiss *et al.,* 1977).

The National Cancer Institute (NCI) conducted a study in which B6C3F$_1$ mice and Osborne Mendel rats were administered PCE in corn oil by gavage, 5 days/week for 78 weeks (NCI, 1977). The time-weighted average daily doses of PCE were 536 and 1072 mg/kg for male mice, 386 and 722 mg/kg for female mice, 471 and 941 mg/kg for male rats, and 474 and 949 mg/kg for female rats. PCE caused a statistically significant increase in the incidence of hepatocellular carcinomas in mice of both sexes and both dosage groups ($p < 0.001$). The time to tumor development was considerably shorter in treated than in control mice. In untreated and vehicle control mice, hepatocellular carcinoma were first detected at about 90 weeks. In comparison, hepatocellular carcinomas in male mice were detected after 27 weeks (low dose) and 40 weeks (high dose) and in female mice after 41 weeks (low dose) and 50 weeks (high dose) (Table 1). The median survival times of mice were inversely related to dose. For control, low dose and high dose male mice, their median survival times were 90 weeks, 78 weeks and 43 weeks, respectively; for female mice, their median survival times were 90 weeks, 62 and 50 weeks, respectively. Early mortality occurred in all groups of rats dosed with PCE. NCI (1977) determined that the early mortality observed in rats in this bioassay were inappropriately high and because the optimum dosage was not used, the rat results preclude any conclusions regarding the carcinogenicity of PCE in rats. In addition, the PCE used in the NCI mouse and rat bioassays had a purity of 99%, with epichlorohydrin (ECH) used as a stabilizer. It has been suggested that the presence of this contaminant may have directly contributed to tumor induction.

The most definitive study of the carcinogenic potential of PCE was conducted by Battelle Pacific Northwest Laboratories for the National Toxicology Program (NTP, 1986). In this experiment, B6C3F$_1$ mice and F344/N rats were exposed to 99.9% pure PCE by inhalation, 6 hours/day, 5 days/week for 103 weeks. Mice were exposed to concentrations of 0, 100, or 200 ppm; rats were exposed to concentrations of 0, 200, or 400 ppm. Both exposure concentrations produced significant increases in mononuclear cell leukemia in female rats (incidence in control, 18/50 animals; in rats receiving 200 ppm, 30/50; and in rats receiving 400 ppm, 29/50). Treated male

rats also developed mononuclear cell leukemia in greater numbers than controls (controls, 28/50 animals; 200 ppm, 37/50; 400 ppm, 37/50) [Table 1]. Male rats (at the 200 ppm and 400 ppm PCE exposure levels) exhibited an increased incidence of both renal tubular-cell adenomas and adenocarcinomas. Although the increases were not statistically significant, they appeared to be dose-related.

Brain glioma (a rare tumor of neuroglial cells) was observed in one male control rat and in four male rats that were exposed to 400 ppm PCE (NTP, 1986). This increase was not statistically significant. However, because the historical incidence of these tumors is quite low (0.2% at Battelle Laboratories), the increased incidence in treated animals in this study is noteworthy. Both concentrations of PCE produced a statistically significant increase of hepatocellular carcinomas in treated mice of both sexes ($p < 0.001$). The incidence of these carcinomas in male mice was as follows: controls, 7/49 animals; low-dose, 25/49; and high-dose, 26/50. The incidence of hepatocellular carcinomas in treated female mice was: controls; 1/48 animals; low-dose, 13/50; high-dose, 36/50. Hepatocellular adenomas occurred in both sexes of mice and at both concentrations of PCE (Table 1). The incidence of adenomas was not statistically significant. However, the combined incidence of hepatocellular adenomas and hepatocellular carcinomas was significant. In males, the combined incidence was: controls, 16/49 animals; low-dose 31/49; ($p = 0.002$); adenomas and carcinomas was: controls, 4/48 animals; low-dose, 17/50 ($p = 0.001$); and high-dose, 38/50 ($p < 0.001$).

Table 1: PCE-induced tumor incidence in mice and rats

Study	Species	Sex	Concentration or dose	Tumor response	
				Type[a]	Incidence
NCI, 1977	Mice	Males	0 mg/kg-d	HC	2/17
			536 mg/kg-d	HC	32/49*
			1072 mg/kg-d	HC	27/48*
		Females	0 mg/kg-d	HC	2/20
			386 mg/kg-d	HC	19/48*
			772 mg/kg-d	HC	19/48*
NTP, 1986	Mice	Males	0 ppm	HC; HAC	7/49 ; 16/49
			100 ppm	HC; HAC	25/49*; 8/49(NS)
			200 ppm	HC: HAC	26/50*; 18/50(NS)
		Females	0 ppm	HC; HAC	1/48 ; 3/48
			100 ppm	HC; HAC	13/50*; 6/50(NS)
			200 ppm	HC; HAC	36/50*; 2/50(NS)

[a] HC = hepatocellular carcinomas; HAC = hepatocellular adenoma; ML = mononuclear cell leukemia.
*$p < 0.001$, Fisher Exact Test; **Probability level, Life Table Analysis. NS = not statistically significant

The NTP (1986) determined that, under the conditions of the study, there was "clear evidence of carcinogenicity" of PCE for male F344/N rats, "some evidence of carcinogenicity" of PCE for female F344/N rats, and "clear evidence of carcinogenicity" of PCE for both sexes of $B6C3F_1$ mice. IARC reevaluated the evidence of carcinogenicity of PCE in 1987 using data from the NTP study and concluded that there was sufficient evidence that PCE is carcinogenic to animals (IARC, 1987). Other studies on PCE included those by Rampy *et al.* (1978) and Theiss *et al.* (1977). Rampy *et al.* (1978) exposed male and female Sprague-Dawley rats to PCE by inhalation (300 or

600 ppm) 6 hours/day, 5 days/week for 12 months. Animals were subsequently observed for 18 months. Pathological changes in the liver or kidney were not observed. Theiss and coworkers studied the ability of PCE to induce lung adenomas in A/St male mice (Theiss *et al.,* 1977). Animals 6 to 8 weeks old were given 80, 200, or 400 mg/kg of PCE in tricaprylin (intraperitoneally) three times a week. Each group received 14, 24, or 48 injections. Treated animals did not exhibit a significant increase in the average number of lung tumors when compared to controls.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Perchloroethylene has been observed to induce mononuclear cell leukemia in male and female rats and liver tumors in male and female mice (NTP, 1986). CDHS (1992) decided that the tumor incidence data from this study were suitable for use in developing a quantitative risk assessment.

Methodology

Results from the 1986 NTP inhalation study were used as the basis for estimating the carcinogenic risk of PCE to humans. In this bioassay, PCE was 99.9% pure, and animals were exposed 6 hours/day, 5 days/week for 103 weeks. The mice in the 100 and 200 ppm dose groups were exposed to a time-weighted-average (TWA) of 16 and 32 ppm, respectively (e.g., 100 ppm × 6 hours/24 hours × 5 days/7 days). Similarly, rats in the 200 and 400 ppm dose groups were exposed to a TWA of 33 and 66 ppm, respectively.

The CDHS staff used the metabolized dose, adjusted to continuous lifetime exposure, to calculate the carcinogenic potency of PCE (CDHS, 1992). There are several uncertainties using this approach: 1) It was assumed that oxidative metabolism leads to the production of carcinogenic metabolites but the ultimate carcinogen(s) has not been well characterized. The metabolism of PCE is not well quantified in humans, and 20-40% of the absorbed PCE has not been accounted for. 2) The pharmacokinetic models used do not account for individual differences in metabolism and storage. The body burden depended on factors such as age, sex, exercise or workload, body mass, adipose tissue mass, pulmonary dysfunctional states, and individual differences in the intrinsic capacity to metabolize PCE.

Two pharmacokinetic models, the steady-state and the PB-PK approaches were used. They incorporated an 18.5% estimated applied dose as the fraction of the dose that is metabolized in humans. For the low-dose PCE risk assessment, the Crump multistage polynomial (Crump, 1984) was chosen. This model, rather than a time dependent form of the multistage model, was chosen because most tumors were discovered only at the time of sacrifice, and survival in this study was relatively good. The cancer potency values derived using the two different pharmacokinetic approaches using the 1986 NTP rat and mouse studies ranged from 0.12 - 0.95 $(mg/kg\text{-}d)^{-1}$. When expressed as a function of human applied dose the values obtained ranged from 0.0025 to 0.093 $(mg/kg\text{-}d)^{-1}$. Using an estimated human weight of 70 kg, estimated breathing rate of 20 m^3/day and the PCE conversion factor of 1 ppb = 6.78 $\mu g/m^3$, the cancer unit risk values for PCE ranged

from 0.2 - 7.2 × 10^{-5} $(ppb)^{-1}$. After considering the quality of the cancer bioassays and the uncertainty of human metabolism, CDHS (1992) decided that the best value for the PCE cancer unit risk was 4.0 × 10^{-5} $(ppb)^{-1}$ [5.9 × 10^{-6} $(\mu g/m^3)^{-1}$]. This value is derived from the tumor incidence data for the most sensitive species, sex, and tumor site, male mouse hepatocellular adenomas or carcinomas (NTP, 1986).

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POLYCHLORINATED BIPHENYLS (PCBs)

CAS No: 1336-36-3 (all congeners)

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995 except as noted)

Molecular weight	154 - 499
Boiling point	Unknown
Melting point	340-375°C
Vapor pressure	4.06E-4 mm Hg @ 25°C (Aroclor 1242)
	7.71E-5 mm Hg @ 25°C (Aroclor 1254)
Air concentration conversion	1 ppm = 10.87 mg/m^3 (Aroclor 1242)
	1 ppm = 13.33 mg/m^3 (Aroclor 1254)

II. HEALTH ASSESSMENT VALUES

1) TEF_{WHO-97} Scheme (For use with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) unit risk factor in cases where measurements or estimates are available for PCB congeners [Table 2 of Appendix A].)

Congener		TEF_{WHO-97}	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg/day)^{-1}$
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin		1.0	3.8 E+1	1.3 E+5
77	3,3',4,4'-TCB	0.0001	3.8 E-3	1.3 E+1
81	3,4,4',5-TCB	0.0001	3.8 E-3	1.3 E+1
105	2,3,3',4,4'-PeCB	0.0001	3.8 E-3	1.3 E+1
114	2,3,4,4',5-PeCB	0.0005	1.9 E-2	6.5 E+1
118	2,3',4,4',5-PeCB	0.0001	3.8 E-3	1.3 E+1
123	2',3,4,4',5-PeCB	0.0001	3.8 E-3	1.3 E+1
126	3,3',4,4',5-PeCB	0.1	3.8 E+0	1.3 E+4
156	2,3,3',4,4',5-HxCB	0.0005	1.9 E-2	6.5 E+1
157	2,3,3',4,4',5'-HxCB	0.0005	1.9 E-2	6.5 E+1
167	2,3',4,4',5,5'-HxCB	0.00001	3.8 E-4	1.3 E+0
169	3,3',4,4',5,5'-HxCB	0.01	3.8 E-1	1.3 E+3
189	2,3,3',4,4',5,5'-HpCB	0.0001	3.8 E-3	1.3 E+1

[TCDD unit risk factor: linearized multistage procedure (GLOBAL79), fitted to male mouse hepatic adenoma and carcinoma data (NTP, 1982), body weight scaling, cross-route extrapolation (CDHS, 1986).

PCB TEQs are added to polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) TEQs for calculation of risk assessment values. In analyses of data that lack measurements of individual PCB congeners, it may be necessary to assess cancer risk using the unit risk factor for unspeciated PCB mixtures.]

2) Unspeciated PCB mixtures

Unit Risk Factor:	5.7 E-4 $(\mu g/m^3)^{-1}$	(For use in cases where food chain exposure, sediment or soil ingestion, dust or aerosol inhalation, dermal exposure (if an absorption factor has been applied to reduce the external dose), presence of dioxin-like, tumor-promoting, or persistent congeners in other media or early-life exposure (all pathways and mixtures) is expected.)
	1.1 E-4 $(\mu g/m^3)^{-1}$	(For use in cases where ingestion of water-soluble congeners, inhalation of evaporated congeners or dermal exposure (if no absorption factor has been applied to reduce the external dose) is expected.)
	2.0 E-5 $(\mu g/m^3)^{-1}$	(For use in cases where congeners with more than four chlorines comprise less than one-half percent of total PCBs)

[Calculated from a cancer potency factor derived by US EPA/IRIS (1996c) from rat liver tumor data (Norback and Weltman, 1985; Brunner *et al*., 1996), using a linear-quadratic multistage procedure and ¾ power body weight scaling to calculate an ED_{10} (estimated dose associated with 10 percent increased incidence), and its lower bound, LED_{10}.]

III. CARCINOGENIC EFFECTS

Human Studies

The evidence for the human carcinogenicity of PCBs has been determined by IARC (1987) to be limited, due to concurrent exposures of test subjects to other chemicals, and to the small numbers of individuals examined. A study of workers heavily exposed to Aroclor 1254 (54% chlorine, by weight) for 9 years, showed 2 out of 31 heavily exposed workers developed malignant melanoma, while 1 out of 41 less heavily exposed workers developed this tumor (Bahn *et al*., 1976; Lawrence, 1977). The expected number of melanomas in a population this size was 0.04. IARC (1978) concluded that there was suggestive evidence of carcinogenicity in humans.

Brown and Jones (1981) and Brown (1987) found an increase in the mortality caused by liver or biliary passage cancer (5 observed, 1.9 expected) in 2567 US workers exposed to Aroclor 1254 during the manufacture of capacitors. Four of the 5 deceased workers were female.

Bertazzi *et al*. (1982) reported on a study of capacitor manufacturing workers in Italy. Workers were exposed to mixtures of PCB congeners containing 54% chlorine prior to 1964, and 42% chlorine after that time. In these workers, significant increases in the incidence of cancers of the digestive, lymphatic, and hematopoietic systems were observed in both male and female workers.

An expanded study was later conducted by Bertazzi *et al*. (1987) who recorded cancer mortality in 2100 male and female workers from 1946 to 1982. Cancers of the gastrointestinal tract were significantly increased in male workers (6 observed, 2.2 expected) and hematopoietic cancers were significantly increased in female workers (4 observed, 1.1 expected).

PCB content in human fat tissues has been correlated with the occurrence of stomach, colon, pancreas, ovary, and prostate cancers (Unger *et al*., 1982; 1984).

A large population of people in Japan were exposed to PCBs from contaminated cooking oil (Umeda, 1984). In these patients, a 5-fold increase in liver cancer was reported, but a dose-response was not established. In a cohort of 887 male PCB-exposed patients with "Yusho" disease, Kuratsune *et al*. (1986) found an increase in mortality from malignant tumors (33 observed, 15.5 expected). Deaths from malignant liver and lung tumors were particularly high (9 observed, 1.6 expected; 8 observed, 2.5 expected, respectively). Female Yusho patients (n = 874) did not show the increase in cancer mortality.

Animal Studies

Early studies by Kimura and Baba (1973) and Ito *et al*. (1974) did not demonstrate carcinogenicity of PCBs in male or female rats orally exposed to highly chlorinated (60% by weight) PCBs in the diet for up to 77 weeks. In this study, 20 rats (10/sex) were exposed to diets ranging from 38.5 to 462 ppm PCBs. Ten rats (5/sex) served as experimental controls. Each rat was exposed to a unique treatment regimen that differed by amount of PCB ingested and duration of exposure. Female rats exhibited several benign adenomatous lesions in the liver, but no statistical comparisons were made. In these studies, small sample sizes (10 per group), less than lifetime exposure, and excess deaths unrelated to PCB exposure prevented definitive conclusions about the carcinogenicity of PCBs.

The NCI (1978) conducted a 2-year bioassay on male or female Fisher-344 rats (24 per group) exposed to Aroclor 1254 in the diet. Concentrations of PCBs in the feed were 0, 25, 50, or 100 ppm. A significant increase in the numbers of lymphomas and leukemias was observed in the male rats. The NCI did not conclude that these hematological tumors were treatment related. The incidence of hepatocarcinomas in the male rats was 0/24, 1/24, and 3/24 for the 0, 50, and 100 ppm groups, respectively. In other tissues, such as the stomach, jejunum, and cecum, rare tumors were found. The incidence of these tumors, while not statistically significant, was considered to be treatment-related due to the low incidence of these tumors in historical controls. The NCI concluded that PCBs were capable of inducing proliferative lesions in the liver, but were not carcinogenic to rats in this bioassay.

A reanalysis of the NCI data by Morgan *et al*. (1981) found that the incidence of focal metaplasia in the stomach increased in a dose-dependent fashion with a 6, 10, 17, and 35% occurrence in the 0, 25, 50, and 100 ppm groups, respectively. The incidence of stomach adenocarcinomas was significantly higher than in historical controls (4% vs. 0.03%, $p < 0.001$). With this reanalysis, the authors concluded that Aroclor 1254 was carcinogenic.

A chronic dietary exposure to Aroclor 1260 in rats was reported by Kimbrough *et al*. (1975). In this study, 200 young rats were fed 0 or 100 ppm Aroclor 1260 for 94 weeks. Actual dosages of PCB were estimated to be 11.6 mg/kg/day for the first week, 6.1 mg/kg/day at 3 months, and 4.3 mg/kg/day at 20 months. The time-weighted average dose was estimated to be 4.42 mg/kg/day (U.S. EPA, 1985). Almost all treated rats developed liver nodules (170/184). In addition, the incidence of hepatocellular carcinomas was highly significantly increased over controls (1/173 for controls vs. 26/184 for treated rats; $p < 1.0E-6$). Neoplastic nodules and total neoplastic lesions were also highly significantly increased over concurrent controls.

Schaeffer *et al*. (1984) reported results from a 2-year bioassay in rats using 2 PCB mixtures: Clophen A 30 (30% chlorine by weight) and Clophen A 60 (60% chlorine by weight) in the diet. Groups consisted of approximately 140 male weanling rats exposed to 100 ppm of either Clophen A 30 or Clophen A 60. A significant increase in the percentage of hepatocellular carcinomas was seen in the rats treated with Clophen A 60 (62%), but not with Clophen A 30 (3%). Hepatocarcinomas were observed in 2% of control animals. Preneoplastic lesions were not observed before 71 weeks.

The incidence of hepatocarcinoma was increased in rats exposed to Aroclor 1260 in a 2-year study by Norback and Weltman (1985). In this study, 70 male or female rats were exposed to 100 ppm Aroclor 1260 in the diet for 16 months, followed by 50 ppm in the diet for 8 months. The time-weighted average doses were calculated to be 5 mg/kg/day for the male rats, and 4.2 mg/kg/day for the females. The hepatocarcinoma incidence in control rats living 18 months or longer was 1.2% (1/81). The treated rats had an incidence of 95% (45/47) for the females, and 15% (7/46) for the males. The combined (male and female) tumor incidences were significantly higher in treated rats compared to controls. The authors also reported an increase in incidence of cholangiomas, but these lesions were designated by CDHS as benign, since no specific discussion of their malignancy was given.

Brunner *et al*. (1996) fed male and female Sprague-Dawley rats (50 animals/sex/Aroclor dose group) diets containing 25, 50 or 100 ppm Aroclor 1260 or 1254; 50 or 100 ppm Aroclor 1242; or 50, 100 or 200 ppm Aroclor 1016 for 104 weeks. Control groups were also included (100 animals/sex). Surviving animals were killed at 104 weeks. Statistically significant increases in liver adenoma or carcinoma incidence were observed in female rats for all Aroclor mixtures tested, and in male rats for Aroclor 1260 (Table 1).

In mice, two studies indicate that PCBs are carcinogenic, particularly with respect to hepatocarcinomas. Kimbrough and Linder (1974) exposed groups of 50 male BALB/cj mice to Aroclor 1254 at 0 or 300 ppm in the diet for 11 months, or for 6 months with a 5 month recovery period. The incidences of hepatoma were 0/34, and 0/24 for the 11- and 6-month control groups, respectively. The treated animals had incidences of 9/22, and 1/24 for the 11- and 6-month groups, respectively.

Ito *et al*. (1973) exposed groups of 12 mice to 500 ppm Kaneclor 500 (54% chlorine) in the diet for 32 weeks. No liver lesions were seen in 6 untreated controls. The incidence of hepatocellular carcinoma in the treated mice was 5/12 and the incidence of liver nodules was 7/12.

Table 1. Liver tumor incidence in Sprague-Dawley rats exposed to PCBs (Brunner *et al*., 1996; contained in US EPA, 1996a)

Mixture	Exposure level (ppm)	Tumor incidence Females	Males
Aroclor 1260	0	**1/85 (1%)	**7/98 (7%)
	25	10/49 (20%)	3/50 (6%)
	50	11/45 (24%)	6/49 (12%)
	100	24/50 (48%)	10/49 (12%)
Aroclor 1254	0	**1/85 (1%)	7/98 (7%)
	25	19/45 (42%)	4/48 (8%)
	50	28/49 (57%)	4/49 (8%)
	100	28/49 (57%)	6/47 (13%)
Aroclor 1242	0	**1/85 (1%)	7/98 (7%)
	50	11/49 (24%)	1/50 (2%)
	100	15/45 (33%)	4/46 (9%)
Aroclor 1016	0	**1/85 (1%)	7/98 (7%)
	50	1/48 (2%)	2/48 (4%)
	100	6/45 (13%)	2/50 (4%)
	200	5/50 (10%)	4/49 (8%)

**Statistically significant trend ($p < 0.05$) by Cochran-Armitage trend test.

In addition to the above studies describing the carcinogenicity of PCB mixtures, there are also some reports demonstrating the cancer promoting activity of dioxin-like PCB congeners.

Haag-Gronlund *et al*. (1997) studied the potential of 2,3',4,4',5-pentachlorobiphenyl (PCB 118) to promote liver tumors in female Sprague-Dawley rats using a two-stage initiation/promotion bioassay. In this study, animals were initiated by administrating N-nitrosodiethylamine after partial hepatectomy. The promotion began five weeks later by the subcutaneous administration of PCB 118 at six dose levels (10, 40, 160, 640, 2500 and 10000 µg/kg body weight) once/week for 20 weeks. Animals were also exposed to 40, 640 or 10000 µg/kg/week once/week for 52 weeks. After 20 weeks, the number of liver foci/cm^3, measured as foci positive for glutathione-S-transferase, was significantly increased in the two highest dose groups. The percentage of liver volume occupied by foci was not significantly increased after 20 weeks. However, after 52 weeks of treatment, the highest dose of PCB 118 significantly increased both the percentage of liver volume occupied by foci and the number of foci/cm^3.

According to Ito *et al.* (1992), the fraction of the liver occupied by foci (volume fraction) can be used as an approximate measure of the total amount of preneoplastic (initiated) cells in the liver available for further neoplastic development. Based on the volume fraction of liver occupied by foci, a relative potency of less than 0.00002 was estimated for PCB 118 when compared to TCDD liver foci development potency after 20 weeks of treatment. This value is less than the TEF_{WHO-97}

value of 0.0001 derived by the World Health Organization for PCB 118 (van den Berg *et al*., 1998). However, a relative potency of 0.0001 was estimated for EROD-induction activity of PCB 118. This value is exactly the TEF_{WHO-97} value proposed for PCB 118. Haag-Gronlund *et al*. (1997) concluded that co-planar *mono-ortho* PCBs, such as PCB 118, could act as tumor promoters by enhancing the growth of initiated cells into preneoplastic lesions.

Following a similar experimental design, Bager *et al*. (1995) treated female Sprague-Dawley rats with either 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153) or 3,3',4,4',5-pentachlorobiphenyl (PCB 126) five weeks after a partial hepatectomy and initiation with the administration of nitrosodiethylamine. The test substances were administered by weekly subcutaneous injection for 20 weeks. Dosage of tested chemicals were 5000 + 1 and 3.16 + 10 µg/kg body weight/week for PCB 153 and PCB 126, respectively. A binary mixture of PCB 153 and PCB 126 was also tested with dosage of 5000 + 1, 5000 + 3.16 and 5000 + 10 µg/kg/week, respectively. Combined administration of both PCBs elicited a more than additive interaction on the formation of gamma-glutamyl-transpeptidase-positive hepatic foci. In addition, co-exposure to PCB 153 and PCB 126 caused a dose-dependent reduction in PCB 153-induced hepatic CYP2B1/2B2. The authors concluded that PCB 126 and PCB 153 can promote altered liver foci growth. They also suggested that the more than additive interaction between PCB 153 and PCB 126 could be due to PCB tested at greater than environmentally relevant levels and/or to different mechanistic pathways.

In contrast, Dean *et al*. (2002) described antagonistic interactions between 3,3',4,4',5-pentazchlorinated biphenyl (PCB 126), a co-planar PCB, and 2,2',4,4',5,5'-hexachlorinated biphenyl (PCB 153), a *di-ortho* PCB, in the promotion of liver carcinogenicity in Fischer 344 rats. Using a medium term (8-week) bioassay for promoters of hepatocarcinogenesis, Dean *et al* (2002) monitored the placental form of glutathione-S-transferase-positive (GST-P+) liver cell foci as preneoplastic markers in female Fischer 344 rats. Animals were treated with an initiator (diethylnitrosamine) and 21 days later partially hepatectomized. Fourteen days after initial DEN administration, animals were exposed by gavage to test chemicals three times weekly through the remainder of the 8-week study. PCB 126 and PCB 153 were administered at a dosage of 0.1, 1.0 and 10, and 10, 100, 1000, 5000, and 10000 µg/kg body weight, respectively. Combined exposure consisted of 0.1 + 10, 1 + 100, 10 + 1000, 10 + 5000, and 10 + 10000 µg/kg PCB 126 and PCB 153, respectively. Results from this experiment demonstrated a dose-dependent increase in liver and adipose tissue concentrations of PCB 126 and PCB 153. Hepatic PCB 153 levels were significantly increased ($p < 0.01$) after combined exposure to PCB 126 and PCB 153. A significant ($p < 0.01$) dose-dependent increase in GST-P+ foci area and number was observed in PCB 126- and PCB 153-treated animals. However, PCB 153 exhibited promotive activity of hepatic foci formation, but at levels 1000 to 5000 × that of PCB 126. Combined exposure to PCB 126 and PCB 153 resulted in an antagonistic response of GST-P+ focus formation ($p < 0.001$) for both foci area and number. A less than additive effect was observed at all 5 PCB 126/PCB 153 dose combinations. Even the lowest combination dosage of 0.1 + 10 µg/kg of PCB 126 and PCB 153, respectively, elicited an antagonistic response based on the formation of liver foci. This is particularly interesting since these doses approach environmentally relevant levels. The antagonistic hepatic tumor promotional response seen after treatment with a combination of PCB 126 and PCB 153 was partly attributed to toxicokinetic interactions. One possible interaction of the PCB153/PCB 126 mixture could be the competitive inhibition of PCB 126 binding to the *Ah* receptor by PCB 153 which has a weak efficacy and a weak affinity for the *Ah* receptor.

Nevertheless, a PCB 153/PCB 126 combination ratio of 1000 could contain enough PCB 153 to inhibit PCB 126 binding to the *Ah* receptor and thus elicit an antagonistic effect. It is probable that the specific congeners in the mixture, the dose level of the individual congeners, route of administration, duration of exposure, and species and strain of animal affect such toxicokinetic interactions (Dean *et al.*, 2002). PCB 153 tumor promotive activity was attributed to a different mechanistic pathway than the *Ah* receptor-mediated pathway responsible for the mode of toxicity demonstrated by PCB 126.

The liver tumor promotive activity of PCB 126 was compared to that of TCDD (2,3,7,8-tetrachloro-*p*-dioxin) by Hemming *et al.* (1995) using an initiation/promotion experimental design. Female Sprague-Dawley rats were partially hepatectomized and initiated by the administration of nitrosodiethylamine. Five weeks later, the promotion treatment started with a weekly administration of PCB 126, TCDD or a mixture of the two substances. The promotion treatment continued for 20 weeks. The results of this study, based on increased development of gamma-glutamyl-transpeptidase-positive altered hepatic foci, indicated that PCB 126 had a liver tumor promotive activity of approximately 10% of that elicited by TCDD. Thus, a relative potency of 0.1 was estimated for PCB 126 based on its relative tumor promotive activity in comparison to that of TCDD. This value is identical to the TEF_{WHO-97} value for PCB 126 used in the WHO-97 TEF scheme (van den Berg *et al*., 1997). Treatment to a binary mixture of PCB 126 and TCDD elicited an additive response for tumor promotive effects. These results support the additivity assumption of the TEF scheme for the tumor promotive activity of TCDD and dioxin-like compounds. Therefore, these results suggest that PCB 126 and TCDD elicit their liver tumor promotive effects through the *Ah* receptor-mediated pathway.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Several studies (Kimbrough *et al*., 1975; Schaeffer *et al*., 1984; Norback and Weltman, 1985; Brunner *et al*., 1996) have demonstrated increased liver tumor incidence in rats exposed to PCB mixtures. The mixtures found to induce liver tumors range in chlorine content from 60% (Aroclor 1260; (Norback and Weltman, 1985; Brunner *et al*., 1996)), through 54% (Brunner *et al*., 1996), to 41% (Brunner *et al*., 1996). Female Sprague-Dawley rat liver tumor incidence data for Aroclor 1260 from the study by Norback and Weltman (1985) were chosen by US EPA as the basis of a cancer potency value for "high risk and persistence" PCB exposures. Female Sprague-Dawley rat liver tumor incidence data for Aroclor 1242 and 1016 from the study by Brunner *et al*. (1996) were chosen by US EPA as the basis of cancer potency values for "low risk and persistence" and "lowest risk and persistence" PCB exposures, respectively.

However, although PCB in many cases enters the environment as commercial formulations containing a relatively defined mixture of specific PCB congeners, the accumulation and retention of specific PCB congeners in various environmental matrices, wildlife, and humans do not directly reflect the PCB profile of the commercial mixtures. It is therefore important to consider the biological fate and activity of individual PCB congeners when assessing the risk that PCBs pose to human health (ATSDR, 2000). For cancer risk assessment, PCB toxicity is believed to be

elicited through the *Ah* receptor-mediated pathway (dioxin-like PCBs). Thus, the TEF_{WHO-97} methodology (Appendix A) can be used to sum the cancer risk associated with exposure to dioxin-like PCB congeners, chlorinated dioxins and chlorinated furans.

US EPA (1991) examined the toxic effects, including cancer, of four structural classes: dioxin-like PCBs, *ortho*-substituted PCBs, hydroxylated metabolites, and sulfonated metabolites. Different mechanisms of carcinogenicity were discussed for dioxin-like and other PCBs. It was concluded that congener toxicity could not be characterized by chlorine content alone. Chlorine content was formerly regarded by some scientists as correlated with cancer risk. Recently, however, Aroclor 1254 was found to be a more potent liver tumor inducer than Aroclor 1260, which was only slightly more potent than Aroclor 1242 (Brunner *et al*., 1996). This suggests that both the number and position of chlorines are a more useful indicator of cancer potency than total chlorine content. Accordingly, this difference can also partly be explained by the greater proportion of PCB 126 congener found in Aroclor 1254 (0.02 % in one of the tested lots) compared to no detectable level of PCB 126 in Aroclor 1260. The toxicological potency of PCB congener 126 in PCB mixtures is well documented and a TEF value of 0.1 (0.1 times the toxicity of TCDD) was attributed to this congener by the World Health Organization in 1997 (van den Berg *et al*., 1998).

Based on their predominant mechanism of toxicity, PCB congeners can be divided into two groups: dioxin-like and non dioxin-like PCBs. There is a large body of research indicating that dioxin-like (co-planar) PCB congeners elicit their toxicological effects through *Ah* receptor binding. *Ah* receptor-mediated PCB toxic effects include: induction of cytochrome P450 1A1/1A2/2B1, and phase II conjugation enzymes, body weight wasting, thymic atrophy and porphyria, and possibly cancer (ATSDR, 2000).

The WHO expert committee proposed the inclusion of dioxin-like PCBs in the TEF_{WHO-97} methodology (van den Berg *et al*., 1998) because of 1) similarities between the spectrum of effects in animals exposed to some PCB mixtures and congeners and that produced by 2,3,7,8-TCDD (Ah receptor-mediated pathway) and 2) the presence of a relationship between the binding affinities of co-planar PCBs for the *Ah* receptor and their potency in producing health effects in rodents such as body weight wasting and inhibition of immunological responses to sheep red blood cells (SRBCs) (ATSDR, 2000; Harper et al., 1993; Safe 1990, 1994). A description of the TEF methodology and its use is provided in Appendix A of this document.

Methodology

Use of the TEF Methodology to Calculate Cancer Risk

Humans are exposed to complex and varying environmental mixtures containing PCBs, PCDDs and PCDFs. However, limited toxicological data are available for these complex mixtures and many of their components (ATSDR 1998; 2000; Safe 1990, 1994; van den Berg *et al*. 1998). Therefore, toxicological equivalents (TEQs) of dioxin-like PCBs in the tested environmental mixture are added up to TEQs for PCDDs and PCDFs using the TEF_{WHO-97} scheme (Appendix A). A cancer risk factor can then be estimated from the product of the calculated total TEQs of the mixture and the risk factor of TCDD (3.8 E+1 $(\mu g/m^3)^{-1}$). This methodology shall be used when

concentration data are available for the PCB congeners listed in Section II (Health Assessment Values) of this summary (also listed in Appendix A of this document).

Use of PCB Mixture Unit Risk Factors for the Calculation of Cancer Risk

Lack of PCB speciation data would require the use of the previously developed unit risk factors for PCB mixtures in cancer risk assessments.

The September 1996 US EPA document "PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures" (US EPA, 1996a) differed from the prior US EPA PCB risk assessment (US EPA, 1988) which was also used for Proposition 65 purposes in that it included data from a new study of rats fed diets containing Aroclor 1260, 1254, 1242, or 1016 which found statistically significant, dose-related, increased incidences of liver tumors from each mixture (Brunner *et al*., 1996). Earlier studies used in the previous US EPA IRIS listing for PCBs found high, statistically significant incidences of liver tumors in rats ingesting Aroclor 1260 or Clophen A 60 (Kimbrough *et al*., 1975; Norback and Weltman, 1985; Schaeffer *et al*., 1984) in addition to partial lifetime studies which found precancerous liver lesions in rats and mice ingesting PCB mixtures of high or low chlorine content. However, the studies used for the previous IRIS listing had no data available indicating that PCBs with chlorine contents of less than 60% induced frank tumors.

The new US EPA PCB risk assessment document also used dose scaling to humans using a factor based on the ¾ power of relative body weight. Cancer potency is described by an ED_{10} (estimated dose associated with 10 percent increased incidence) and its lower bound, LED_{10}. These measures are expressed as equivalent human doses. Formerly, upper-bound slopes were calculated by the linearized multistage procedure; these were reported as "q1*"s. The LED_{10} method and the linearized multistage procedure give similar upper-bound slopes; for example, for female rats fed Aroclor 1254, the LED_{10} method and the linearized multistage procedure give upper-bound slopes of 1.5 and 1.6 per mg/kg-d, respectively. These changes conform to the 1996 draft US EPA cancer risk assessment guidelines (US EPA, 1996b).

The range of potency values is summarized in Table 2. It is based primarily on the range for Aroclor 1260, 1254, 1242, and 1016 in female Sprague-Dawley rats (Brunner *et al*., 1996), but considers the other available studies also.

Table 2. Range of human potency and slope estimates (from US EPA, 1996a)

	ED_{10} (mg/kg-d)	LED_{10}[a] (mg/kg-d)	Central slope[b] $(mg/kg\text{-}d)^{-1}$	Upper-bound slope[c] $(mg/kg\text{-}d)^{-1}$
Highest observed potency	0.046	0.086	1.2	2.2
Lowest observed potency	1.4	2.4	0.04	0.07

[a]95% lower bound on ED_{10}.
[b]Computed as $0.10/ED_{10}$ and rounded to one significant digit.
[c]Computed as $0.10/LED_{10}$ and rounded to one significant digit.

The new upper-bound slopes are lower than the previous estimate of 7.7 per mg/kg-d average lifetime exposure (U.S. EPA, 1988). The previous estimate was derived from female rats in the

Norback and Weltman (1985) study; the new estimate from the same study is 2.2 per mg/kg-d. This difference is attributable to three factors, each responsible for reducing the slope by approximately one-third: a rat liver tumor reevaluation (Moore *et al*., 1994), use of the new cross-species scaling factor (U.S. EPA, 1996b), and not using a time-weighted average dose. The difference between the highest observed new upper-bound slope (2.2 per mg/kg-d) and the lowest (0.07 per mg/kg-d) is entirely attributable to the availability of tests on several commercial mixtures (Brunner *et al*., 1996). This 30-fold range in potency reflects differences in commercial mixture composition, as reflected in Table 3.

Table 3. Typical composition (%) of some commercial Aroclor PCB mixtures (from US EPA, 1996a)

	1016	1242	1248	1254	1260
Mono-CBs	2	1	—	—	—
Di-CBs	19	13	1	—	—
Tri-CBs	57	45	21	1	—
Tetra-CBs	22	31	49	15	—
Penta-CBs	—	10	27	53	12
Hexa-CBs	—	—	2	26	42
Hepta-CBs	—	—	—	4	38
Octa-CBs	—	—	—	—	7
Nona-CBs	—	—	—	—	1
Deca-CB	—	—	—	—	—

US EPA designated three reference points for each range (see Table 4): a "high risk" point based on studies of Aroclor 1260 and 1254, which give the highest observed potencies; a "low risk" point, based on the study of Aroclor 1242; and a "lowest risk" point, based on the study of Aroclor 1016. The "high risk" point is used for exposure pathways associated with environmental processes that tend to increase risk, including early life exposure. The "low risk" point is used for exposure pathways resulting in mid-range risk. The "lowest risk" point is used in cases where congener or isomer analyses verify that congeners with more than four chlorines comprise less than one-half percent of total PCBs.

Table 4. Tiers of human potency and slope estimates for environmental mixtures (from US EPA, 1996)

HIGH RISK AND PERSISTENCE				
ED_{10}	LED_{10}	Central slope	Upper-bound slope	Criteria for use
0.086	0.067	1.0	2.0	Food chain exposure Sediment or soil ingestion Dust or aerosol inhalation Dermal exposure, if an absorption factor has been applied to reduce the external dose Presence of dioxin-like, tumor- promoting, or persistent congeners in other media Early-life exposure (all pathways and mixtures)
LOW RISK AND PERSISTENCE				
ED_{10}	LED_{10}	Central slope	Upper-bound slope	Criteria for use
0.38	0.27	0.3	0.4	Ingestion of water-soluble congeners Inhalation of evaporated congeners Dermal exposure, if no absorption factor has been applied to reduce the external dose
LOWEST RISK AND PERSISTENCE				
ED_{10}	LED_{10}	Central slope	Upper-bound slope	Criteria for use
2.4	1.4	0.04	0.07	Congener or isomer analyses verify that congeners with more than 4 chlorines comprise less than 1/2% of total PCBs

Less-than-lifetime exposure induced statistically significant increased incidences of liver tumors in female rats fed Aroclor 1260, 1254, and 1242 (Brunner *et al*., 1996). This result was most pronounced for Aroclor 1260, where tumor incidences at the highest dose were higher for a 12-month exposure than for a 24-month lifetime exposure. Only Aroclor 1016 showed no significant increases from less-than-lifetime exposure. The earlier less-than-lifetime studies in rats and mice suggest that less-than-lifetime exposure can quickly induce high incidences of early stages of tumor development (Kimbrough *et al*., 1972; Ito *et al*., 1973, 1974). With further exposure, these can progress to malignancy (Kimbrough *et al*., 1975; Norback and Weltman, 1985). Tumor incidences from less-than-lifetime exposure were sometimes lower (Kimbrough and Linder, 1974), and sometimes similar (Rao and Banerji, 1988), to those from full lifetime exposure to PCBs.

Infants can be highly exposed to PCBs during pregnancy and lactation (Dewailly *et al*., 1991, 1994). The accumulation of PCBs in human adipose tissue creates a store for subsequent release of PCBs into the bloodstream and then into the fetal circulation. During the postpartum period, PCBs are mobilized from adipose stores, transferred into human milk, and delivered to the neonate via nursing (Dewailly *et al*., 1991). This pathway may account for a substantial fraction of neonatal exposure to dioxin-like and other PCBs.

Additionally, normal fetal development depends on the timing and rate of release of T3 and T4. Some evidence indicates that PCBs can alter normal T3 and T4 metabolism, thereby disturbing thyroid function and provoking secondary impacts on organogenesis during development. Any estrogenic/anti-estrogenic, androgenic/anti-androgenic, or other hormonal activity of PCB mixtures has the possibility of altering the development of reproductive organs or the urogenital tract, potentially causing cancer or other adverse effects through a mechanism different from those causing liver cancer (US EPA, 1996b).

Few studies, however, have investigated early-life sensitivity. In human infants, glucuronidative mechanisms are not fully developed; additionally, some breast-fed infants experience an inhibition of glucuronyl transferase activity, further reducing PCB metabolism and elimination (Calabrese and Sorenson, 1977). In animals, Aroclor 1260 induced high incidences of liver tumors when fed to 5-week-old rats for a short time (Rao and Banerji, 1988). On the other hand, acute perinatal dosing with Aroclor 1254 promoted nitrosamine-initiated lung and liver tumors in mice but did not induce cancer in the offspring when administered alone (Anderson *et al.*, 1983, 1986, 1994). A study of polybrominated biphenyls (PBBs) found that perinatal exposure enhanced susceptibility to liver tumors for female rats also exposed as adults and increased the incidence of liver tumors in male and female mice not further exposed as adults (NTP, 1993). Because of the potential magnitude of early-life exposures, the possibility of greater perinatal sensitivity, and the likelihood of thyroid and hormone-dependent development perturbation, it is reasonable to conclude that early-life exposures may be associated with increased risks; this would indicate using the "high-risk" potency estimates for early-life exposure.

US EPA has listed three different cancer potency values for PCBs; the choice of which factor to use depends on the physical form of the PCBs and the expected route of exposure. However, US EPA states that the "high risk and persistence" factor (2.2 $(mg/kg\text{-}day)^{-1}$) should be used when an "early-life exposure (all pathways and mixtures)" exposure scenario is expected. Since this is the most likely exposure scenario expected for Hot Spots emissions, this is the appropriate cancer potency factor to list for PCBs in the Hot Spots cancer document, with the exception of PCB emissions in cases where 1) an early-life exposure scenario is not expected, and ingestion of water-soluble congeners, inhalation of evaporated congeners or dermal exposure (if no absorption factor has been applied to reduce the external dose) is anticipated - “low risk” category, or 2) congener or isomer analyses verify that congeners with more than four chlorines comprise less than one-half percent of total PCBs - "lowest risk and persistence" category. For these cases, this would support use of the “low risk” or "lowest risk and persistence" cancer potency value (0.4 $(mg/kg\text{-}day)^{-1}$ and 0.07 $(mg/kg\text{-}day)^{-1}$, respectively).

Inhalation unit risk factors of 5.7 E-4 $(\mu g/m^3)^{-1}$ ("high risk and persistence"), 1.1 E-4 $(\mu g/m^3)^{-1}$ ("low risk") and 2.0 E-5 $(\mu g/m^3)^{-1}$ ("lowest risk and persistence") were calculated from the cancer potency values 2.0 $(mg/kg\text{-}day)^{-1}$, 0.4 $(mg/kg\text{-}day)^{-1}$ and 0.07 $(mg/kg\text{-}day)^{-1}$, respectively, using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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POTASSIUM BROMATE

CAS No: 7758-01-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	167.01
Boiling point	not available
Melting point	434 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 6.8 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.4 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 4.9 E-1 $(mg/kg\text{-}day)^{-1}$
[Male rat kidney tumor data (Kurokawa *et al*., 1983), contained in Gold *et al.* (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of potassium bromate in humans are known to exist.

Animal Studies

Male and female Wistar rats (90/sex/group) (Fisher *et al*., 1979) and "Theiller's Original" strain mice (60/sex/group) (Ginocchio *et al*., 1979) were fed diets consisting of 79% bread crumbs made from untreated flour, or flour containing 50 mg/kg or 75 mg/kg potassium bromate. Mice and rats were fed treated diet for 80 and 104 weeks, respectively. No significant increase in tumor induction was reported; however, IARC (1986) noted that bromates are substantially degraded during bread baking.

Male and female Fischer 344 (F344) rats were exposed to 0, 250 or 500 mg/l potassium bromate in drinking water for 100 weeks (Kurokawa *et al*., 1983). Group sizes were 52-53/sex/group. Total doses were 9.6 and 21.3 mg/kg body weight for low and high dose males, respectively, and 9.6 and 19.6 mg/kg body weight for low and high dose females, respectively. Significant increases in the incidences of renal andenomas and adenocarcinomas were noted in both males and females; significant increases were also noted in the incidence of peritoneal mesotheliomas in males, and of thyroid tumors in females. Tumor incidence data is listed in Table 1.

Table 1. Potassium bromate-induced tumor incidences in male and female Fisher 344 rats (Kurokawa *et al*., 1983)

Sex	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male	control	0	kidney tumors[3]	3/53
	low dose	12.4		32/53
	high dose	22.5		46/52
	control	0	peritoneal mesotheliomas	6/53
	low dose	12.4		17/52
	high dose	22.5		28/46
female	control	0	kidney tumors[3]	0/47
	low dose	14.2		28/50
	high dose	28.3		39/49
	control	0	thyroid tumors	3/52
	low dose	14.2		10/52
	high dose	28.3		12/52

1. Doses as reported by Gold *et al.* (1987).
2. Tumor incidences as reported by Gold *et al*. (1987).
3. Adenomas and adenocarcinomas

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al*. (1987) list the results from positive drinking water studies in male and female F344 rats (Kurokawa *et al*., 1983) and from negative feeding studies in male and female Wistar rats (Fisher *et al*., 1979) and "Theiller's Original" mice (Ginocchio *et al*., 1979). Male and female rats are of similar sensitivity. Cancer potency is based on results from Kurokawa *et al.* (1983). The dose-response data for renal adenomas and adenocarcinomas in male rats are listed in Table 1 and are the basis for the cancer potency for potassium bromate (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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1,3-PROPANE SULTONE

CAS No: 1120-71-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	122.1
Boiling point	180°C at 30 mm Hg
Melting point	31°C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.01 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.9 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 2.4 E+0 $(mg/kg\text{-}day)^{-1}$
[Male rat cerebellar malignant glioma tumor data (Ulland *et al*., 1971; Weisburger *et al*., 1981), contained in Gold *et al*. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992)]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 1,3-propane sultone on humans are known to exist.

Animal Studies

Several studies exist on the potential carcinogenic effects of 1,3-propane sultone in animals. These studies have been reviewed by IARC (1974).

BD rats (12/group, sex unspecified) were given 30 mg/kg body weight 1,3-propane sultone as a 3% aqueous solution weekly by gavage (Druckrey *et al*., 1970). Four of 10 survivors developed tumors between days 248 and 377; tumors noted were 1 glial-mesodermal mixed tumor, 1 advential cell sarcoma of the brain, 1 nephroblastoma and 1 subcutaneous spindle cell sarcoma.

Local sarcomas resulting in mortality were induced in all of 18 BD rats given weekly subcutaneous injections of 15 mg/kg 1,3-propane sultone in water (total dose 225 mg/kg) between 208 and 387 days. Additionally, single subcutaneous injections of 30 or 100 mg/kg produced local sarcomas at the injection site resulting in mortality in 12/18 animals and 18/18 animals, respectively (Druckrey *et al*., 1970). In the same study, BD rats were given 1,3-propane sultone as a 1% solution in arachis oil by subcutaneous injection weekly at doses of 15 or 30 mg/kg. Mortality resulted from local sarcomas which developed (myosarcomas and fibrosarcomas) at the site of injection (7/12 and 11/11 rats in the low and high-dose groups, respectively) within 217-360 days (total dose up to 390 mg/kg) (Druckrey *et al*., 1968, 1970).

Weekly intravenous injections of a 2% solution of 1,3-propane sultone in water at doses of 10, 20 or 40 mg/kg (total doses 300, 570 and 560 mg/kg, respectively) were administered to groups of 10 BD rats (the 40 mg/kg group treatment was suspended after 16 weeks due to tail vein sclerosis) (Druckrey *et* al., 1970). Three animals in the 40 mg/kg group died of tumors after 280-410 days (sarcoma of the mediastinum with right lung and kidney metastases, glial-mesodermal mixed tumor of the brain, neurosarcoma); 2/12 and 3/8 animals respectively in the 10 and 20 mg/kg groups died of tumors (10 mg/kg group: ganglioneuroma, neurocytoma; 20 mg/kg group: nephroblastoma, ileocaecal carcinoma, glial-mesodermal mixed tumor of the brain and mammary carcinoma) after 381-492 days. In the same study, a single intravenous injection of 1,3-propane sultone (150 mg/kg) induced tumors at various sites resulting in mortality within 459 days in 10/32 BD rats. Single intravenous injections of 20 or 60 mg/kg 1,3-propane sultone administered to pregnant BD rats on gestation day 15 resulted in malignant neurogenic tumors in 3/25 offspring born to the 20 mg/kg group, and in malignant tumors in 4/14 offspring (2 neurogenic tumors, 1 pancreatic tumor, 1 ovarian tumor) born to the 60 mg/kg group.

Female ICR/Ha Swiss mice (30/group) given weekly subcutaneous injections of 0.3 mg 1,3-propane sultone in 50 µl distilled water developed tumors in 21/30 mice at the injection site (1 papilloma, 7 adenoacanthomas, 12 sarcomas, 1 undifferentiated carcinoma) within 63 weeks, compared to 0/30 controls after 78 weeks (Van Duuren *et al*., 1971).

Male and female Charles River CD rats (26/sex/group) were exposed to an aqueous solution of 1,3-propane sultone by gavage twice weekly at doses of 28 mg/kg body weight for 60 weeks and 56 mg/kg for 32 weeks (Ulland *et al*., 1971; Weisburger *et al*., 1981). Control groups (32/sex) were also included; however, only 6 animals/sex were killed and necropsied at 61 weeks. Tumor types induced by 1,3-propane sultone are listed in Table 1.

Table 1: 1,3-propane sultone-induced tumor incidences in male and female CD rats

Exposure group (mg/kg)	28		56	
Sex	Male	Female	Male	Female
Tumor type				
Breast	1/26	7/26	1/26	13/26
Glioma	12/26	15/26	16/26	13/26
Ear duct	1/26	0/26	3/26	3/26
Leukemia	0/26	2/26	4/26	3/26
Intestinal adenocarcinoma	4/26	1/26	3/26	1/26
Miscellaneous	5/26	7/26	4/26	6/26

One female control died of a cerebral glioma after 33 weeks, and a pituitary chromophobe adenoma was discovered in a female control. No other control animal tumor incidences were reported.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The carcinogenicity bioassay using male and female Charles River CD rats exposed to 1,3-propane sultone by gavage (Ulland *et al*., 1971; Weisburger *et al*., 1981) demonstrated that 1,3-propane sultone induced tumors in both sexes at multiple sites; the sensitivity of both sexes was similar. The dose-response data for cerebellar malignant glioma incidence in male rats, the most sensitive site in males, was chosen as the basis for a cancer potency factor.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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PROPYLENE OXIDE

CAS No: 75-56-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	58.08
Boiling point	34.2°C
Melting point	-112°C
Vapor pressure	543 mm Hg @ 25°C
Air concentration conversion	1 ppm = 2.37 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.7 E-6 $(\mu g/m^3)^{-1}$
[Calculated by US EPA (1995) from male rat nasal cavity hemangioma/hemangio-sarcoma data (NTP,1985) using a linearized multistage procedure, extra risk.]

Oral Cancer Potency Factor: 2.4 E-1 $(mg/kg/day)^{-1}$
[Calculated by US EPA (1995) from female Sprague-Dawley rat forestomach squamous cell carcinoma tumor data (Dunkelberg, 1981), using a linearized multistage procedure, extra risk.]

III. CARCINOGENIC EFFECTS

Human Studies

Theiss *et al*. (1981) conducted a retrospective cohort study of 602 active and former employees who had worked for 6 months or more in one of 8 German alkylene oxide production plants. The workers had been exposed to alkylene oxides (propylene oxide and ethylene oxide) as well as to other chemicals such as dichloropropane and epichlorohydrin. No ambient propylene oxide concentrations were reported and the study included workers employed as early as 1928; propylene oxide production did not begin until 1959. No significant difference was observed between the observed and expected numbers of cancer deaths.

Animal Studies

Exposure to propylene oxide by gavage at dose levels of 0, 15 or 60 mg/kg twice weekly for 150 weeks has been shown to induce forestomach tumors (primarily squamous cell carcinomas) in female Sprague-Dawley rats (Dunkelberg, 1982). Female NMRI mice treated with 0.1, 0.3, 1.0 or 2.5 mg propylene oxide once a week for 95 weeks via subcutaneous injection demonstrated a dose-dependent increase in injection site tumors (mostly fibrosarcomas) (Dunkelberg, 1984). Subcutaneous injection of a total dose of 1500 mg/kg propylene oxide over 325 days in rats (sex and strain not specified) resulted in the induction of injection site sarcomas (8/12 and 3/12 rats

receiving propylene oxide in oil and water vehicle, respectively) (Walpole, 1958). However, the study did not include an appropriate control group.

F344 rats and B6C3F$_1$ mice (50/sex/dose) were exposed to 0, 200 or 400 ppm (0, 475 or 950 mg/m^3) of propylene oxide for 6 hours/day, 5 days/week for 102 weeks (NTP, 1985; Renne *et al*., 1986). In rats, positive trends were demonstrated for papillary adenomas of the nasal turbinate epithelium (males and females), thyroid gland C-cell adenomas or carcinomas (females) and keratoacanthomas (males). A significantly increased incidence of endometrial stromal polyps and sarcomas combined was noted for all doses. However, the NTP decided that only the nasal epithelial tumors were treatment-related because the other tumors were either relatively common (thyroid) or were of low incidence relative to historical controls. In mice, the low-dose group was killed due to an inadvertent overdose 19 weeks after the initial start date. New groups of low-dose mice of both sexes were started, but additional control groups were not included. Hemangiomas (males) and hemangiosarcomas (both sexes) were significantly increased at the high dose. One squamous cell carcinoma and one papilloma were observed in the nasal cavity of 2 high-dose males; nasal cavity adenocarcinomas were reported in 2 high-dose females. Although not statistically significant, historical controls have demonstrated an extremely low incidence of these tumor types. A significant dose-related trend and incidence of mammary gland adenocarcinomas was observed in high-dose females.

Cpb:WU Wistar rats (100/sex/group) were exposed to 0, 30, 100 or 300 ppm (0, 71, 238 or 713 mg/m^3) propylene oxide for 6 hours/day, 5 days/week for 123-124 weeks (Reuzel and Kuper, 1983; Kuper *et al*. , 1988). No nasal cavity tumors were observed; however, significant increases in degenerative changes and neoplasia of the olfactory and respiratory epithelium were noted in both sexes of all exposure groups. Significant increases were also found in mammary gland adenocarcinomas in high-dose females. Squamous-cell carcinomas of the nose, larynx/pharynx and trachea, and adenocarcinoma of the larynx/pharynx and lungs were reported in 5 high-dose males. Although not statistically significant, none of these tumor types were reported in control males.

Male F344 rats exposed to 0, 100 or 300 ppm propylene oxide for 7 hours/day, 5 days/week for 104 weeks displayed a significant increase in nasal epithelium hyperplasia in the high-dose group (Lynch *et al*., 1984). The incidence of adrenal pheochromocytomas was also increased.

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Studies by Dunkelberg (1981) and NTP (1985) demonstrated that oral and inhalation exposure, respectively, to propylene oxide can result in increased animal tumor incidence. In the study by Dunkelberg (1981), female Sprague-Dawley rats exposed to total average doses of 0, 2714 or 10,798 mg/kg-day propylene oxide for 150 weeks demonstrated a significant increase in forestomach squamous cell carcinoma tumor incidence (0/100, 2/50 and 19/50 for control, low-dose and high-dose animals, respectively). These data were used to calculate an oral cancer potency factor for propylene oxide. In the NTP carcinogenicity study (1985), F344 rats and B6C3F$_1$ mice (50/sex/dose) were exposed to 0, 200 or 400 ppm (0, 475 or 950 mg/m^3) of propylene

oxide for 6 hours/day, 5 days/week for 102 weeks. High-dose rats exhibited an increased incidence of nasal papillary adenomas (2/50 for males, 3/50 for females), suggesting a carcinogenic response. However, these increases were not significant when compared to controls (0/50 for both sexes), making them unsuitable for carcinogenicity risk estimation. The incidence of nasal cavity hemangiomas or hemangiosarcomas in mice was 10/50 and 5/50 in the high-dose males ($p = 0.001$) and females ($p = 0.028$), respectively. These data, from a study where adequate numbers of animals of both sexes were treated for a lifetime, demonstrate that inhalation exposure to propylene oxide results in respiratory tract carcinogenicity. The male rat hemangioma/hemangiosarcoma data was used as the basis for a inhalation unit risk factor.

Methodology

Oral Cancer Potency Factor

Transformed animal doses (0, 2.58 and 10.28 mg/kg/day) and human equivalent doses (0, 0.44 and 1.76 mg/kg-day) were calculated from the administered doses using a rat body weight of 0.35 kg, a human body weight of 70 kg, 1029 days as the length of the exposure, and 1050 days as the length of the experiment and animal lifespan. A human oral cancer potency factor of 2.4 E-1 $(mg/kg/day)^{-1}$ was calculated using the linearized multistage procedure developed by Kenneth Crump and adopted by US EPA (1980).

Inhalation Unit Risk Factor

Transformed animal doses (0, 55 and 110 mg/kg/day) were calculated from administered doses assuming 50% pulmonary absorption, 0.03 kg mouse body weight, 0.039 m^3/day as the daily inhalation volume for mice and an exposure duration and length of experiment of 103 weeks. The absorption factor is consistent with that observed for epichlorohydrin in rat respiratory tract (Stott and McKenna, 1984). Human equivalent doses were 0, 4.15 and 8.3 mg/kg/day. The transformed animal dose level was used to calculate an animal slope factor of 9.3E-4 $(mg/kg/day)^{-1}$ using the linearized multistage procedure developed by Kenneth Crump and adopted by US EPA (1980). A human unit risk factor of 3.7 E-6 $(\mu g/m^3)^{-1}$ was determined using an animal body weight of 0.03 kg, a human body weight of 70 kg and an animal lifetime of 103 weeks. US EPA has stated that the unit risk should not be used if the air concentration exceeds 3 mg/m^3, since above this concentration the unit risk may not be appropriate.

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1,1,2,2-TETRACHLOROETHANE

CAS No: 79-34-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	167.9
Boiling point	146.5ºC
Melting point	-44ºC
Vapor pressure	9 mm Hg @ 30ºC
Air concentration conversion	1 ppm = 6.87 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 5.8 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 2.0 E-1 $(mg/kg\text{-}day)^{-1}$
[Calculated by US EPA from NCI (1978) female mouse hepatocellular carcinoma tumor data using a linearized multistage procedure, extra risk]

III. CARCINOGENIC EFFECTS

Human Studies

Norman *et al*. (1981) studied Army personnel assigned to treat chemical warfare protective equipment with material dissolved in tetrachloroethane. Of 3859 workers assigned to this process, 1099 whites and 124 blacks had probable exposure to the solvent. No statistically significant excess cancer mortality was noted. Slight excesses were noted for leukemia (SMR = 272, based on 4 deaths) and cancer of the genital organs (SMR = 158, based on 3 deaths).

Animal Studies

Theiss *et al*. (1977) exposed groups of 20 male A/st mice to 1,1,2,2-tetrachloroethane in tricaprylin by intraperitoneal injection (3/week) at doses of 80 mg/kg body weight, 200 mg/kg or 400 mg/kg. All survivors (10, 15 and 5 at the three doses, respectively) were killed 24 weeks after the first injection. The average number of tumors/animal were not significantly increased in the treated mice (0.3, 0.5 and 1.0 at the three doses, respectively compared to 0.27 for controls). However, the poor survival of treated animals and inadequate length of observation made this study unusable for a determination of the carcinogenicity of 1,1,2,2-tetrachloroethane.

$B6C3F_1$ mice (50 male, 50 female) were treated with technical grade (90% pure) 1,1,2,2-tetrachloroethane in corn oil by gavage 5 days/week (NCI, 1978). Low-dose and high-dose mice initially received 100 and 200 mg/kg body weight/day, respectively. Doses were increased to 150 and 300 mg/kg respectively at 18 weeks, 200 and 400 mg/kg at 21 weeks and 150 and 300 mg/kg at 26 weeks. Total duration of exposure was 78 weeks. Animals were killed 12 weeks after

exposure termination. The low and high time-weighted average doses for males and females was 142 and 282 mg/kg/day, respectively. Control groups (20 male, 20 female) were left untreated or given corn oil alone for 78 weeks, and were then killed after 90 weeks. Only 1 high-dose male survived to 90 weeks, compared with 34% of the females. The incidence of hepatocellular carcinoma was positively correlated with dose level ($p < 0.001$) in both male and female mice; tumor incidence in males was 1/18 for vehicle-treated controls, 13/50 for the low-dose group and 44/49 for the high-dose group. The respective tumor incidence for females was 0/19, 30/48 and 43/47.

Osborne-Mendel rats (50 male, 50 female) were treated with technical grade 1,1,2,2-tetrachloroethane in corn oil by gavage 5 days/week (NCI, 1978). High-dose animals initially received 100 mg/kg body weight/day. In males, doses were increased to 130 mg/kg at 14 weeks, followed by 9 cycles of 4 weeks at 130 mg/kg followed by 1 week treatment-free starting at 32 weeks. In females, the dose was reduced at 25 weeks to 80 mg/kg, then followed at 32 weeks by the cyclic dosing protocol described for males (dose level 80 mg/kg). The duration of the cyclic dosing for both males and females was 45 weeks. Low-dose rats were initially exposed to 50 mg/kg/day. Doses were increased for males to 65 mg/kg at 14 weeks; doses were decreased for females to 40 mg/kg at 25 weeks. The total duration of exposure for both dose groups was 78 weeks, followed by 32 weeks without treatment. The low and high time-weighted average doses were 62 and 108 mg/kg/day for males and 43 and 76 mg/kg/day for females. Control groups (20 male, 20 female) were left untreated or given corn oil alone for 78 weeks; all surviving control and exposed animals were killed at 110 weeks. No significant increases in tumor incidence for any tumor type were noted in exposed animals. However, 2 of 49 high-dose males developed hepatocellular carcinomas and another developed a neoplastic nodule, compared with 0/20 vehicle controls.

Detailed reviews of these studies have been performed by IARC (1979) and US EPA (1980).

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Data from the bioassay of 1,1,2,2-tetrachloroethane by NCI (1978) was selected as the basis of a cancer potency factor because it demonstrated a dose-responsive induction of carcinogenicity after exposure to 1,1,2,2-tetrachloroethane in both sexes of a susceptible species ($B6C3F_1$ mice). Tumor incidence data from the most sensitive sex was used (hepatocellular carcinomas in females).

Methodology

The linearized multistage procedure developed by Kenneth Crump and adopted by US EPA (1980) was used to calculate a slope factor of 2.0 E-1 $(mg/kg/day)^{-1}$ from the NCI (1978) female $B6C3F_1$ mouse hepatocellular carcinoma incidence data. Calculation of the unit risk from the slope factor assumed a body weight of 70 kg and an inspiration rate of 20 m^3/day. US EPA has stated that the unit risk should not be used if the air concentration exceeds 200 $\mu g/m^3$, since above this concentration the unit risk may not be appropriate.

V. REFERENCES

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THIOACETAMIDE

CAS No: 62-55-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	75.14
Boiling point	not available
Melting point	113-114 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 3.1 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.7 E-3 ($\mu g/m^3$)$^{-1}$
Slope Factor: 6.1 E+0 (mg/kg-day)$^{-1}$
[Female mouse liver tumor data (Gothoskar *et al.*, 1970), contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of thioacetamide in humans are known to exist.

Animal Studies

Male albino rats (10/group) were exposed to thioacetamide in the diet for 18 months (Fitzhugh and Nelson, 1948). Dietary thioacetamide levels were 0, 50, 100, 250, 500 or 1000 mg/kg diet. Animals exposed to 1000 mg/kg diet thioacetamide survived for less than one month; animals exposed to 250 or 500 mg/kg diet thioacetamide also had increased mortality. One animal in the 500 mg/kg diet exposure group developed a hepatocellular carcinoma (the number of surviving animals in this group was unspecified). One animal of the 6 survivors in the 50 and 100 mg/kg diet exposure groups developed a hepatocellular adenoma. No liver tumors were observed in the control animals.

Gupta (1955, 1956) exposed 150 male and female Wistar rats to 32 mg/kg diet thioacetamide in the diet for more than 23 weeks; an untreated control group of 50 animals was included in the study. Bile duct tumors (unspecified type) were observed in 18/36 animals killed between 9 and 23 weeks; no liver tumors were noted in the control animals. Liver tumor metastases to the ovaries were noted in 4/5 animals treated for 47 weeks or longer.

Male and female Swiss mice were fed diet containing 0.03% thioacetamide for 65 weeks (89 mice total); an untreated control group was included in the study (Gothoskar *et al*., 1970). Interim

sacrifices were performed at 6, 9 and 13 months. An increased incidence of liver tumors (hepatomas) was noted in both males and females. Tumor incidence data is listed in Table 1.

Table 1. Thioacetamide-induced hepatoma incidence in male and female Swiss mice (Gothoskar *et al*., 1970)

Dose group	Average dose[1] (mg/kg-day)	Tumor incidence
male control	0	0/6
male treated	36	6/6
female control	0	0/6
female treated	39	6/7

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al.* (1984) list results from the study of thioacetamide by Gothoskar *et al.* (1970) in male and female Swiss mice. A total of 89 mice of both sexes were fed a diet containing 0.03% thioacetamide for 6, 9, 13 or 17 months. The group studied for 17 months consisted of 12 control mice (6 male and 6 female) and 13 treated mice (6 male and 7 female). Hepatomas were seen in all treated male mice, precluding estimation of the upper bound on potency in these animals. Females were slightly less sensitive; six of the seven dosed female mice developed hepatomas. Because this is the only dose-response data available in Gold *et al*., the data for the females are used to derive potency (see Table 1). The value presented here may be an underestimate, but is the best value currently available (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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TOLUENE DIISOCYANATE
CAS No: 26471-62-5

2,4-TOLUENE DIISOCYANATE
CAS No: 584-84-9

2,6-TOLUENE DIISOCYANATE
CAS No: 91-08-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	174.15
Boiling point	251°C at 760 mm Hg
Freezing point	22°C (pure toluene-2,4-diisocyanate (IARC, 1985); 7.2°C (pure toluene-2,6-diisocyanate (IARC, 1985)
Vapor pressure	0.01 mm Hg at 20°C
Air concentration conversion	1 ppm = 7.12 mg/m^3 (IARC, 1985)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 3.9 E-2 $(mg/kg\text{-}day)^{-1}$
[Male rat subcutaneous fibroma/fibrosarcoma tumor data (NTP, 1986) contained in Gold *et* al. database (1990), expedited Proposition 65 methodology (Cal/EPA, 1992)]

III. CARCINOGENIC EFFECTS

Human Studies

A case report reviewed by IARC (1985) described a 47-year old nonsmoking spray painter with a lung adenocarcinoma who had been exposed to TDI and 4,4'-methylenediphenyl diisocyanate for 15 years and had a 10-year history of lung disease thought to be caused by isocyanate exposure (Mortillaro and Schiavon, 1982).

Hagmar *et al*. (1993) performed a cohort based case-referent study to assess any potential cancer risk associated with occupational exposure to TDI or methylene diphenyldiisocyanate. The subjects were 7023 workers employed during the period 1958 to 1987 in nine Swedish polyurethane foam manufacturing plants. Odds ratios were adjusted with respect to matching factors (age at risk, calendar year at risk, sex, and plant), calculated from a conditional logistic regression model. An association was found between intermediate/high exposure to isocyanates and prostate cancer (OR 2.96, 90% confidence interval (90% CI) 0.45-19.4); however, this association was not statistically significant. An association between isocyanate exposure and colon cancer (OR 3.25, 90% CI 0.5 - 21.3) was also not statistically significant. Study limitations included a small number of subjects (102 controls, 155 in the intermediate/high exposure group), a lack of quantitative exposure characterization, and a lack of control for potential confounding factors (tobacco smoking, etc.).

Sorahan and Pope (1993) conducted a historical prospective cohort study in order to determine specific mortality and site specific cancer morbidity among workers employed in factories that produce polyurethane foams, and to determine if any part of the experience may be due to occupation, and in particular to exposure to diisocyanates. The subjects were 8288 male and female production employees from 11 factories in England and Wales with some employment in the period 1958-79, and with a minimum period of employment of six months.

Standardized mortality ratios (SMRs) for all causes and all neoplasms were 97 (expected deaths (Exp) 844, observed deaths (Obs) 816) and 88 (Exp 251, Obs 221) respectively, compared to the general population of England and Wales. The exposed women demonstrated statistically significant increased incidences of death due to pancreatic cancer (Exp 2.2, Obs 6, SMR 271, 95% CI 100-595, $p < 0.05$) and lung cancer (Exp 9.1, Obs 16, SMR 176, 95% CI 100-285, $p < 0.05$). Similar cancer mortality increases were not noted for the male workers. Statistically significant increases in tumor incidences among women were found for cancers of the larynx (Exp 1.6, Obs 3, SRR 1024, 95% CI 105-755, $p < 0.05$) and kidney (Exp 0.9, Obs 4, SRR 449, 95% CI 122-1146, $p < 0.05$). Incident cancers of the lung and pancreas among women were also in excess, although these findings were not independent of the findings for mortality. Poison regression did not indicate that ever having been employed in jobs attracting either higher or lower exposure to isocyanates was a risk factor for the mentioned cancers. A nested case-control design was used to investigate any associations with nine other occupational exposures. No statistically significant association was found. This study did not include any corrections for cigarette smoking-induced cancer morbidity or mortality; therefore, cigarette smoking must be considered a potential confounder. Other study limitations included a lack of quantitative exposure characterization.

Schnorr *et al*. (1996) evaluated cancer mortality among United States workers exposed to TDI in the manufacture of polyurethane foam. This cohort mortality study included 4611 men and women employed in four polyurethane foam plants for at least three months between the late 1950s and 1987. The mortality experience of the cohort was compared with that of the general United States population. Industrial hygiene data indicated that air concentrations in 1984-5 were below the current United States standard of 0.04 mg/m^3 but exceeded the standard before 1980. Mortality from rectal cancer (SMR 2.78, 95% CI 0.57-8.13) and non-Hodgkin's lymphoma (SMR 1.54, 95% CI 0.42-3.95) were increased, but not significantly. There was one male breast cancer (SMR 18.52). However, breast cancer was not increased in women (SMR 0.74). No other cancer category had an increased number of deaths compared with the general population. Only non-Hodgkin's lymphoma and Hodgkin's disease showed a possible relation with time since first employment and no cancer death category showed a strong relation with duration of employment. The authors noted that the cohort was young, had few deaths and a short follow up, rendering the findings inconclusive.

Animal Studies

The National Toxicology Program (NTP) (1986) exposed male and female Fischer 344 344/N rats and $B6C3F_1$ mice (50/sex/exposure group) to commercial grade TDI (86% 2,4 isomer; 14% 2,6 isomer) in corn oil by gavage 5 days/week for 106 and 105 weeks, respectively. Rat exposure groups were 30 or 60 mg/kg for males and 60 or 120 mg/kg for females. Mouse exposure groups were 120 or 240 mg/kg body weight for males and 60 or 120 mg/kg for females. Vehicle control groups (50/sex/species) were included.

A dose-dependent reduction in survival occurred in treated rats; 36/50 (72%) controls, 14/50 (28%) low-dose and 8/50 (16%) high-dose males, and 36/50 (72%) controls, 19/50 (38%) low-dose and 6/50 (12%) high-dose females survived to study termination (108 weeks). A treatment-related induction of subcutaneous fibromas and fibrosarcomas was noted in males and females. The combined fibroma/fibrosarcoma incidence was 3/50 (6%) in controls, 6/50 (12%) in low-dose and 12/50 (24%) in high-dose males, and 2/50 (4%) in controls, 1/50 (2%) in low-dose and 5/50 (10%) in high-dose females. Fibromas and fibromasarcomas occurred in male and female rats with a statistically positive trend, and the incidence in both high-dose males and females was significantly greater than controls. Increased mammary gland tumor incidence in female rats was found to be significant in both the low- and high-dose groups by life table and incidental tumor analysis. The first mammary tumor was seen in an animal dying at week 84; the survival-adjusted mammary tumor incidences were 17/45 (38%) for controls, 25/36 (69%) for low-dose and 21/28 (75%) for high-dose animals. Increased incidences of pancreatic acinar cell adenomas with a statistically significant trend were observed in male rats; the incidence in the high-dose group was significantly greater than that in the controls. Pancreatic acinar nodular hyperplasia incidence was also increased in male rats in a dose-dependent manner (control, 0%; low-dose, 4%; high-dose, 8%). A statistically significant trend was noted for pancreatic islet cell adenoma incidence in both male and female rats; the incidences were significantly greater than those in the controls in both dose groups for females, and in the high-dose group for males. A significant dose-related increase in hepatic neoplastic nodule incidence in high-dose female rats was also noted.

Survival of high-dose male mice was reduced; 26/50 (52%) animals in this group were still alive at study termination (week 107) compared to 46/50 (92%) controls and 40/50 (80%) in the low-dose group. No statistically significant increase in tumor incidence was noted in treated male mice. A statistically significant positive trend was observed in the incidence of hemangiomas and hemangiosarcomas (in liver, ovaries or peritoneum), lymphomas, and hepatocellular adenomas and carcinomas in female mice. Overall hemangioma and hemangiosarcoma incidence was 0/50 in controls, 1/50 (2%) in the low-dose group and 5/50 (10%) in the high-dose group. Pairwise comparisons between the control and high-dose groups also indicated a significantly increased tumor incidence in the high-dose group. Combined hepatocellular adenoma and carcinoma incidence was 4/50 (8%) in controls, 5/50 (10%) in the low-dose group and 15/50 (30%) in the high-dose group. Tumor incidence in the high-dose group was significantly greater than in the controls. Overall lymphoma incidence was 10/50 (20%) in controls, 17/50 (34%) in the low-dose group, and 16/50 (32%) in the high-dose group; high-dose group tumor incidence was significantly greater than controls.

Male and female CD-1 mice and Sprague-Dawley CD rats (120/sex/group) were exposed to 0, 0.05 or 0.15 ppm (0, 0.36 or 1.07 mg/m^3) industrial-grade TDI (approximately 80% 2,4 isomer, 20% 2,6 isomer) by inhalation for 6 hours/day, 5 days/week, for 104 (mice), 108 (female rats) or 110 (male rats) weeks (Loeser, 1983). No treatment-induced increase in tumor incidence was noted in rats or mice. However, the rat histopathological evaluation was incomplete. Also, NTP (1986) noted that the exposure levels used corresponded to daily gavage doses of less than 1 mg/kg, and may not have been adequate doses to detect a potential carcinogenic response.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NTP carcinogenicity study (1986) demonstrated that TDI induced tumors in several species (rats and mice), in both sexes in at least one of those species, at multiple sites. The male rat subcutaneous fibroma/fibrosarcoma tumor data was chosen as the basis of a cancer potency factor because it was the most sensitive endpoint in the most sensitive of the responsive species and sexes tested.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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1,1,2-TRICHLOROETHANE (VINYL TRICHLORIDE)

CAS No: 79-00-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1995) except as noted)

Molecular weight	133.42
Boiling point	113.8°C at 760 mm Hg
Melting point	-36.5°C
Vapor pressure	23 mm Hg at 25°C
Air concentration conversion	1 ppm = 5.55 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.6 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 5.7 E-2 $(mg/kg\text{-}day)^{-1}$
[Calculated by US EPA/IRIS (1980, 1994) from male mouse hepatocellular carcinoma tumor data (NCI, 1978), using a linearized multistage procedure, extra risk.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 1,1,2-trichloroethane in humans are known to exist.

Animal Studies

The carcinogenicity of 1,1,2-trichloroethane in rats and mice was studied by the National Cancer Institute (NCI, 1978). Groups of 50 male and female $B6C3F_1$ mice (5 weeks of age) and Osborne-Mendel rats (6 weeks of age) were exposed to technical-grade 1,1,2-trichloroethane (92.7% pure, impurities unspecified) by gavage on 5 consecutive days/week for 78 weeks of a 90-91 week (mice) or 111-113 week (rats) experimental period.

Low and high dose mice received 150 and 300 mg/kg body weight, respectively, for 8 weeks, followed by 200 and 400 mg/kg, respectively, for 70 weeks, followed by 12-13 weeks without treatment, after which the experiment was terminated. The time-weighted average doses were 195 and 390 mg/kg, respectively. Untreated control and vehicle control groups were included (20 animals/sex/group).

Low and high dose rats received 35 and 70 mg/kg body weight, respectively, for 20 weeks, followed by 50 and 100 mg/kg, respectively, for 58 weeks, followed by 34-35 weeks without treatment, after which the experiment was terminated. The time-weighted average doses were 46 and 92 mg/kg, respectively. Untreated control and vehicle control groups were included (20 animals/sex/group).

No statistically significant increase in 1,1,2-trichloroethane-induced tumor incidence was noted in either male or female rats. Increases in hepatocellular carcinoma incidence were noted in all male and female mouse 1,1,2-trichloroethane-exposed treatment groups. The Fisher exact test comparing tumor incidences of dosed to control groups and the Cochran-Armitage test for positive dose-related trend indicated a highly significant association ($p < 0.001$) between hepatocellular carcinomas and 1,1,2-trichloroethane exposure. A positive dose-related association between 1,1,2-trichloroethane exposure and adrenal gland pheochromocytoma incidence in male and female mice was also indicated by the Cochran-Armitage test ($p = 0.003$ for males, $p < 0.001$ for females). Fisher exact tests confirmed these results for high dose female mice ($p = 0.006$) but not for other mouse treatment groups. Mouse tumor incidence data is listed in Table 1.

Table 1. 1,1,2-Trichloroethane-induced $B6C3F_1$ mouse tumor incidence data (NCI, 1978)

Treatment group[1] (mg/kg/day)	Time-weighted[2] average dose (mg/kg/day)	Human equivalent dose[2] (mg/kg/day)	Tumor incidence[3]
			hepatocellular carcinomas
males			
vehicle control	0	0	2/20
low dose	139	9.3	18/49
high dose	279	18.6	37/49
females			
vehicle control	0	0	0/20
low dose	139	9.3	16/48
high dose	279	18.6	40/45

1. Low and high doses: 150 and 300 mg/kg body weight, respectively, for 8 weeks, followed by 200 and 400 mg/kg, respectively, for 70 weeks, followed by 12-13 weeks without treatment.
2. Doses as reported by US EPA (1994).
3. Tumor incidences as reported by US EPA (1994).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NCI (1978) carcinogenicity bioassay of 1,1,2-trichloroethane indicated that 1,1,2-trichloroethane induced tumor formation in male and female $B6C3F_1$ mice. The cancer potency value is based on the dose-response data for hepatocellular carcinomas in male mice.

Methodology

Doses are time-weighted averages adjusted for frequency of exposure (5 of 7 days/week) (US EPA, 1994). Weight of the mice was assumed to be 0.033 kg. A linearized multistage procedure was used to calculate a slope factor of 5.7 E-2 $(mg/kg/day)^{-1}$ and a unit risk value of 1.6 E-5 $(\mu g/m^3)^{-1}$ from the NCI (1978) male mouse hepatocellular carcinoma incidence data. US EPA has stated that the unit risk should not be used if the air concentration exceeds 600 $\mu g/m^3$, since above this concentration the unit risk may not be appropriate.

V. REFERENCES

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TRICHLOROETHYLENE

CAS No: 79-01-6

I. PHYSICAL AND CHEMICAL PROPERTIES (Fan, 1988)

Molecular weight	131.4
Boiling point	87.7° C
Melting point	-72.8° C
Vapor pressure	77 mm Hg @ 25° C
Air concentration conversion	1 ppm = 5.37 mg/m^3 @ 25° C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor:	2.0 E-6 $(\mu g/m^3)^{-1}$
Slope Factor:	7.0 E-3 $(mg/kg\text{-}day)^{-1}$

[Male mouse hepatocellular adenoma and carcinoma incidence, female mouse lung adenocarcinoma and malignant lymphoma incidence (Bell *et al.*, 1978; Henschler *et al.*, 1980; Fukada *et al.*, 1983; Maltoni *et al.*, 1986). Cancer unit risks calculated using a linearized multistage procedure, metabolized dose of TCE determined using a physiologically-based pharmacokinetic (PBPK) model, geometric mean of unit risks (CDHS, 1990a).]

III. CARCINOGENIC EFFECTS

Human Studies

Hardell *et al.* (1981) conducted a retrospective study of 169 men, aged 25 to 85 years in Umea, Sweden, between 1974 and 1978 for histologically confirmed malignant lymphoma. Sixty cases had Hodgkin's disease and 109 had non-Hodgkin's lymphoma. Seven cases and three controls reported high-grade exposure to TCE (odds ratio of 7.88). When compared with 162 cases and 335 controls that were not exposed to high-grade levels of TCE, but including those persons exposed to other chemicals and low-grade levels of TCE, the odds ratio dropped to 4.8, but remained significant ($p < 0.05$, chi-squared test). This study yielded an estimate of the relative risk of developing malignant lymphoma that is more than seven times greater for those who recall a high-grade exposure to TCE compared with those that report no exposure to phenoxy acids, chlorophenols, or organic solvents.

Imperial Chemical Industries conducted a retrospective study of 95 primary liver cancer cases diagnosed between 1951 and 1977 in England (Paddle, 1983). Paddle calculated the expected number of cases of primary liver cancer among workers from 1951 to 1977 to be about 0.3.

Axelson *et al.* (1978) who performed a mortality analysis of a cohort of workers occupationally exposed to TCE from 1955 to 1975, revealed 49 deaths from all causes (62 were expected using Swedish national death-rates). No significant elevated risk of tumor-related deaths was observed. The study size was probably too small to detect a positive association between exposure to TCE

and specific cancer deaths. Therefore, an upper bound on potential cancer risk of TCE to humans cannot be estimated on the basis of data from this study.

US EPA (1985) reported an historical cohort study by Malek *et al.* (1979) of 57 dry cleaners who used TCE as a cleaning solvent. Exposure to TCE was confirmed by urine analyses of the metabolite trichloroacetic acid (TCA). The follow-up time ranged from 5 to 50 years with a median greater than 20 years. The 6 cases of cancer observed were not significantly ($p < 0.05$) different from the number expected in the general population. The small size of the cohort severely limited the power of the study to detect a significant increase in cancer incidence.

Tola *et al.* (1980) established a cohort of 2117 workers (1148 men, 969 women) who had been occupationally exposed to TCE at some time between 1963 and 1976. The observed number of deaths (58) was lower than those expected (84.3). The percentage of deaths attributable to cancer among the workers (11/58 = 19%) was slightly greater than expected, but the difference was not significant ($p > 0.05$). The results from this study did not demonstrate an increased tumor incidence among workers exposed to TCE relative to that of the general Finnish population. Several limitations, such as unknown duration of exposure to TCE and exposure to other organic solvents, prevent a firm conclusion.

Shindell and Ulrich (1985) studied a cohort of 2,646 people who had worked at least 3 months between 1957 and 1983 at a facility that used TCE as a degreasing agent. The cohort showed a healthy worker effect (Standard Mortality Ratio = 0.79 for all causes of death) and much lower levels of heart disease and hypertension than the general population.

There are a number of cohort studies on workers exposed to TCE as a dry-cleaning solvent. Use of TCE as a dry-cleaning solvent began in the 1930's and waned in the 1960's (Waters *et al.*, 1977). Cohort studies of dry-cleaning workers have been reviewed in the past (IARC, 1979; Apfeldorf and Infante, 1981). The value of these studies is greatly limited by an undefined exposure to TCE and is confounded by exposure to other dry-cleaning agents such as tetrachloroethylene, carbon tetrachloride, and petroleum solvents.

Significant ($p < 0.05$) increases in the incidence of cancers of the lung, cervix, and skin contributed to an overall significant excess of cancer deaths among 330 deceased laundry and dry-cleaning workers (Blair *et al.*, 1979). This cohort also showed a slight increase in leukemia, liver, and kidney cancer, and a deficit of breast cancer compared to that expected. The authors warn that the cohort mortality pattern may reflect inherent biases, such as socioeconomic status and smoking, and should be interpreted cautiously.

Katz and Jowett (1981) reported a significant elevated risk for cancers of the kidney ($p < 0.05$) and genitals ($p < 0.01$) in a cohort of 671 deceased white female laundry and dry-cleaning workers. The cohort also exhibited smaller excesses of lymphosarcoma, bladder cancer, and skin cancer. An increase in cervical cancer disappeared when compared to low-wage controls.
A mortality analysis of a cohort of metal platers and polishers revealed significantly ($p < 0.05$) higher proportionate mortality ratios for esophageal and liver cancer deaths relative to a general white male population (Blair, 1980). The positive results were, however, confounded by

occupational exposure to known carcinogens, including chromium, nickel, and other metals, along with acids and other solvents.

Animal Studies

The National Cancer Institute (NCI, 1976) study was the first major long-term cancer bioassay of TCE. TCE was administered by gavage 5 days/week for 78 weeks to B6C3F$_1$ mice and Osborne-Mendel rats of both sexes (n = 50). The industrial grade of TCE used contained 1,2-epoxybutane (0.19%), ethyl acetate (0.04%), epichlorohydrin (0.09%), N-methylpyrrole (0.02%), and diisobutylene (0.03%) as stabilizers.

Male mice received initial daily doses of 2000 mg/kg of body weight in the high-dose group and 1000 mg/kg in the low-dose group. Dose levels were increased during the course of the study resulting in corresponding experimental time-weighted average (TWA) doses of 2339 and 1169 mg/kg. Initial doses to female mice were 1400 and 700 mg/kg, and the corresponding experimental TWA doses were 1739 and 869 mg/kg. For rats, high-dose groups of both sexes initially received 1300 mg/kg, but a lower TWA dose of 1097 mg/kg. The low-dose groups initially received 650 mg/kg, but a lower TWA dose of 549 mg/kg.

Higher incidences of hepatocellular carcinoma in mice were statistically significant in both high- (31/48, $p < 0.001$) and low-dose (26/50, $p = 0.004$) males and high-dose females (11/47, $p = 0.008$) relative to the matched controls.

In contrast to the positive results in the mouse study, analysis of tumor incidences in rats showed no significant difference in specific or total tumors between treated and control groups.

Questions have been raised about the possible impact of the epichlorohydrin (ECH) impurity in the TCE used. While it is possible that ECH contributed to the observed increased tumor incidence in TCE-exposed mice in the NCI (1976) bioassay, it is unlikely that ECH was responsible for all or most of the increased incidence observed. US EPA (1985) also noted that TCE-treated animals in the NCI (1976) experiments were housed in the same rooms as animals treated with other compounds but considered it unlikely that other compounds were responsible for the observed response.

To address the question of contaminant effects on the results of the 1976 NCI mouse study, the National Toxicology Program (NTP, 1983) repeated the carcinogenicity studies in B6C3F$_1$ mice and F344/N rats. The TCE contained no epichlorohydrin and was stabilized with 8 ppm diisopropylamine. Treated mice and high-dose rats received 1000 mg/kg TCE 5 days/week. Low-dose rats received 500 mg/kg TCE 5 days/week. The dosing period lasted 103 weeks.

The incidences of renal tubular-cell adenocarcinoma in male rats dosed with TCE were not significantly different from controls. However, high-dose male rats that survived until the end of the experiment exhibited a statistically significant higher incidence (3/16) of renal tubular-cell adenocarcinoma than the study controls (0/33) or F344/N male rats historical vehicle gavage controls (3/748). The NTP (1983) considers these results equivocal and "inadequate to evaluate the presence or absence of a carcinogenic response" of these rats to TCE. Significantly higher

incidences of hepatocellular carcinoma in dosed male mice (30/50, $p < 0.001$) and dosed female mice (13/49, $p < 0.05$) relative to those of their controls (8/48 and 2/48, respectively) confirmed the positive results of the 1976 NCI mouse study. Dosed female mice were also found to have a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular adenomas (8/49) relative to that of the controls (2/48). This bioassay provided evidence that epichlorohydrin is not needed to induce hepatocarcinogenesis in $B6C3F_1$ mice.

In another NTP study (1988), 4 strains of rat (ACI, August, Marshall, and Osborne-Mendel) received high (1000 mg/kg) or low (500 mg/kg) daily doses of TCE in corn oil by gavage 5 days/week for 103 weeks. The TCE used contained no epichlorohydrin. Test groups consisted of 50 animals of each sex. An increased incidence of renal tubular cell tumors was observed in dosed animals, and an increased incidence of interstitial cell tumors of the testes was observed in dosed Marshall rats. Results of audits conducted in 1983 and 1984, revealed problems with the laboratory conducting the study (NTP, 1988) making interpretation of the bioassay results difficult.

Bell *et al.* (1978) reported the results of a study in which Charles River rats (120/group) and $B6C3F_1$ mice (140/group) were exposed to TCE vapor at concentrations of 100, 300, or 600 ppm for 6 hours/day, 5 days/week, for 104 weeks. Animals were sacrificed upon termination of treatment. The test chemical was greater than 99% pure but contained impurities such as diisobutylene, butylene oxide, ethyl acetate, N-methylpyrrole, and epichlorohydrin.

The incidences of hepatocellular carcinoma in male mice exposed to TCE at concentrations of 100 ppm (28/95), 300 ppm (31/100), and 600 ppm (43/97) were statistically significant ($p < 0.05$, $p = 0.03$, and $p < 0.001$, respectively) when compared to controls (18/99). The level of significance increased when the incidences of both hepatocellular carcinoma and hepatocellular adenoma combined in treated versus control mice are compared by the Fisher exact test. Female mice exposed to TCE at a concentration of 600 ppm exhibited a significant ($p < 0.05$) increase in the incidence of hepatocellular adenomas and hepatocellular carcinomas combined (17/99) relative to that of the controls (8/99). No statistically significant increase in the incidence of any other tumor type was observed among the treated rats. An audit revealed marked deficiencies and flaws in both the rat and mouse studies. According to US EPA (1985), the usefulness of these bioassays is limited by deficiencies in their conduct.

Van Duuren *et al.* (1979) exposed Ha/ICR male and female mice to purified TCE by 3 different routes: skin application, subcutaneous injection, and gavage. No significant increase in any tumor was observed in treated animals by any route of administration.

Henschler *et al.* (1980) exposed 3 species of rodents (Han:NMRI mice, and Syrian hamsters) to concentrations of pure amine-based TCE at 100 and 500 ppm for 6 hours/day, 5 days/week, for 78 weeks. Neither rats, hamsters, nor male mice had significantly increased tumor incidence. Dosed female mice, however, exhibited significantly ($p < 0.05$) higher incidences of malignant lymphoma relative to that of the controls which may be due to immunosuppression by TCE or some other nonspecific agent (US EPA, 1985).

In a study by Fukuda *et al.* (1983), female Sprague-Dawley rats and female ICR mice were exposed to concentrations of 50, 150, and 450 ppm of reagent grade TCE for 7 hours/day, 5 days/week, for

104 weeks (49-51 animals/test group). Chemical analysis revealed the test sample TCE, 99.824% pure, to contain impurities such as carbon tetrachloride, benzene, epichlorohydrin, and 1,l,2-trichloroethane in the vapor phase. The incidence of lung adenocarcinomas among mice in the 2 higher exposure groups (150 ppm, 8/50; 450 ppm, 7/46) was significantly ($p < 0.05$) higher than that of the controls (1/49), but the incidence was not dose-related. The incidence of total lung tumors (adenomas and adenocarcinomas combined) in exposed mice was not significantly different from that of the controls. Statistical analysis of the tumor incidences among rats showed no significant increases or trends.

Henschler *et al.* (1984) tested different samples of TCE with or without epichlorohydrin (ECH) and/or 1,2-epoxybutane, in groups of 50 5-week-old male or female ICR/Ha-Swiss mice. Treated animals received TCE, with or without epoxides, by corn oil gavage 5 days/week for 18 months. Males received 2400 mg/kg, while females received 1800 mg/kg. All doses were reduced after the 40th week giving an experimental TWA daily doses of 1900 mg/kg for males and 1400 mg/kg for females.

Mice dosed with pure TCE did not exhibit a statistically significant increase in the incidence of any tumor type. The administration of TCE with 0.8% ECH or both 0.25% ECH and 0.25% 1,2-epoxybutane was associated with a significant ($p < 0.05$) increase in forestomach papillomas or carcinomas in both sexes. These predicted increased risks from ECH more than account for the observed increased incidence of forestomach tumors cited above. Thus, results from this study support the hypothesis that ECH may be the proximate cause of increased tumor incidence observed in some studies of rodents exposed to ECH-stabilized TCE.

Maltoni *et al.* (1986) reported the results of a series of 8 TCE carcinogenicity experiments performed between 1976 and 1983, using mice and rats. In bioassay BT301, TCE was administered by stomach tube to Sprague-Dawley rats (30/sex/group) at dose levels of 50 or 250 mg/kg, 4 to 5 days/weeks, for 52 weeks. No significant increase in any tumor was observed in treated animals. This was probably due to the dosing period of 52 weeks which was less than a potential lifetime exposure.

Two short-term inhalation bioassays were conducted by Maltoni *et al.* (1986) with Sprague-Dawley rats (BT302) and Swiss mice (BT303). The animals were exposed to 100 or 600 ppm TCE for 7 hours/day, 5 day/weeks, for 8 weeks. No statistically significant effect was observed.

Bioassays BT304-bis were two similar long-term inhalation experiments whose results were combined and evaluated together. Sprague-Dawley rats were exposed to either 100, 300 or 600 ppm TCE for 7 hours/day, 5 days/week, for 104 weeks. A statistically significant, exposure-related increase in the incidence of Leydig cell tumors of the testes was observed in treated rats: 31/130 at 600 ppm, 30/130 at 300 ppm and 16/130 at 100 ppm, compared to 6/135 in the control group. Five of 260 rats exposed to 600 ppm TCE developed kidney adenocarcinomas that, although lacking statistical significance, must be considered biologically significant due to their rarity.

In experiment BT305, Swiss mice were exposed to TCE at a concentration of 100, 300 or 600 ppm for 7 hours/day, 5 days/week, for 78 weeks. Males exposed to the 2 higher levels showed statistically significant increases in the incidence of pulmonary tumors (27/90 at 600 ppm, 23/90

at 300 ppm) relative to that of the control group (11/90). Males exposed to 600 ppm TCE also had a higher frequency of hepatomas (13/90, $p < 0.05$) than that of controls (4/90). Females did not show any significant response to TCE exposure in this bioassay.

Bioassays BT306 and BT306-bis were both conducted with B6C3Fl mice under similar exposure conditions as above. A dose-related increase in the incidence of pulmonary tumors was observed in females but was significant ($p < 0.05$) only at 600 ppm (15/90) relative to the control group (4/90).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Based on their designation of "limited evidence" of carcinogenicity in animals and "inadequate evidence" of carcinogenicity in humans, IARC (1984) determined that TCE cannot be classified as to its carcinogenicity to humans. US EPA placed TCE in Group B2, a probable human carcinogen (US EPA, 1985). CDHS staff reviewed the literature and disagreed with IARC's conclusion. CDHS considers TCE to be carcinogenic and not to have a threshold for carcinogenicity (CDHS, 1990a).

A quantitative risk assessment for TCE was conducted by CDHS (1990a) using the dose-response data for carcinogenicity from four inhalation studies in mice (Bell *et al.*, 1978; Henschler *et al.*, 1980; Fukada *et al.*, 1983; Maltoni *et al.*, 1986).

Methodology

The metabolized dose for TCE for each of the studies evaluated was determined using a physiologically-based pharmacokinetic model (PBPK) and used for the calculation of carcinogenic potency. Because absorbed TCE is completely metabolized, metabolized dose mirrors applied dose. The metabolized dose of TCE was included because it takes into account uptake and distribution factors. The data obtained for uptake and distribution factors are in good agreement with experimental results obtained with human volunteers. Interspecies variation was accounted for by utilizing surface area scaling.

Carcinogenic responses in the inhalation studies included increased incidences of hepatocellular carcinoma and adenoma in male mice and increased incidences of lung adenocarcinomas and malignant lymphomas in female mice. Since most tumors were discovered at the time of sacrifice rather than at the time of their appearance, the GLOBAL79 and GLOBAL86 computer programs for the linearized multistage modes, without a time-to-tumor factor, were used for the low-dose risk assessment. The above adjustments to the animals' exposure results in a lifetime time-weighted average dose, either applied or metabolized. The range of 95% upper confidence limit (UCL) potency estimates (q_1*) obtained using the human equivalent applied and metabolized doses and the tumor incidences in the four inhalation studies notes above is 0.006 to 0.098 $(mg/kg\text{-}day)^{-1}$. Based on the same data, the individual risk for a 70-year lifetime exposure of a 70 kg person breathing 20 m^3 per day of ambient air containing 1 $\mu g/m^3$ (0.19 ppb) of TCE is 8×10^{-7} to 1×10^{-5}. A best estimate of the unit risk was obtained by taking the geometric mean of the unit

risks from the four inhalation studies. From the metabolized dose approach a unit risk of 2.0×10^{-6} $(\mu g/m^3)^{-1}$ was obtained, and from the applied dose a unit risk of 3.0×10^{-6} $(\mu g/m^3)^{-1}$ was obtained. CDHS (1990b) chose the cancer unit risk value of 2.0×10^{-6} $(\mu g/m^3)^{-1}$ calculated using the metabolized dose approach as the "best value" for TCE inhalation cancer unit risk.

Table 1: Dose-response data used by CDHS (1990a) in quantitative risk assessment for trichloroethylene exposure[1]

Study Species / sex Strain	Tumor Type	Daily experimental applied concentration	LTWA Metabolized Dose[2] (mg/kg-day)	Tumor Incidence[3]
Bell *et al.,* 1978	hepatocellular	0 ppm – 6 hr	0	20/99
Mice (male)	carcinoma or	100 ppm – 6 hr	42.3	35/95
$B6C3F_1$	adenoma	300 ppm – 6 hr	127	38/100
		600 ppm – 6 hr	254	53/97
Henschler *et al.*, 1980	malignant	0 ppm – 6 hr	0	9/29
Mice (female)	lymphoma	100 ppm – 6 hr	33.2	17/30
Han:NMRI		500 ppm – 6 hr	166	18/28
Fakuda *et al.*, 1983	lung	0 ppm – 7 hr	0	1/49
Mice (female)	adenocarcinoma	50 ppm – 7 hr	25.8	3/50
ICR		150 ppm – 7 hr	77.4	8/50
		450 ppm – 7 hr	232	7/46
Maltoni *et al.*, 1986	malignant	0 ppm – 7 hr	0	4/90
Mice (male)	hepatoma	100 ppm – 7 hr	35.3	2/90
Swiss		300 ppm – 7 hr	106	8/90
		600 ppm – 7 hr	212	13/90

[1]Source: CDHS (1990a).
[2]Lifetime, time-weighted-average metabolized dose.
[3]Tumor incidence denominator excludes animals dying before the occurrence of the first corresponding tumor type observed in the NCI (1976) and NTP (1983) studies. See CDHS (1990a) for more detail.

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2,4,6-TRICHLOROPHENOL

CAS No: 88-06-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	197.5
Boiling point	246°C
Melting point	69°C
Vapor pressure	0.012 mm Hg @ 25°C
Air concentration conversion	1 ppm = 8.00 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.0 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 7.0 E-2 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no human carcinogenicity studies available for 2,4,6-trichlorophenol.

Animal Studies

Innes *et al.* (1969) administered 100 mg/kg body weight 2,4,6-trichlorophenol by oral gavage to two F_1 generation strains of mice, B6C3F_1 (C57BL/6 × C3H/Anf) and B6AKF_1 (C57BL/6 × AKH) (18/sex/strain) from day 7 to 28 of life, without adjusting the initial dose to account for weight gain. After 28 days, 2,4,6-trichlorophenol was added to feed at 260 ppm for 74 weeks. Surviving animals were sacrificed at 78 weeks. Survival data and tumor incidence are reported in Table 1. Incidence of tumors of all types was found to be significantly increased only among treated B6C3F_1 males (p =0.004; Fisher's exact test). Incidence of reticulum cell tumors was also found to be significantly increased among pooled male and female treated B6C3F_1 animals (p =0.005). Pairwise comparison of summary incidence data shows an increased incidence of hepatomas among treated B6C3F_1 females (p =0.028) and reticulum cell sarcomas among treated B6C3F_1 males (p =0.021). Some results of this study were published separately (Bionetics Research Laboratories, 1968).

A lifetime feeding study of 2,4,6-trichlorophenol was conducted by the National Cancer Institute in two species, B6C3F_1 mice and F344 rats (NCI, 1979). Rats (50/sex/group) were treated with 5,000 or 10,000 ppm 2,4,6-trichlorophenol in feed for 106-107 weeks, plus a control group of 20 rats/sex given only standard feed. Tumor incidence data are presented in Table 2. Significant

increases in hematopoietic tumor (malignant lymphoma and monocytic leukemia) incidence was observed among males of both the low-dose ($p = 0.013$) and high-dose ($p = 0.002$) groups.

In the same study (NCI, 1979), $B6C3F_1$ mice were treated with 2,4,6-trichlorophenol in feed for 105 weeks. Male mice (50/group) were treated with 5,000 or 10,000 ppm 2,4,6-trichlorophenol. Female mice (50/group) were initially treated with diets containing 10,000 and 20,000 ppm 2,4,6-trichlorophenol; however, indications of reduced growth rate at 38 weeks led the investigators to reduce the level of compound to 2,500 and 5,000 ppm 2,4,6-trichlorophenol for the balance of the experiment, leading to time-weighted average concentrations of 5,214 and 10,428 ppm. The control group consisted of mice (20/sex) given the standard diet. Tumor incidence data are presented in Table 3. A significant increase in hepatoma incidence was observed among male mice in both treatment groups and among female mice in the high dose group ($p < 0.001$, Fisher's exact test).

In an effort to establish whether 2,4,6-trichlorophenol may be acting as a tumor initiator, Bull *et al.* (1986) treated female SENCAR mice (30/group) with 200 mg/kg 2,4,6-trichlorophenol by several routes of exposure, including gavage, intraperitoneal injection, subcutaneous injection, and dermal application, followed by dermal application of 1.0 μg 12-o-tetradecanoylphorbol-13-acetate three time per week for 20 weeks. No skin tumors were found when survivors were examined 52 weeks after first exposure.

Table 1. Survival and tumor incidence in male and female $B6AKF_1$ and $B6C3F_1$ mice treated with 2,4,6-trichlorophenol (Innes *et al.*, 1969).

		tumor incidence				
		$B6C3F_1$			$B6AKF_1$	
tumor type	treatment[1]	total	male	female	male	female
total tumors	treated	16/36	9/18[2]	7/18[3]	3/17	2/17
	control	30/166	22/79	8/87	16/90	7/82
hepatomas	treated	5/36[4]	3/18	2/18[5]	1/18	1/18
	control	17/166	17/79	0/87		
reticulum cell sarcomas	treated	6/36[6]	4/18[7]	2/18	0/18	1/18
	control	5/166	3/79	2/87		

[1] $B6C3F_1$ and $B6AKF_1$ mice were treated with 100 mg/kg body weight 2,4,6-trichlorophenol by oral gavage from day 7 to 28 of life, then fed diet containing 260 ppm 2,4,6-trichlorophenol for 74 weeks, at which time surviving animals were sacrificed.
[2] $p = 0.064$, Fisher's exact test.
[3] $p = 0.004$, Fisher's exact test.
[4] $p = 0.059$, Fisher's exact test.
[5] $p = 0.028$, pairwise comparison of summary incidence data.
[6] $p = 0.005$, Fisher's exact test.
[7] $p = 0.021$, pairwise comparison of summary incidence data.

Table 2. Tumor incidence in Fischer F344 rats treated with 2,4,6-trichlorophenol (NCI, 1979).

tumor type/ treatment[1]		tumor incidence male	female
total hemato-	control	4/20	3/20
poietic tumors	low-dose	25/50[2]	11/50
	high-dose	29/50[3]	13/50
malignant	control	1/20	0/20
lymphoma	low-dose	2/50	0/50
	high-dose	0/50	2/50
monocytic	control	3/20	3/20
leukemia	low-dose	23/50[4]	11/50
	high-dose	29/50[5]	11/50

[1] F344 rats were treated with diet containing 5,000 or 10,000 ppm 2,4,6-trichlorophenol for 106-107 weeks at which time animals were sacrificed.
[2] $p = 0.019$, Fisher's exact test.
[3] $p = 0.004$, Fisher's exact test.
[4] $p = 0.013$, Fisher's exact test.
[5] $p = 0.002$, Fisher's exact test

Table 3. Hepatoma incidence in $B6C3F_1$ mice treated with 2,4,6-trichlorophenol (NCI, 1979).

treatment[1]/hepatoma type		tumor incidence male	female
control	adenoma	3/20	1/20
	carcinoma	1/20	0/20
	total	4/20	1/20
low-dose	adenoma	22/49	12/50
	carcinoma	10/49	0/50
	total	32/49[2]	12/50[3]
high-dose	adenoma	32/47	17/48
	carcinoma	7/47	7/48
	total	39/47[2]	24/48[2]

[1] Male $B6C3F_1$ mice were treated with diet containing 5,000 or 10,000 ppm 2,4,6-trichlorophenol for 105 weeks, then sacrificed. Female $B6C3F_1$ mice were treated with diet containing 10,000 or 20,000 ppm 2,4,6-trichlorophenol for 38 weeks at which time diet concentrations were reduced to 2,500 or 5,000 ppm 2,4,6-trichlorophenol, respectively, until they were sacrificed at 105 weeks.
[2] $p < 0.001$, Fisher's exact test.
[3] $p = 0.059$, Fisher's exact test.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Two studies, Innes *et al.* (1969) and NCI (1979), have been deemed adequate for the derivation of cancer potencies. Both demonstrate statistically significant increases in tumor incidence among 2,4,6-trichlorophenol exposed animal populations. Innes *et al.* (1969) show increased incidence of reticulum cell sarcomas in male $B6C3F_1$ mice and heptomas in female $B6C3F_1$ mice. The NCI (1979) study shows increased incidence of hepatomas in both male and female $B6C3F_1$ mice, and leukemia in male Fischer F344 rats. The US EPA estimate of cancer potency of 2,4,6-trichlorophenol derived from the rat study is lower than that for mice (US EPA, 1988 and below). Since selection of the potency value is made on the basis of the most sensitive species, site, and study in the absence of evidence that the data are not representative, tumor induction in $B6C3F_1$ mice has been chosen as the basis for derivation of a cancer potency value for 2,4,6-trichlorophenol.

Methodology

The multistage Doll-Armitage model polynomial was fit to tumor incidence data from Innes *et al.*(1969) and NCI (1979) (Armitage and Doll, 1954). Dosage estimates for the studies were based on food intake assumptions of 12% and 13% of body weight for male and female mice, respectively (Gold, 1984). In the NCI (1979) study, final dose values were calculated to be 1200 and 600 mg/kg-day for high- and low-dose females, and 1356 and 678 mg/kg-day for high- and low-dose males. In the Innes *et al.*(1969) study, dosage estimates were based on the method of Crouch to account for variation in dosing during the course of the experiment (Crouch, 1983). Dosage estimates were calculated to be 32.5 and 34.7 mg/kg-day for male and female mice, respectively. Using a multistage polynomial, the cancer potency was derived using the probability of dying with a tumor from a given dose and the background lifetime cancer incidence (Crump and Howe, 1984). The upper 95% confidence bound on the cancer potency was termed q_1^*. Estimates of q_1^* for tumor induction in $B6C3F_1$ mice are presented in Table 4.

Calculation of the cancer potency in animals (q_{animal}) can be made using q_1^* and the following relationship, where T is the natural lifespan of the animal (104 weeks) and T_e is the experimental duration (Innes *et al.*, T_e = 104 weeks; NCI, T_e = 78 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

The resulting q_{animal} can be converted to human cancer potency (q_{human}) based on the following relationship, where bw_{animal} is the assumed body weight for the test species (Innes *et al.* (1969), bw_{animal} = 0.030 kg; NCI (1979), bw_{animal} = 0.04 kg-males and 0.035 kg-females) and bw_{human} is the assumed human body weight (70 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

Table 4. Derivation of cancer potencies from NCI (1979) and Innes *et al.*(1969).

study	tumor/group	q_1^* $(mg/kg\text{-}day)^{-1}$	q_{animal} $(mg/kg\text{-}day)^{-1}$	q_{human} $(mg/kg\text{-}day)^{-1}$	maximum likelihood estimate	LCB (95%)
NCI, 1979	hepatoma/ male	0.0017	12.1	0.021	0.016	0.004
	hepatoma/ female	0.0006	12.6	0.008	0.003	0
Innes, 1969	reticulum cell sarcoma/ male	0.035	0.035	0.47	0.2	0.05
	hepatoma/ female	0.021	0.021	0.28	0.11	0.03

LCB = Lower confidence bound.

The highest upper bound cancer potency for humans (q_{human}) was derived from the results of the Innes *et al.* (1969) study showing reticulum cell tumor induction in male $B6C3F_1$ mice. However, confidence in this value is reduced because the number of animals used in the study is small (18/group) and data were reported incompletely. Innes *et al.* (1969) and NCI (1979) both present data showing induction of hepatomas in female $B6C3F_1$ mice. However, lack of overlap between the 95% confidence bounds of the two potencies suggests there may be a greater sensitivity to this effect in the strain used by Innes *et al* (1969). Selection of a cancer potency value is made based on the most sensitive species, site, and study in the absence of evidence indicating the value is not representative (CDHS, 1985). On balance, the evidence favors neither the higher sensitivity of the Innes *et al.* (1969) study nor the high quality of the NCI (1979) study. For this reason, a method of Anderson (1983) was chosen for combining the results of these studies. The resulting cancer potency derived from the geometric mean of the four potencies shown in Table 4 is 0.07 $(mg/kg\text{-}day)^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.0 E-5 $(\mu g/m^3)^{-1}$.

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URETHANE

CAS No: 51-79-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	89.09
Boiling point	182-184°C
Melting point	48-50°C
Vapor pressure	0.36 mm Hg @ 25°C
Air concentration conversion	1 ppm = 3.64 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.9 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.0 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a potency factor derived by RCHAS/OEHHA (CDHS, 1989)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no studies available directly linking urethane exposure to induction of cancer in humans. Urethane is, however, frequently present in alcoholic beverages, particularly brandy, whisky and wine, and IARC has recognized alcoholic beverages as carcinogenic to humans (IARC, 1988). Although other compounds present in alcoholic beverages may account for this effect, urethane may be a contributor to alcohol-related increases in cancer incidence.

Animal Studies

CDHS (1989) has identified nearly 200 studies which demonstrate the carcinogenicity of urethane in animals. Below are summaries of those determined to be most relevant in the establishment of the reference cancer potency value, with emphasis on studies performed by realistic routes of exposure and in multiple doses.

Pietra and Shubik (1960) exposed male and female Syrian golden hamsters (10/sex) to drinking water containing 0.2% urethane for life. Control animals (49 male and 14 female) received plain drinking water. Animals were autopsied at death. Among exposed animals, males showed increased incidence of dermal melanotic tumors (7/10 exposed, 1/49 control; $p < 0.01$, Fisher's exact test). Male and female animals showed an increased incidence of forestomach papillomas (males: 4/10 exposed, 0/49 control; females: 6/10 exposed, 0/14 control; $p < 0.01$). Other tumors noted in exposed animals but not control animals include single cases of thyroid adenoma and liver hemangiosarcoma in males, malignant lymphoma and bronchial adenoma in females.

Toth *et al.* (1961a) exposed Syrian golden hamsters (31 male; 30 female) to drinking water containing 0.2% urethane. Control groups of 54 male and 47 female received plain drinking water. Dosing began at 5 weeks and continued to 25 weeks at which point the drinking water urethane concentration was increased to 0.4%. At 40 weeks treatment was discontinued due to diarrhea among the animals. At 48 weeks, treatment with 0.4% urethane resumed, but was discontinued permanently at 50 weeks due to diarrhea. Survival was significantly decreased in exposed male and female hamsters. Among exposed animals, significant increases in incidence of dermal melanotic tumors (12/27 exposed males vs. 0/54 control males; 11/25 exposed females vs. 0/47 control females; $p \leq 10^{-6}$; Fisher's exact test), forestomach papillomas (22/27 exposed vs. 0/54 control, $p < 10^{-15}$, males; 18/25 exposed vs. 1/47 control; $p < 10^{-9}$, females) and carcinomas (3/27 exposed vs. 0/54 control; $p = 0.04$, males; 2/25 exposed vs. 0/47 control; $p = 0.1$, females), pulmonary adenomatosis (3/27 exposed vs. 0/54 control; $p = 0.04$, males), mammary tumors (3/25 exposed vs. 0/47 control; $p = 0.04$, females), hepatomas (3/27 exposed vs. 0/54 control; $p = 0.04$, males), and hepatic or splenic hemangiomas (5/27 exposed vs. 0/54 control; $p = 0.04$, males) were found.

Toth and Boreisha (1969) exposed Syrian golden hamsters (48 male and 52 female) to drinking water containing 0.1% urethane for life, beginning at 5 weeks of age. Control groups (100/sex) received plain drinking water. Survival was significantly decreased in exposed male and female animals. An increased incidence of dermal melanocytosis (26/49 exposed males vs. 1/88 control males; 25/41 exposed females vs. 0/79 control females; $p = 10^{-14}$; Fisher's exact test), forestomach papillomas (36/49 exposed vs. 6/88 control, $p = 10^{-15}$, males; 35/44 exposed vs. 2/84 control, $p = 10^{-20}$, females) and adenomatous polyps of the cecum (4/40 exposed vs. 0/79 control, $p = 0.01$, males; 7/33 exposed vs. 0/72 control, $p = 0.001$, females) was noted in both males and female animals. Among females an increased incidence of gall bladder papillomas, adrenal cortex carcinomas, thyroid carcinomas, ovarian carcinomas, vaginal carcinomas, and lung adenomatosis was observed ($p < 0.05$). Hemangiosarcoma incidence was increased in exposed males.

Tannenbaum *et al.* (1962) exposed Sprague-Dawley rats (15/group) to drinking water containing 0.1% urethane. Two "young" groups, one virgin females and the other males, were treated from age 7 weeks to 32 weeks. A third group of virgin females was treated for 14 weeks from age 32 weeks. Age and sex matched control groups of 15 each receiving plain drinking water were included in the study. Animals were autopsied at the time of natural death unless sacrificed when moribund. Survival was reduced in the treated groups. Incidence of Zymbal gland carcinoma was increased in treated "young" male rats (4/15 treated vs. 0/15 control, $p = 0.05$, Fisher's exact test) and female rats (3/15 treated vs. 0/15 control, $p = 0.11$). Control animals showed higher incidence of mammary tumors than treated animals, most likely because of the reduced survival of treated animals. Tumors noted among treated animals, but not control animals, include malignant lymphoma, sarcoma, and kidney tumors.

Schmähl *et al.* (1977) and Port (1976) report on exposure of rats and mice to urethane in drinking water. Tumor specific incidence data are reported by Port (1985). Male and female NMRI mice and Sprague-Dawley rats (40/sex/group) were exposed to urethane in drinking water from 8 weeks of age for their lifetime such that the daily dose rate was 0, 0.1, 0.5, 2.5, or 12.5 mg/kg body weight. Animals were given the appropriate dose in 20 ml drinking water. Animals were observed until their natural death. Among mice, significant increases in tumor incidence ($p < 0.1$ by Fisher's

exact test) were found for pulmonary adenoma in males (6/40, 9/40, 14/40 in the 0.5, 2.5, and 12.5 mg/kg dose groups, respectively vs. 0/40 controls), and pulmonary adenoma (12/40 treated with 12.5 mg/kg urethane vs. 5/40 controls), pulmonary carcinoma (5/40 treated with 12.5 mg/kg urethane vs. 0/40 controls), angiosarcoma of the liver (4/40 treated with 12.5 mg/kg urethane vs. 0/40 controls), and mammary carcinoma (4/40 treated with 12.5 mg/kg urethane vs. 0/40 controls) in females. For each of these tumor types, the trend toward increased incidence was found to be dose-related ($p < 0.01$ by Mantel-Haenszel trend test). Among female rats, a significant increase in the incidence of mammary carcinoma (1/40, 2/40, 9/40 in the 0.5, 2.5, and 12.5 mg/kg urethane dose groups, respectively vs. 0/40 in the 0.1 mg/kg urethane dose group, $p = 0.0011$) and the combined incidence of mammary adenoma and carcinoma was found (2/40, 3/40, 4/40, 13/40 in the 0.1, 0.5, 2.5, and 12,5 mg/kg urethane dose groups, respectively vs. 2/40 in the 0.1 mg/kg urethane dose group, $p = 0.0016$ by Fisher's exact test). The incidence data for the untreated control animals were lost. The trend was found to be dose-related ($p < 10^{-4}$ by Mantel-Haenszel trend test).

Klein *et al.* (1962) treated 7-8 day old $B6AF_1/J$ mice (C57BL/6 female × A/J male) with 2.8 or 5.5 mg urethane in 0.05 ml 0.1% dioctylester of sodium sulfosuccinic acid by oral gavage 3 times per week for 5 weeks. Control groups for the low-dose group included both males receiving vehicle only and males receiving no treatment. Males and females receiving no treatment served as a control for the high-dose group. Survivors of the treatment period comprised the study group and ranged from 39 to 57 animals. Survival in the treated groups was significantly lower than in controls. Among animals receiving the higher dose of urethane, treated males had a higher incidence of leukemias (32/42 treated vs. 0/38 vehicle controls, $p = 10^{-13}$; Fisher's exact test), lung adenomas (42/42 treated vs. 10/38 vehicle controls, $p = 10^{-12}$) and hepatoma (4/42 treated vs. 0/38 vehicle controls, $p = 0.07$) than animals receiving vehicle alone. Among animals receiving the lower dose of urethane, males showed a higher incidence of lung adenomas (40/41 treated vs. 3/40 untreated controls, $p = 10^{-17}$), hepatoma (23/41 treated vs. 0/40 untreated controls, $p = 10^{-8}$), and leukemias (19/41 treated vs. 0/40 untreated controls, $p = 10^{-6}$) relative to untreated control animals. In the same dose group, females showed a higher incidence of leukemias (16/40 treated vs. 1/57 controls, $p = 10^{-6}$) , lung adenomas (39/40 treated vs. 9/57 controls, $p = 10^{-6}$), hepatomas (5/40 treated vs. 0/57 controls, $p = 0.01$), and forestomach papillomas (3/40 treated vs. 0/57 controls, $p = 0.07$) relative to untreated control animals.

Della Porta *et al.*(1963a) exposed 5 groups of male and female CTM mice to drinking water containing 0.4% urethane in several exposure scenarios ranging from a total exposure time of 5 to 15 days. Effective group size was the number of survivors at 25 weeks for treated animals (range: 30-83 mice) and survivors at 45 weeks for controls (88 males and 99 females). Among all exposed animals there was a significant increase in the incidence of lung adenomas over control animals ($p < 10^{-8}$; Fisher's exact test). Among all exposed female mice, the incidence of lymphosarcoma was increased over controls ($p < 0.05$). Among all exposed male mice, the incidence of reticulosarcoma was increased over controls ($p < 0.04$). Other tumor types showing some significant increase ($p < 0.05$) in incidence over controls in some but not all exposure scenarios include lymphosarcomas and Harderian gland adenomas in male mice, and mammary gland adenocarcinoma, hepatoma, and Harderian gland adenomas in female mice.

Table 1. Tumor incidence in CTM mice exposed to drinking water containing 0.4% urethane (Della Porta *et al.*, 1963a).

	A*		B		C		D		E		control	
tumor type	male	female	male	female	male	female	male	female	male	female	male	female
lung adenoma	29/36	53/63	42/56	53/83	58/71	51/68	19/45	26/48	25/30	30/39	2/88	7/99
lympho-sarcoma	12/36	17/63	14/56	13/83	14/71	15/68	8/45	7/48	2/30	10/39	4/88	5/99
reticulo-sarcoma	3/36	4/63	6/56	1/83	8/71	6/68	3/45	2/48	3/30	2/39	0/88	7/99

*Exposure scenarios: A - two 10 day exposures, separated by 10 days; B - one 10 day exposure; C - three 5 day exposures, separated by 10 days; D - two 5 day exposures, separated by 10 days; E - one 5 day exposure.

Della Porta *et al.* (1963b) conducted another study similar to that described above, but exposed CTM mice (75 male and 108 female) to drinking water containing 0.4% urethane for 10 days or two 10-day periods separated by 10 days. Control animals received plain drinking water (130 males and 120 females). Surviving animals were sacrificed at 75 weeks. The effective group size was considered the size of the group at the time of appearance of the first malignant lymphoma. Among male and female mice in both treatment groups, the incidence of malignant lymphoma was elevated over control animals (15/40 in the 20-day treatment group, 19/61 in the 10-day treatment group, vs. 4/103 controls, $p < 10^{-4}$ by Fisher's exact test). Among female mice, the incidence of mammary gland tumors was increased over controls (21/70 in the 20-day treatment group vs. 15/108 controls,$p < 0.008$; 34/83 in the 10-day treatment group vs. 15/108 controls, $p = 10^{-4}$). Other tumors observed included lung adenomas, mammary carcinomas, liver angiosarcomas, hepatomas, Harderian gland adenomas, and forestomach and skin papillomas.

Della Porta *et al.* (1967) exposed four inbred mouse strains (C57BL, C3H, C3Hf, SWR) and one hybrid mouse strain ($B6C3F_1$) to drinking water containing 0.4% urethane. Five-week old male and female animals were exposed for 15-20 days in 5- or 10-day periods separated by 10 days, and 10-day old animals were exposed five times, once every other day. The effective group size for analysis of tumor incidence was considered the initial number of animals less those dying without tumors before the 25th week for urethane-exposed animals or the 45th week for control animals. The effective group size ranged from 30 to 158 animals for animals showing significant increases in tumor incidence. Among male and female $B6C3F_1$ mice exposed for 10 days, the incidence of Harderian gland tumors (45/51 exposed vs. 3/32 control, males; 44/81 exposed vs. 0/39 control, females; $p < 10^{-10}$, Fisher's exact test) and lung adenomas (23/51 exposed vs. 7/32 control, males; 18/81 exposed vs. 4/39 control, females; $p < 0.1$) was increased. Among female $B6C3F_1$ mice alone, the incidence of thymic lymphosarcoma (10/81 exposed vs. 0/39 control; $p = 0.02$) and mammary gland adenocarcinoma (23/81 exposed vs. 1/39 control; $p = 10^{-3}$) was also increased. Among male and female C3Hf mice exposed for 15 days, the incidence of lung adenoma (45/79 exposed vs. 3/30 control, males, $p = 10^{-5}$; 46/87 exposed vs. 12/62 control, females, $p = 10^{-4}$) and Harderian gland adenoma (32/79 exposed vs. 3/30 control, males, $p = 0.001$; 25/87 exposed vs. 2/62 control, females, $p = 10^{-4}$) was increased. Among female C3Hf mice alone, the incidence of mammary adenocarcinoma (36/87 exposed vs. 6/62 control; $p = 10^{-5}$), thymic lymphosarcoma (2/87 exposed vs. 0/39 control; $p = 0.02$), and hepatoma (29/87 exposed vs. 15/62 control; $p = 0.15$) was increased.

Innes *et al.* (1969) treated male and female $B6C3F_1$ and $B6AKF_1$ mice (24/sex) with 158 mg/kg body weight urethane (on day 7) by oral gavage from day 7 to 28 of life. Thereafter, animals were exposed to a concentration of 600 ppm urethane in their diet. Control groups (90/sex/strain)

received received vehicle alone, then normal diet. Surviving animals were sacrificed and autopsied between 78 and 88 weeks of age. Significant increases in the incidence of pulmonary adenomas or carcinomas and hepatomas were observed in treated animals of both sexes and strains (see Table 2, $p < 0.05$, Fisher's exact test). The incidence of angiomas was increased in male and female $B6AKF_1$ mice ($p < 0.01$). Harderian gland adenomas were increased in $B6C3F_1$ females and $B6AKF_1$ males and females ($p < 0.01$). Lymphomas were increased in $B6AKF_1$ male mice ($p < 0.01$).

Table 2. Tumor incidence data on two strains of mice exposed to urethane by oral gavage and in drinking water (Innes, 1969).

	$B6C3F_1$				$B6AKF_1$			
	male		female		male		female	
tumor type	treated	control	treated	control	treated	control	treated	control
pulmonary adenomas or carcinomas	6/20	5/79	6/23	3/87	15/22	10/90	17/19	3/82
Hepatomas	8/20	8/79	12/23	0/87	14/22	5/90	5/19	1/82
Angiomas					4/22	0/90	11/19	0/82
Harderian gland adenomas			5/23	4/87	11/22	0/90	7/19	0/82
lymphomas					6/22	1/90		

Tomatis *et al.* (1972) report on a study in which urethane treatment was used as a positive control in a study of DDT's long-term health effects. Male and female CF-1 mice (60/sex) were exposed continuously to drinking water containing 0.01% urethane for 6 generations. Control animals (60/sex) were given plain drinking water. Parent generation animals were sacrificed at 140 weeks and subsequent generations at 130 weeks. Survival among animals of both sexes was reduced by urethane treatment. For statistical purposes, group size was determined by the number of animals surviving at the time of the appearance of the first tumor of any type. Comparison of groups was made by combining data from all generations. Lung tumor incidence was found to be significantly increased in urethane treated male mice (261/314 exposed vs. 157/328 controls, $p = 10^{-21}$, Fisher's exact text) and female mice (181/241 exposed vs. 124/340 controls, $p = 10^{-20}$). Among treated males, lymphoma incidence was increased (100/314 exposed vs. 79/328 controls, $p = 0.02$) and among treated female mice, osteoma incidence was increased (55/241 exposed vs. 39/340 controls, $p < 0.001$).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Although IARC (1988) has recognized urethane as a possible human carcinogen, inadequate information relating cancer incidence to specific exposure levels precludes the development of a cancer potency value from human data. An abundant body of literature relating urethane exposure to the development of tumors in animals is available. Standard carcinogenesis models applied to the data, along with some data useful for making pharmacokinetic adjustments, permit quantitative estimates of cancer potency from the animal studies. Estimated potency values are summarized below along with the rationale for development of the reference unit risk value.

Methodology

Estimates of cancer potency from the available data on the carcinogenicity of urethane can be made based on the multistage procedure initially described by Armitage and Doll (1954). For studies in which variable dosing over time has occurred, a mathematical dosage modification was made based on the estimation procedures described by Crouch (1983) and Crump and Howe (1984). Several studies have been conducted which also permit making pharmacokinetic adjustments in the estimation of carcinogenicity. Specifically, a model has been developed describing the pharmacokinetics of urethane either administered continuously or in discrete increments (Mitchell and Gauthier Associates Inc., 1975). Urethane distribution in the body and kinetic constants for rats and mice have been determined from the studies of O'Flaherty and Sichak (1983) and Nomeir *et al.* (1989). When appropriate, a proportional correction factor was applied to the experimental dose rate to estimate the effective dose rate.

Estimates of human cancer potency (q_{human}) were estimated from derived animal values (q_{animal}) based on a scaling factor proportional to the third power of the human to experimental animal body weight ratio (bw_h and bw_a). The relationship is described as follows:

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

Table 3 presents the estimated human cancer potency values from animal studies in which significantly increased in tumor incidences have been found, including the species studied, most sensitive site of tumor development, the multistage procedure applied to the incidence data, and whether a pharmacokinetic adjustment was applied. For details of the methodology and assumptions made in deriving the potency, see Salmon and Zeise (1991). A measure of the "expected" or "average" value of the potency (q_1) estimated from the experimental data, termed q_{bar} , is also presented. The q_{bar} is derived when there are a large number of positive data points and the probability mass function (arithmetic mean) becomes less meaningful. It is derived by numerical computation, using the same continuous, asymptotic distribution as when deriving the upper confidence limit. The q_{bar} value is derived as follows,

$$q_{bar} = \int_0^\infty f(q_1) \cdot q_1 \, dq_1$$

with $f(q_1)$ as the frequency distribution whose log-likelihood function follows a chi-square distribution.

The selection of a cancer potency value should be made on the basis of the most sensitive site, species, and study, in the absence of evidence that such a value is not representative. The hamster studies of Pietra and Shubik (1960) and Toth *et al.* (1961a, 1969) indicate the hamster may not be as sensitive as the mouse when individual tumor sites are compared. Although the limited data available do not rule out the possibility that the hamster may be the more sensitive species, data are not available to make quantitative comparisons of hamsters and mice. This, coupled with the fact that there are extensive studies on mice, suggests the mouse urethane studies are more appropriate than hamster studies in developing a cancer potency value. Only two studies in the rat are useful for deriving cancer potency values. The Tannebaum *et al.* (1962) study showing development of Zymbal's gland tumors is of limited use since there is no supporting evidence that this site of tumor development is the most sensitive. The Schmähl *et al.* (1977) study is also of questionable value because of incomplete reporting of tumor incidence in untreated animals, in spite of showing sensitive induction of mammary tumors in female rats. In light of these limits on the studies in hamster and rats, the body of data showing tumor induction in mouse has been deemed most appropriate for the development of a cancer potency value.

Calculation of the geometric mean of q_{human} and q_{bar} values from the most sensitive sites of malignancy development in the oral mouse studies resulted in values of 0.5 and 1.4 $(mg/kg\text{-}day)^{-1}$, respectively. The geometric mean of the q_{bar} values provides an estimate of the upper 95% confidence limit on the distribution of values. Calculation of the geometric mean of q_{human} and q_{bar} values from mouse studies where the lung was the most sensitive site of malignancy development resulted in values of 0.8 and 1.9 $(mg/kg\text{-}day)^{-1}$, respectively. These mean values, coupled with the q_{human} values from the sensitive multiple dose study by Schmähl *et al.* (1977), indicate the most plausible estimate of cancer potency for urethane falls in the range of 0.6 to 3.0 $(mg/kg\text{-}day)^{-1}$. Therefore, as a reasonable estimate to the cancer potency, 1.0 E+0 $(mg/kg\text{-}day)^{-1}$ has been adopted as a cancer potency value.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.9 E-4 $(\mu g/m^3)^{-1}$.

Table 3. Cancer potency estimates from oral studies in animals (adapted from CDHS (1989)).

study/tumor	species/strain	sex	model*	q_{human} (95 %) $(mg/kg\text{-}day)^{-1}$	q_{bar} $(mg/kg\text{-}day)^{-1}$
Pietra (1960)	hamster/ Syrian G		MST		
skin melanotic tumor		M		0.19	0.11
forestomach papilloma		M		0.11	0.060
forestomach papilloma		F		0.18	0.094
Toth (1961a)	hamster/Syrian G		AD		
forestomach papilloma		M		0.13	0.091
forestomach papilloma		F		0.15	0.11
Toth (1969)	hamster/Syrian G		MST		
forestomach papilloma		M		0.10	0.077
forestomach papilloma		F		0.20	0.15
Tannenbaum (1962)	rat/Sprague-Dawley		MPK		
Zymbal gland carcinoma		M		0.12	0.061
Schmähl (1977)	rat/Sprague-Dawley		WPK		
mammary gland carcinoma		F		0.83	0.48
Toth (1961b)	mouse/Swiss		APK		
lung adenoma		M		3.8	3.0
lung adenoma		F		3.6	2.9
lymphoma		M		0.30	0.18
lymphoma		F		0.46	0.25
Tannenbaum (1962)	mouse/		APK		
lung alveolar cell tumor	DBA	M		0.9	0.61
mammary gland carcinoma	DBA	F		1.2	0.90
lung adenoma	DBA	M		0.4	0.29
lung adenoma	C3H	F		0.4	0.28
Klein (1962)	mouse/$B6AF_1$		APK		
lung adenoma		M		0.85	0.54
lung adenoma		F		0.76	0.48
leukemia		M		0.090	0.071
leukemia		F		0.10	0.066
Della Porta (1963a)	mouse/CTM		APK		
lung adenoma		M		0.62	0.17
lung adenoma		F		0.60	0.12
Della Porta (1963b)	mouse/CTM		APK		
malignant lymphoma		M		0.55	0.17
mammary gland		F		0.50	0.12
Della Porta (1967)	mouse/		APK		
Harderian gland tumor	$BC3F_1$	M		0.88	0.66
Harderian gland tumor	$BC3F_1$	F		0.32	0.25
Harderian gland tumor	C3Hf	M		0.22	0.15
Harderian gland tumor	C57BL	M		0.32	0.25
Harderian gland tumor	C57BL	F		0.23	0.19
mammary gland carcinoma	C3Hf	F		0.23	0.16
lung adenoma	C3H	M		0.18	0.13
lung adenoma	SWR	M		0.94	0.67
lung adenoma	SWR	F		1.0	0.76

Table 3 (continued). Cancer potency estimates from oral studies in animals [adapted from CDHS (1989)].

study/tumor	species/strain	sex	model*	q_{human} (95 %) $(mg/kg\text{-}day)^{-1}$	q_{bar} $(mg/kg\text{-}day)^{-1}$
Innes (1969)	mouse/		MPK		
liver hepatoma	$B6C3F_1$	M		0.40	0.23
liver hepatoma		F		0.61	0.27
lung adenoma	$B6AKF_1$	M		0.78	0.51
lung adenoma		F		1.5	0.99
Tomatis (1972)	mouse/CF-1		MPK		
lung adenoma		M		0.90	0.75
lung adenoma		F		0.67	0.55
Schmähl (1977)	mouse/NMRI				
lung adenoma		M	WPK	3.0	1.7
lung carcinoma		M	MPK	0.85	0.55
lung adenoma		F	WPK	1.9	-
lung carcinoma		F	MPK	0.56	0.12
			W1PK	3.0	1.7

*MST- multistage; APK - Armitage-Doll model; MPK - multistage with pharmacokinetic adjustment; WPK - Weibull time-dependent with pharmacokinetic adjustment; W1PK - Weibull linear in dose time-dependent model with pharmacokinetic adjustment.

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VINYL CHLORIDE

CAS No: 75-01-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	62.5
Boiling point	-13.37ºC
Melting point	-153.8°C
Vapor pressure	2660 mm Hg @ 25°C
Air concentration conversion	1 ppm = 2.56 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 7.8 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 2.7 E-1 $(mg/kg\text{-}day)^{-1}$
[Female mouse lung tumor incidence (Drew *et al*., 1983), extra risk calculated using a linearized multistage procedure (CDHS, 1990).]

III. CARCINOGENIC EFFECTS

Human Studies

In 1974, Creech and Johnson described three cases of angiosarcoma of the liver (LAS) among workers at the B.F. Goodrich Tire and Rubber Co. in Louisville, Kentucky. Because LAS is a very rare cancer (20-25 cases per year in the U. S.), the clustering of three cases in one vinyl chloride (VC) polymerization facility indicated an abnormally high incidence of this cancer. Based on this report, as well as data indicating that VC is carcinogenic in laboratory animals, multiple studies of workers exposed to this agent were conducted. By 1985, at least 15 epidemiologic studies relating VC exposure to the incidence of various cancers had been completed. A summary of the data from these studies is provided in Table 1.

Between 1961 and 1977, 23 cases of LAS were reported among approximately 20,000 VC workers in the U.S. (Lelbach and Marsteller, 1981; Spirtas and Kaminski, 1978). The expected incidence of LAS is 0.014 cases per 100,000 per year in the general population in the U.S. (Heath *et al*., 1975). Based on analysis of these data, the relative risk for developing LAS following VC exposure among this country's VC workers is 483.

The epidemiologic studies also demonstrate a strong and consistent association between VC exposure and primary cancer of the liver. All of the studies that assessed risk for primary liver cancer note a statistically significant increase in standardized mortality ratios (SMRs). The average relative risk for liver cancer among VC workers is five to six times greater than the incidence of that seen in the general population. The evidence strongly suggests that exposure to VC can cause liver cancer. All reports published to date indicate that the SMRs of exposed workers are elevated, and risk of liver cancer was seen to increase with both increased dose and a longer follow-up time.

Table 1: A Summary of Epidemiologic Data for Occupationally Exposed Vinyl Chloride Workers

Study	Place	Cohort	Deaths (%)	Exposure in years	SMR				
					All Sites	Liver (LAS)	Brain	Lung	Lymphoma
Tabershaw and Gaffey[1] (1974)	U.S.	8,384	352 (4.7)	> 1 10.2%>20 yrs	110	94[3] (6)	155[4]	112	106
Duck *et al.* (1975)	U.K.	2,122	152 (7.2)	> 0	96	93[3] (0)	--	103	--
Nicholson *et al.* (1975)	U.S.	257	24 (9.3)	> 5	231	- (3)	--	--	--
Ott *et al.*[2] (1975)	U.S.	594	79 (13.3)	> 0	81	- (0)	--	77	--
Byren *et al.* (1976)	Sweden	771	58 (75)	> 0	--	413[a] (2)	612[a]	168	--
Waxweiler *et al.* (1976)	U.S.	1,294	136 (10.5)	> 5 (f/u > 10 yrs)	149[a]	1,155[b] (11)	329[a5]	156	159
				> 5 (f/u > 15 yrs)	189[b]	1,606[b] -	498[a]	194[a]	176
Fox and Collier (1977)	U.K.	7,717	409 (5.3)	> 0 8% > 20 yrs	90.7	1,408[a] (2)	54.6	89.8	90.9
EEH (1975)[1]	U.S.	10,173	707 (6.9)	> 1 19.3%>20 yrs	104	75[3] (5)	203[a]	107	112
Buffler *et al.* (1979)	Texas	464	28 (6.0)	> 0	138	- (0)	--	208[a]	--
Bertazzi *et al.* (1979)	Italy	4,777	62 (1.3)	> 0.5	97	800[a] (3)	125	81	133
Masuda *et al.* (1979)	Japan	304	26 (8.5)	> 1	138	500[a] (0)	--	125	--
Weber *et al.* (1981)	Germany	7,021 production	414 (5.9)	> 0	112	1,523[b] -	162	--	214[a]
		4,007 processing	360 (9)	> 0	85	434[a] -	535[a]	--	34
		4,910 unexposed	417 (8.5)	n/a	83	401[a] -	184	--	77
Cooper[1] (1981)	U.S.	10,173	707 (6.9)	> 1	104	75[3] (8)	203[a]	107	112
Heldaas *et al.* (1984)	Norway	454	50 (11)	> 1	114	- (1)	--	180	--
					Relative Risk				
Theriault and Allard (1981)	Canada	451 exposed	59 (2.6)	> 5	1.48	6.25[a] (10)	--	.36	--
		871 unexposed	233 (26.8)	n/a					

Table 1 (continued): A Summary of Epidemiologic Data for Occupationally Exposed Vinyl Chloride Workers

LAS = angiosarcoma of the liver; f/u = follow-up
[1]The studies of Cooper and EEH are reanalyses of the Tabershaw and Gaffey Cohort
[2]SMR subjects also in the Tabershaw and Gaffey Cohort
[3]SMR is for the "digestive system cancer", not liver cancer
[4]SMR is for "other and unspecified cancer", 40% of which were brain cancer
[5]SMR is for cancer of CNS, not brain
[a] $p < 0.05$ [b] $p < 0.01$

The association between VC exposure and increased risk for other cancers is not as clear as that for liver cancer. Some evidence associates exposure to VC with increased mortality ratios for brain cancer, lung cancer, and lymphoma. Since these cancers appear more commonly in the general population than LAS and primary liver cancer, it becomes more difficult to show increased risk.

Workers exposed to VC appear to be at greater risk for brain cancer than do non-exposed populations. Of the six studies that assessed the risk of brain cancer, five showed a positive trend for increased risk of this cancer type following exposure to VC, with four demonstrating statistical significance ($p < 0.05$). Cancer risk increased an average of four times above that expected in the general population in those studies that exhibited a significantly increased risk. Of the two studies not showing a significant increase in risk for brain cancer, statistical power in the Bertazzi and associates study was only about 35% (Bertazzi *et al*., 1979), while that of Fox and Collier (1977) was approximately 80% (Beaumont and Breslow, 1981). In the Fox and Collier study, the number of deaths overall was low and, most importantly, a large percentage of workers in the cohort was very recently employed in the VC industry and thus had a short follow-up time. These factors may partially explain why this study failed to detect an association between VC exposure and brain cancer.

The evidence linking VC exposure with lung cancer remains inconclusive. Analyses of SMRs for cancer of the lung were performed in 12 studies. Of these, seven studies showed an increased risk for lung cancer, but only one was statistically significant at the 5% level (Buffler *et al*., 1979). This increased risk persisted after adjusting for personal smoking habits (for this particular cohort). However, this cohort was small and the study was unable to demonstrate an increased risk for any other cancer. The Waxweiler *et al*. (1976) cohort (which had a follow-up period greater than 15 years) also used a small group.

An association between VC exposure and lymphoma has not been established. Five studies evaluated the risk of lymphoma development among workers occupationally exposed to VC. Four of the studies showed a positive trend for lymphoma among VC workers, but statistical significance was noted only by Weber *et al*. (1981). However, the statistical power in all of these studies was less than 80% to demonstrate a relative risk of two, and less than 40% to show a relative risk of 1.5.

Animal Studies

Reviews of VC carcinogenicity data from exposed laboratory animals available at the time the document "*Health Effects of Airborne Vinyl Chloride*" (CDHS, 1990) was released include those by Kalmaz and Kalmaz (1984), IARC (1979), SRI (1983), Kuzmack and McGaughy (1975), and Purchase *et al*. (1987). Adequate experimental evidence exists to indicate that VC is carcinogenic in mice, rats, and hamsters when given orally and by inhalation. VC has been found to cause tumors in a dose-related manner at several sites, including liver, lung and mammary gland. The oncogenic response appears to be a function of the site, VC concentration, tumor type, species of animal, and route of administration.

Although some evidence of VC-induced carcinogenesis has been observed by all routes of administration and in all species tested, important discrepancies in the protocols of many studies have limited their usefulness in quantitative risk assessment. These discrepancies include the lack of appropriate control groups, insufficient exposure time, or incomplete histopathology of the animals. Studies that have been used previously in risk assessment include feeding studies (Feron *et al*., 1981; Til *et al*., 1983) and a series of inhalation studies (Maltoni *et al*., 1984).

Groups of 60-80 male and 60-80 female five-week old Wistar rats were fed polyvinyl chloride powder (10% of diet) with or without a high VC monomer content (0 to 4000 ppm) in the diet for their lifetimes (Feron *et al*., 1981). The actual doses of VC given to rats in the feed were 0, 1.7, 5.0, and 14.1 mg/kg/day.

Necrosis, centrilobular degeneration and mitochondrial damage were seen in the hepatic parenchyma of rats administered VC. Significantly increased incidences of liver and lung angiosarcomas and hepatocellular carcinomas were observed in both male and female rats. Tumor incidences are listed in Table 2. It is possible that underreporting of tumors at all sites occurred because of the incomplete histopathology performed and the fact that only the longest-surviving high-dose animals were chosen for complete histopathology.

As a follow-up to the study of Feron and co-workers (1981), groups of 100 male and 100 female Wistar rats (except for the top-dose group, which was composed of 50 animals of each sex) were fed polyvinyl chloride (up to 1% of diet) with a high content of VC monomer for up to 149 weeks (Til *et al*., 1983). Levels of VC administered in the powder were 0, 0.017, 0.17, and 1.7 mg/kg/day for 149 weeks. Actual oral exposure to VC monomer (calculated by measuring the evaporative loss of VC during the four-hour feeding periods, the rate of food intake, and the level of VC in the feces) was estimated to be 0.014, 0.13, or 1.3 mg VC/kg/day for the low, middle, and high dose groups, respectively.

The results of this study demonstrated increases in the incidences of hepatic foci or cellular alteration, neoplastic nodules, hepatocellular carcinomas, liver-cell polymorphism, and cysts in the highest dose group. Two females and one male in this group developed liver angiosarcomas. Females, but not males, of the low- and mid-dose groups developed a higher incidence of hepatic basophilic foci of cellular alteration. No pathologic effects in other organ systems were attributed to VC exposure (Til *et al*., 1983). Histopathology of all organs was not performed on all animals;

therefore, tumors not grossly observable or palpable could have been missed. Because of the shortcomings of the study, its utility for the evaluation of carcinogenic risk is limited.

Several researchers have investigated the potential carcinogenicity of VC administered by inhalation (Viola, 1977; Caputo *et al*., 1974; Keplinger *et al*., 1975; Lee *et al*., 1977; Hong *et al*., 1981; Suzuki, 1981; Groth *et al*., 1981; Drew *et al*., 1983; Maltoni *et al*., 1984; Bi *et al*., 1985). All experiments confirm the carcinogenicity of VC, although only a few of the studies are adequate for a quantitative evaluation of carcinogenic risk. This summary will concentrate on the studies (Drew *et al*., 1983; Maltoni *et al*., 1984; Bi *et al*., 1985) used by CDHS (1990) for quantitative risk assessment purposes.

Table 2: Tumor incidences in male and female Wistar rats exposed to dietary vinyl chloride (Feron *et al*., 1981).

	Incidence[1] Vinyl chloride (mg/kg-day)			
Tumor type/Sex	0	1.7	5.0	14.1
Liver angiosarcoma				
male	0/55	0/58	6/56[*2]	27/59[***]
female	0/57	0/58	2/59	9/57[**]
Hepatocellular carcinoma				
male	0/55	1/58	2/56	8/59[**]
female	0/57	4/58	19/59[***]	29/57[***]
Neoplastic nodules				
male	0/55	1/58	7/56[**]	23/59[***]
female	2/57	26/58[***]	39/59[***]	44/57[***]
Lung angiosarcoma				
male	0/55	0/58	4/56[*]	19/59[***]
female	0/57	0/58	1/59	5/57[*]
Abdominal mesotheliomas				
male	3/55	1/58	7/56	8/59
female	1/57	6/58[*]	3/59	3/57
Mammary tumors[3]				
female	3/57	2/58	5/59	9/57

[1] Number in denominator = number of animals necropsied.
[2] values marked with asterisks differ significantly from controls as determined using the Chi-square test. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.
[3] Including mammary adenomas, adenocarcinomas and anaplastic carcinomas.

Bi *et al*. (1985) evaluated the tumorigenic potential of VC in male Wistar rats following inhalation exposure to 0, 10, 100 or 3000 ppm (six hours/day, six days/week) for up to 12 months. The incidence of liver angiosarcomas was 0/19, 0/20, 7/19 and 17/19 for the four exposure groups, and 0/19, 0/20, 2/19 and 9/20 for lung angiosarcomas, respectively. The incidence of liver angiosarcomas in the 100 and 3000 ppm groups was significantly greater than controls ($p = 0.004$, $p < 0.001$, respectively); the incidence of lung angiosarcomas in the 3000 ppm group was also significantly greater than controls ($p = 0.001$). This study probably underestimated the

carcinogenic potential of VC because of the less-than-lifetime exposure and the small number of animals per group.

Drew *et al*. (1983) examined the effect of age and exposure duration on VC oncogenicity in females of several different species of rodents. Groups of female CD-1 Swiss mice, $B6C3F_1$ mice, Fischer 344 rats, and Golden Syrian hamsters (n = 54 for mice, n = 56 for rats and hamsters) were exposed to VC for six hours/day, five days/week for six, 12, 18, or 24 months, beginning at eight weeks of age, and observed for their lifespans. Other groups were held until six or 12 months of age, exposed for six or 12 months, and then observed for the remainder of their lifespans. The exposures were conducted at a single dose level for each species; mice, rats and hamsters were exposed to 50, 100, and 200 ppm VC, respectively. All animals exposed to VC at age eight weeks (the start of the experiment) exhibited decreased survival relative to controls (Drew *et al*., 1983). $B6C3F_1$ mice experienced the most significant life-shortening regardless of the age at which exposure was begun. No significant decrease in survival was observed in rats, hamsters, or Swiss mice initially exposed after six months of age. Other clinical signs of VC toxicity were not evident and liver necrosis was not observed.

In rats, exposure to VC was associated with hemangiosarcomas, mammary gland adenocarcinomas and adenomas, and hepatocellular carcinomas. The incidence of hemangiosarcomas was a function of the duration of exposure and age at start of exposure; the longer the exposure period the greater the incidence of hemangiosarcomas. A six-month exposure produced a low incidence of hemangiosarcomas and hepatocellular carcinomas only if begun early in life. One-year exposures produced a significant incidence of tumors, especially if begun early in life. The incidence of mammary gland adenocarcinomas and fibroadenomas was not always related to exposure duration, but the incidence was higher in rats whose exposure began at eight weeks of age. Hepatocellular carcinomas were induced in a dose-related manner in rats when exposures began at eight weeks. Tumor incidences in VC-exposed rats are listed in Table 3.

In hamsters, hemangiosarcomas, mammary gland carcinomas, stomach adenomas, and skin carcinomas were associated with VC exposure (Drew *et al*., 1983). The highest incidence of hemangiosarcomas and stomach adenomas occurred in animals exposed early in life for only six months. The highest incidence of mammary gland carcinomas was seen in animals exposed at an early age for up to twelve months. Exposure beginning at or after eight months of age resulted in a markedly lower tumor incidence, possibly because the lifespans of chronically exposed hamsters were significantly reduced to the point that late-appearing tumors would not be expressed. Tumor incidences in VC-exposed hamsters are listed in Table 4.

Mice, especially the $B6C3F_1$ strain, appeared to be the species most sensitive to the carcinogenic effects of VC (Drew *et al*., 1983). Hemangiosarcomas and mammary gland carcinomas in both strains and lung carcinomas in Swiss mice were associated with VC exposure. In $B6C3F_1$ mice, exposure to VC for six months resulted in 60-70% incidence of hemangiosarcomas, regardless of the age at exposure initiation. The incidence of mammary gland carcinomas in $B6C3F_1$ mice was

Table 3: Tumor incidences in 100 ppm vinyl chloride-exposed female Fisher 344 rats (Drew *et al*., 1983).

Tumor type	Length of Exposure (months)	LDE (ppm)[a]	Tumor incidence[b] (%)
Liver hemangiosarcomas	control	0	1/112 (0.9)
	6	4.5	4/76 (5.3)
	12	8.9	11/55 (20.0)***
	18	13.4	13/55 (23.6)***
	24	17.9	19/55 (34.7) ***
Mammary adenocarcinomas	control	0	5/112 (4.5)
	6	4.5	6/76 (7.9)
	12	8.9	11/56 (19.6) **
	18	13.4	9/55 (16.4) *
	24	17.9	5/55 (9.1)
Hepatocellular carcinomas	control	0	1/112 (0.9)
	6	4.5	3/75 (4.0)
	12	8.9	4/56 (7.1) *
	18	13.4	8/54 (14.8) ***
	24	17.9	9/55 (16.4) ***

[a] LDE = Lifetime Daily Exposure. [b] Value in parentheses is percent incidence.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Fisher's exact test)

Table 4: Tumor incidences in 200 ppm vinyl chloride-exposed female Golden Syrian hamsters (Drew *et al*., 1983).

Tumor type	Length of Exposure (months)	LDE (ppm)[a]	Tumor incidence[b] (%)
Hemangiosarcomas (all sites)	control	0	0/143 (0)
	6	8.9	13/88 (14.8) ***
	12	17.9	4/52 (7.7) **
	18	26.8	2/103 (1.9)
Mammary carcinomas	control	0	0/143 (0)
	6	4.5	28/87 (32.2) ***
	12	8.9	31/52 (59.6) ***
	18	13.4	47/102 (46.1) ***
Skin carcinomas	control	0	0/133 (0)
	6	4.5	2/80 (2.5)
	12	8.9	9/47 (18.8) ***
	18	13.4	3/90 (3.3)

[a] LDE = Lifetime Daily Exposure. [b] Value in parentheses is percent incidence.
** $p < 0.01$; *** $p < 0.001$ (Fisher's exact test)

greatest when the animals were exposed early in life. Lower incidences of this tumor were seen when initial exposure occurred at a later age. In Swiss mice, exposure to VC at an early age resulted in the highest incidence of hemangiosarcomas, mammary gland carcinomas, and lung carcinomas, regardless of duration of exposure. Lower incidences of all tumors were observed in animals exposed later in life. Tumor incidences in VC-exposed mice are listed in Table 5.

Table 5: Tumor incidences in 50 ppm vinyl chloride-exposed female $B6C3F_1$ and CD-1 Swiss mice (Drew *et al*., 1983).

Strain/Tumor type	Length of Exposure (months)	LDE (ppm)[a]	Tumor incidence[b] (%)
$B6C3F_1$			
hemangiosarcomas (all sites)	control	0	4/69 (5.8)
	6	2.23	46/67 (68.7) ***
	12	4.46	69/90 (76.7) ***
	18	--	--
mammary carcinomas	control	0	3/69 (4.3)
	6	2.23	29/67 (43.2) ***
	12	4.46	37/90 (41.1) ***
	18	--	--
CD-1 Swiss			
hemangiosarcomas (all sites)	control	0	1/71 (1.4)
	6	2.23	29/67 (43.3) ***
	12	4.46	30/47 (63.8) ***
	18	6.69	20/45 (44.4) ***
mammary carcinomas	control	0	2/71 (2.8)
	6	2.23	33/67 (49.3) ***
	12	4.46	22/47 (46.8) ***
	18	6.69	22/45 (48.9) ***
	control	0	9/71 (12.7)
	6	2.23	18/65 (27.7) *
	12	4.46	15/47 (31.9) *
	18	6.69	11/45 (24.4)

[a] LDE = Lifetime Daily Exposure. [b] Value in parentheses is percent incidence.
* $p < 0.05$; *** $p < 0.001$ (Fisher's exact test)

Maltoni and co-workers performed a series of chronic inhalation studies on rats, mice, and hamsters in the Bentivoglio Laboratories (BT) or the Bologna Institute of Oncology (Maltoni *et al*., 1984). The investigators studied the effects of exposure to 14 concentrations of VC (1-30,000 ppm) in male and female rats and six concentrations of VC in male and female mice and male hamsters. In each experiment, animals were exposed to VC for four hours daily, five days per week for various durations, and observed for the rest of their lives. A number of the experimental procedures were not described or were inadequately described in the report by Maltoni *et al*. (1984). Details of the experimental protocol for the BT experiments are provided in Table 6.

Data on noncarcinogenic toxic effects of vinyl chloride were sparsely reported in the Maltoni BT experiments. Vinyl chloride appeared to be toxic at the higher concentrations, but reportedly the high mortality at these dose levels was due to a high incidence of vinyl chloride-induced tumors. The available information on survival, including Kaplan-Meier survival curves, indicates that vinyl chloride decreased survival in a dose-dependent manner.

Table 6: Experimental protocol for vinyl chloride inhalation studies performed by Maltoni *et al*. (1984).

Experiment number	Dose (ppm)	Exposure duration (weeks)[1]	Species/ strain	Starting exposure age (weeks)	animals/exposure concentration[2]
BT1	0, 50, 250, 500, 2500, 6000, 10000	52	rat/SD	13	30 M, 30 F
BT2	1, 100, 150, 200	52	rat/SD	13	60 M, 60 F (85 M, 85 F)
BT3	0, 50, 250, 500, 2500, 6000, 10000	17	rat/SD	12	30 M, 30 F
BT4	0, 50, 250, 500, 2500, 6000, 10000	30	mouse/ Swiss	11	30 M, 30 F (80 M, 70 F)
BT5	6000, 10000	1	rat/SD	19 (fetus)	30 F 13-29 M, F (no controls)
BT6	30000	52	rat/SD	17	30 M, 30 F (no controls)
BT7	0, 50, 250, 500, 2500, 6000, 10000	52	rat/ Wistar	11	30 M (40 M)
BT8	0, 50, 250, 500, 2000, 6000, 10000	30	hamster/ Syrian Golden	11	30 M (62 M)
BT9	0, 50	52	rat/SD	13	150 M, 150 F (50 M, 50 F)
BT14	6000, 10000	5	rat/SD	21 (parents)	6 F (no controls)
		5		1day (offspring)	21-22 M, F (no controls)
BT15	0, 1, 5, 10, 25	52	rat/SD	13	60 M, 60 F
BT4001	0, 2500	76	rat/SD	13	54 F (60 F)
		69		1 day	68 M, 68 F (158 M, 149F)
BT4006	0, 2500	15	rat/SD	1 day	60 M, 60 F

[1] Exposures were for four hours/day, 5 days/week. [2] Number in parentheses = number of control animals when not equal to number of animals in experimental groups.

In the Maltoni experiments, exposure to vinyl chloride was associated with an increased incidence of malignant tumors at a variety of tissue sites in all of the species tested. A summary of these tumor sites is provided in Table 7 (Maltoni *et al*., 1984). A direct relationship between exposure levels and tumor incidence was apparently demonstrated, although no statistical tests for trends were performed. Results of experiments on Sprague-Dawley rats exposed to vinyl chloride for 52 weeks were statistically analyzed using the Fischer exact probability test. A summary of the lowest concentrations at which a statistically significant excess of tumors was observed is given in Table 8. When adjusted to average lifetime exposure, the lowest concentration associated with tumor production is 0.06 ppm (1 ppm * 4/24 * 5/7 * 12/24 - 0.3 ppm).

Table 7: Tumors correlated to inhalation exposure to vinyl chloride in rats, mice, and hamsters in the BT experiments (Maltoni *et al*., 1984).

Tumors	Rat	Mouse	Hamster
Liver angiosarcomas	+	+	+
Hepatomas	+	(+)	
Encephalic neuroblastomas	+		
Lung adenomas		+	
Lymphomas/leukemias			(+)
Angiosarcomas at other sites	+	+	(+)
Zymbal gland epithelial tumors	+		
Nephroblastomas	+		
Cutaneous epithelial tumors	(+)	(+)	(+)
Mammary adenocarcinomas	+	+	
Forestomach papillomas, acanthomas	+	(+)	+

\+ Tumor incidence was statistically significant ($p < 0.05$) by the Fisher exact test.

(+) Association was not statistically significant, but was considered biologically significant.

Table 8: Lowest concentration of VC at which a significant incidence of tumors ($p < 0.05$) was reported by Maltoni *et al*. (1984) at specific sites in Sprague-Dawley rats.

Tumor type	Vinyl chloride concentration (ppm)
forestomach papilloma	30,000 (male, female)
Zymbal gland carcinoma	10,000 (male, female)
neuroblastoma	10,000 (female)
nephroblastoma	250 (female)
liver angiosarcoma	200 (male); 25 (female)
mammary adenocarcinoma	1 (female)

Experiment BT1

Most previous risk assessments have been based on the data from experiment BT1 (Maltoni *et al*., 1984). In this study, 30 Sprague Dawley rats of each sex were exposed to concentrations of vinyl chloride ranging from 50 to 10,000 ppm for four hours daily, five days per week for 52 weeks, beginning at 13 weeks of age. A positive control group received 2,500 ppm of vinyl acetate. After treatment the animals were observed for their lifespans up to 135 weeks. Survival of both males and females decreased in a dose-related manner, especially at concentrations above 500 ppm. Vinyl chloride was more toxic to females than to males in this experiment. Vinyl chloride was associated with an increased incidence of liver angiosarcomas in a dose-related fashion. These results are presented in Table 9 (Maltoni *et al*., 1984). In addition to liver angiosarcomas, vinyl chloride (at concentrations above 2500 ppm) caused an increased incidence of zymbal gland carcinomas, nephroblastomas, hepatomas, and neuroblastomas. The incidence of liver angiosarcomas was probably underestimated at the higher exposure levels due to mortality resulting from tumors at other sites.

Table 9: Incidence of liver angiosarcomas (LAS) in male and female Sprague-Dawley rats exposed to 52 weeks to vinyl chloride (Maltoni *et al*., 1984)

Study	Exposure level (ppm)	LAS incidence[1]	corrected LAS incidence[2]

		male	female	male	female
BT1	0	0/30	0/30	0/22	0/29
	50	0/30	1/30	0/26	1/29
	250	1/30	2/30	1/28	2/26
	500	0/30	6/30	0/22	6/28
	2,500	6/30	7/30	6/26	7/24
	6,000	3/30	10/30	3/17	10/25
	10,000	3/30	4/30	3/21	4/25
BT2	0*	0/85	0/100	0/61	0/68
	100	0/60	1/60	0/37	1/43
	150	1/60	5/60	1/36	5/46
	200	7/60	5/60	7/42	5/44
BT6	30,000	5/30	13/30	5/22	13/24
BT9	0	0/50	0/50	0/29	0/38
	50	1/150	12/150	2/70	12/110
BT15	0	0/60	0/60	0/25	0/44
	1	0/60	0/60	0/48	0/55
	5	0/60	0/60	0/43	0/47
	10	0/60	1/60	0/42	1/46
	25	1/60	4/60	1/41	4/40
LAS incidence in historical controls		1/1179	2/1202	1/364	2/541

[1] Number in denominator - number of animals necropsied.
[2] Number in denominator - number of animals alive when first liver angiosarcoma was observed.

Experiment BT 15
Groups of 60 male and 60 female Sprague-Dawley rats were exposed to 0, 1, 5, 10, or 25 ppm of vinyl chloride for four hours daily, five days per week for 52 weeks, beginning at 13 weeks of age (Maltoni *et al*., 1984). Following exposure the animals were observed for the remainder of their lives (up to 147 weeks). Available data,. including Kaplan-Meier survival curves, indicated that vinyl chloride did not affect survival at the concentrations tested.

No statistical analyses of mortality and body weight data were reported. Mortality was greater in the male control group than in the treated groups: the time at which 50% of the male control group had died was week 72, compared with week 100 in the 25-ppm vinyl chloride group. No explanation was given for this decreased survival. The incidence of mammary gland carcinomas in treated females was higher than in controls at all concentrations of vinyl chloride exposure. The differences from control values were statistically significant at concentrations of 1 ppm and above. The mammary gland adenocarcinoma incidence for this and the other relevant BT experiments are presented in Table 10.

Table 10: Incidence of mammary gland carcinomas in female Sprague-Dawley rats and Swiss mice exposed by inhalation to vinyl chloride (Maltoni *et al*., 1984)

Study No.	Experimental Dose Level (ppm)	Tumor Incidence[1]	Corrected Tumor Incidence[2]
BT1 (Rat)	0	0/30	0/29
	50	2/30	2/30
	250	2/30	2/27
	500	1/30	1/28
	2,500	2/30	2/25
	6,000	0/30	0/28
	10,000	3/30	3/29
BT2 (Rat)	0	2/60	2/100
	100	4/60	4/60
	150	6/60	6/60
	200	5/60	5/60
BT6 (Rat)	30,000	2/30	2/30
BT9 (Rat)	0	9/50	9/43
	50	59/150	59/142
BT15 (Rat)	0	6/60	6/60
	1	14/60	14/60
	5	22/60	22/60
	10	21/60	21/60
	25	16/60	16/60
Tumor Incidence in Historical Controls		100/1202	100/1202
BT4 (Mice)	0	1/80	1/67[3]
	50	12/30	12/30[3]
	250	13/30	13/29[3]
	500	10/30	10/28[3]
	2,500	9/30	9/30[3]
	6,000	9/30	9/28[3]
	10,000	14/30	14/28[3]
Tumor Incidence in Historical Controls		21/554	21/554[3]

[1] Number in denominator - number of animals examined.
[2] Number in denominator - number of animals alive when first malignant mammary tumor was observed (type unspecified).
[3] Number in denominator - number of animals alive when first mammary tumor was observed (type unspecified).

Experiment BT4

Thirty male and 30 female Swiss mice were exposed to 0, 50, 250, 500, 2,500, 6,000, or 10,000 ppm of vinyl chloride four hours daily, five days weekly for 30 weeks, beginning at 11 weeks of age (Maltoni *et al*., 1984). The study was terminated 81 weeks after the exposure period began. Vinyl chloride was highly toxic to both males and females, but males appeared more sensitive than females to the toxic effects of vinyl chloride. Survival decreased in a dose-related manner, although statistical analysis apparently was not performed on the data presented.

A very high incidence of lung adenomas was observed in vinyl chloride-treated male and female mice. A statistically significant increase in the incidence of liver angiosarcomas was seen in male and female mice exposed to vinyl chloride, but a dose response was not seen in the male animals. In addition, a high incidence of mammary gland adenocarcinomas occurred in treated female mice. These results are presented in Table 10 (data from Maltoni *et al*., 1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Human occupational studies demonstrate a strong and consistent association between VC exposure and primary cancer of the liver. All of the studies that assessed risk for primary liver cancer note a statistically significant increase in standardized mortality ratios (SMRs). The average relative risk for liver cancer among VC workers is five to six times greater than the incidence of that seen in the general population. The evidence strongly suggests that exposure to VC can cause liver cancer. All reports published to date indicate that the SMRs of exposed workers are elevated, and risk of liver cancer was seen to increase with both increased dose and a longer follow-up time. CDHS (1990) decided that the Waxweiler *et al*. (1976) study was most suitable for quantitative risk assessment use.

Three sets of animal cancer bioassays (Drew *et al*., 1983; Maltoni *et al*., 1984; Bi *et al*., 1985) were also considered by CDHS (1990) to provide adequate data for quantitative risk assessment purposes. The Maltoni *et al*. experiments together provide an unusually large set of data on cancer incidence in both males and females rats over a large range of exposures at many concentrations - altogether fifteen groups beyond the four control groups. The Drew *et al*. experiments provide incidence data on female rodents for an unusual exposure protocol in that the duration varied for two or three groups beyond controls, while the concentration remained fixed for each species. The Bi *et al*. experiments provide incidence data on male rats for three exposures beyond controls. CDHS (1990) chose to develop cancer risk estimates for VC using both the human and animal data described above.

Methodology

Human-derived risk estimates

The review of the epidemiological studies strongly suggests a causal association between vinyl chloride and several different types of cancer, including liver, lung, and brain. However, none of the occupational cohort studies presented exposure data for a large enough cohort to derive a dose-response curve; so the CDHS (1990) analysis used historical industrial hygiene data to reconstruct a range of likely exposures, from which risk estimates can be extrapolated.

This risk analysis proceeds by selecting the Waxweiler *et al*. (1976) study of 1294 workers who experienced high sustained exposures to vinyl chloride and who were followed long enough (10 years) to develop substantial numbers of cancers that appeared to be related to the exposure. The retrospective estimates of Barnes *et al*. (1976) for the relevant industrial processes furnished

concentrations of the exposures of vinyl chloride, having an overall average value of 647 ppm. The analysis converts these annual average exposure estimates to a lifetime daily equivalent tissue exposure of 3.6 ppm on the assumption of a saturable metabolic process (Michaelis-Menten) leading to active carcinogens. This is based on extrapolated measurements of binding rates to macromolecules (Gehring *et al*. 1977). The seven liver cancer deaths reported for that cohort project to a lifetime risk of .039 (.089 upper confidence limit) per worker for liver cancers. That risk divided by the overall lifetime daily equivalent of effective exposure yields unit risk estimates for that malignancy.

The calculations provided the following upper confidence limits (UCL) on unit risks: 2.5×10^{-5} ppb^{-1} for liver cancers, and 4.5×10^{-5} ppb^{-1} for three sites of cancer combined, liver, lung and brain. Each of these three sites of cancer had a significantly elevated SMR when calculated for a 15-year follow up time. The unit risks calculated in this manner are about six times greater than would be calculated by using actual exposures instead of the effective exposures that take account of the metabolic saturation in the tissue.

Animal-derived risk estimates

The animal bioassay-based quantitative risk assessment analyses performed by CDHS (1990) used the computer program GLOBAL86 to calculate potential risks using a linearized multistage procedure that were associated with vinyl chloride exposure. Significant trends for liver angiosarcoma dominated the results of the modeling. All three analyses of female rats and two of the three analyses of male rats met the statistical criterion ($p > 0.05$) for goodness of fit of the dose-dependent response of liver angiosarcoma (LAS) to vinyl chloride. In addition, the following experimental groups met that criterion: lung carcinoma in the Swiss mice of Drew *et al*. (1983), lung angiosarcoma in the Wistar rats of Bi *et al*. (1985), and mammary tumors in both the Sprague Dawley rats of Maltoni *et al*. (1984) and the F-344 rats of Drew *et al*. (1985).

Table 11 gives unit risk estimates calculated by using the linearized multistage procedure for LAS and other tumor types from both male. and female rats and for female mice for inhalation experiments done by Maltoni *et al*. (1984), Bi *et al*. (1985), and Drew *et al*. (1983). The entries in Table 11 include all those instances in which an adequate fit of the data is achieved by the model using all data points for each species, sex, and tumor type at exposures not greater than 500 ppm, when practical. This exposure limitation tends to reduce the effects of the parent compound (including mortality) at the higher exposure levels. The analyses did include one higher exposure, the 3000 ppm exposure of Bi *et al*., which was retained in order to obtain an adequate number of exposure groups (four) to establish a clear trend.

The results of Table 11 do not include the analyses for angiosarcoma and mammary tumors in mice or the angiosarcoma, skin carcinoma, and mammary tumors in hamsters. The estimates for q_1^* for angiosarcomas and mammary tumors in mice were in the range of 20×10^{-5} to 50×10^{-5} ppb^{-1}, greatly elevated above those for rats while the estimates for those tumors in hamsters (6×10^{-5} and 1×10^{-4}) were about the same as the highest results in rats. None of these analyses met the stringent criteria for goodness of fit of the MLE as defined above, so they were not included in the tabulation of risk estimates.

Table 11: Risks of carcinogenicity from vinyl chloride exposure estimated from rodent data

Experiment	Strain/species, sex	Tumor	Rodent q_1^* (10^{-5} ppb^{-1})	Human[a] q_1^* (10^{-5} ppb^{-1})
Maltoni *et al*., (1984)				
BT-1,2 (≤ 500 ppm)	SD/rat, female	LAS	1.9	4.9
	SD/rat, female	mammary	1.4	3.7
BT-9, 15	SD/rat, female	LAS	6.7	18.0
	SD/rat, male	LAS	2.5	6.5
Bi *et al*. (1985)	Wi/rat, male	LAS	5.0	13.0
	Wi/rat, male	lung angiosarcoma	1.7	4.5
Drew *et al*. (1983)	F344/rat, female	LAS	3.2	8.4
	F344/rat, female	hepatocellular carcinoma	1.7	4.4
	F344/rat, female	mammary	1.6	4.2
	Sw/mouse, female	lung	6.9	20.0

[a] Determined by multiplying by the scaling factor on rodent dose.
SD = Sprague-Dawley; Wi = Wistar; F344 = Fischer 344; Sw = Swiss; LAS = liver angiosarcoma.

The effect of combining the BT (Maltoni *et al*. 1984) experiments was to lower the value of the resulting q_1^* by a modest amount. Thus BT-1 and BT-2 individually yielded values of 2.5×10^{-5} and 2.2×10^{-5} ppb^{-1} respectively, compared to 1.9×10^{-5} ppb^{-1} when combined. Also, BT-9 and BT-15 individually yielded values of 6.9×10^{-5} and 1×10^{-4} ppb^{-1}, compared to 6.7×10^{-5} ppb^{-1} when combined. The use of metabolized exposure rather than ambient exposure had the effect of increasing the values of q_1^* by about 30-50% in the BT-1 and BT-2 experiments. The effect on BT-9 and BT-15 was virtually negligible because of the much lower exposures experienced in those experiments.

Uncertainties in estimates of unit risk arise from uncertainties mentioned earlier about the accuracy of the model used to determine metabolized exposure. Departures from the present fit of the Michaelis-Menten model could cause calculations of risk to lose accuracy. Cumulative effects or different metabolism, for example, may cause the true risk to differ from that predicted. Nevertheless, uncertain as it is, the metabolic model appears much more likely to provide a more accurate measure of risk than does ambient exposure.

Final cancer unit risk calculation

Cancer risk estimates for VC derived from human and animal data provided the range of 95% UCLs on cancer unit risk for humans: from 2.5×10^{-5} to 2×10^{-4} ppb^{-1}. Because many of the tumors associated with vinyl chloride exposure (particularly LAS) exhibit a long latency period, exposure at an early age would produce a greater risk. The average latency period for the development of LAS in one study of occupationally exposed vinyl chloride workers was determined to be 22.1 years (Stafford, 1983). Drew *et al*. (1983) demonstrated that in rats, mice and hamsters, the highest incidence of neoplasms was observed when vinyl chloride exposure was started early in life.

Exposures early in life may produce up to a 10-fold greater incidence in tumors compared to exposures late in life.

Because of these considerations, CDHS decided that the best estimate of unit risk coincided with the top of the range, which was, when rounded, 2×10^{-4} ppb^{-1}, or 7.8×10^{-5} $(\mu g/m^3)^{-1}$. This is approximately the value obtained from the more recent Maltoni *et al*. experiments, with lower exposure concentrations than the previous experiments. That result is at the top of the range of six experiments that provided clear dose response relationships for liver cancer. The selected top of the range, 2×10^{-4} ppb^{-1} is also equal to the Drew *et al*. result for lung carcinoma in mice. That result is one of the lowest for mice. The other, higher results for mice are not explicitly reported in the present risk analysis because of scattering of points in each case not providing a clear exposure-response trend. The results for hamsters, not reported quantitatively for the same reason, were close to those for the rats. This approach was considered to provide adequately health protective estimates of human unit risks, which represent the 95% upper confidence limits for risk calculations.

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