PRIORITIZED CANDIDATE CHEMICALS UNDER CONSIDERATION FOR CARCINOGENICITY EVALUATION:

BATCH #1

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

May 1997

Data summaries for 33 chemicals under consideration for carcinogenicity evaluation (i.e., Batch #1) have been finalized, and are presented here. Batch #1 chemicals were selected for prioritization from the tracking database under a process described in the draft document entitled "Procedure for Prioritizing Candidate Chemicals for Consideration Under Proposition 65 by the State's Qualified Experts" and presented to the Carcinogen Identification Committee (CIC) in May 1995. Draft data summaries for these chemicals were released for public comment in May 1996 and presented to the CIC at a public meeting on July 22, 1996. Several refinements to the prioritization process have been suggested since the selection of this initial batch of chemicals; as a result, these data summaries were the subject of a second public comment period and a public workshop, held November 15, 1996. Public comments received on the data summaries during the two 60-day comment periods and at the two public meetings were reviewed and considered as part of the assignment of final priorities.

nitro-o-toluidine, 5-	medium	23
MEDIUM Carcinogenicity Concern		
acrolein	high	25
chloroacetaldehyde	high	28
C.I. Disperse Yellow 3	high	30
clomiphene and its salts	high	32
coumarin	high	34
nitrofurantoin	high	36
ozone	high	38
pentachloroanisole (pentachloromethoxybenzene)	high	41
trifluralin	high	43
acetoxime	medium	46
dichloro-p-phenylenediamine, 2,6-	medium	48
chlorofluoromethane (fluorocarbon 31)	low	50
mercuric chloride	low	52
nitro-p-phenylenediamine, 2-	low	54
semicarbazide hydrochloride	low	56
LOW Carcinogenicity Concern		
acetaminophen (paracetamol)	high	58
benzyl acetate	high	61
butyl benzyl phthalate	high	64
decabromobiphenyl oxide	high	66
eugenol	high	68
isophorone	high	71
naphthalene	high	73

propyl gallate	high	75
chloramben	low	77
ethyl parathion	low	79

CARCINOGENICITY DATA SUMMARY: QUINOLINE

Quinoline (CAS No. 91-22-5) is used as an intermediate in manufacturing, and is formed as a result of natural combustion and pyrolysis processes (e.g., tobacco smoke) (CHIP, 1983). It is a component of creosote, coal tar, and other products derived from fossil fuels (CHIP, 1983).

Carcinogenicity Data available:

Epidemiological studies

No data on carcinogenic effects of human exposure to quinoline were identified.

Animal bioassays

1. Rat long-term feed study: Hirao *et al.,* 1976. Following exposures of less than 40 weeks to 0, 0.05%, 0.1%, and 0.25% quinoline in feed to male Sprague-Dawley rats, hepatocellular carcinomas (0/6, 3/11, 3/16, 0/19) and hemangioendotheliomas of the liver (0/6, 6/11, 12/16, 18/19) were found.

2. Rat long-term feed bioassay: Hasegawa *et al.,* 1989. Groups of male Wistar rats were given 0.2% quinoline in the diet for 4, 8, 12, 16 or 29 weeks and sequentially killed at these time points. Liver hemangioendotheliomas were induced in 1/11, 2/12, and 5/12 rats treated for 12 weeks and without treatment for an additional 0, 4, and 8 weeks, respectively. Of rats treated for 16 weeks, 4/14 and 4/18 had these tumors when followed for an additional 0 and 4 weeks, respectively. Following a 20-week exposure, hemangioendotheliomas of the liver were found in 12/16 animals. None of 12 untreated rats were observed with these tumors after 20 weeks of observation.

3. Rat feed studies: Shinohara *et al.,* 1977. Following 30 weeks of treatment with 0.2% quinoline in feed, the incidence of hemangioendotheliomas of the liver was 73% (11/15) in male and 31% (7/22) in female Wistar rats. Thirty weeks of treatment with 0.075% quinoline in the feed resulted in hemangioendotheliomas of the liver in 30% (6/20) rats (sex unspecified), whereas none were observed in 10 controls.

4. Mouse feed studies: Shinohara *et al.,* 1977. Following exposure to 0.2% quinoline in the diet for 30 weeks, the incidence of hemangioendotheliomas of the liver was 80% (8/10) in male and 80% (8/10) in female ddy mice.

5. Hamster and guinea pig feed studies: Shinohara *et al.,* 1977. Neither hemangioendotheliomas nor hepatocellular carcinomas were observed in 25 male and 19 female hamsters or 21 male and 17 female guinea pigs following exposure to 0.2% quinoline in the diet for 30 weeks.

6. Newborn mice and rats: LaVoie *et al*., 1988. For CD-1 mice receiving ip injections at days 1, 8, and 15 of life, 15/19 males developed liver adenomas or hepatomas, and 3/27 and 5/27 females developed lung tumors and leukemia, respectively. Except for leukemia in one animal, these tumors were not observed in 21 male and 21 female vehicle controls. No significant elevations of tumors were observed in Sprague-Dawley rats similarly treated.

7. Newborn mice: Weyand *et al.,* 1993. 60% of male newborn CD-1 mice treated with quinoline developed liver tumors, which were primarily adenomas.

Other relevant data

Quinoline was also found to be mutagenic in *Salmonella typhimurium* and Chinese hamster ovary cells and caused unscheduled DNA synthesis in rat liver (Weyand *et al.,* 1993). Quinoline is also reported to be mitogenic to mouse and rat liver (Lefevre and Ashby, 1992).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **HIGH** level of **carcinogenicity concern** over quinoline since evidence of carcinogenicity has been observed in rats and mice of both sexes in studies of less than one year of duration. It is noteworthy that one type of tumor observed in both species, namely, hemangioendotheliomas, is uncommon in both rats and mice. The concern is further reinforced by the observations of mutagenicity and genotoxicity in short-term tests.

There is a **HIGH** level of **concern over the extent of exposure.** Quinoline is used as an intermediate in manufacturing: In 1990, 38,000 lbs. were used in the US, as reported in the TSCA Inventory Update Rule data collection (Sherlock, 1995). Quinoline is a component of creosote and certain other products made from fossil fuels. The Agency for Toxic Substances and Disease Registry reported that US production of creosote in 1986 was approximately 68 million gallons and that quinoline comprised 0.7% and 0.9% of two samples of creosote analyzed for composition (ATSDR, 1990). It is among the more prevalent aza-arenes present as environmental pollutants; its wide distribution is primarily the result of its production during natural combustion and pyrolysis processes (CHIP, 1983). The level of concern is strengthened by the detection of quinoline in urban air. In one series of studies, two particulate samples collected from New York City air were analyzed for quinoline. The calculated concentrations of quinoline on particulates in each air sample were 69 and 22 ng/1000m^3, respectively (Dong and Locke, 1977a; Dong and Locke, 1977b, Dong *et al.*, 1978). The level of concern is reinforced by the detection of quinoline in tobacco smoke. In one study Dong *et al.* (1978) detected 1.67 μg quinoline/non-filtered cigarette in mainstream smoke, and 18 μg quinoline/non-filtered cigarette in sidestream smoke. In addition, wastewater from synthetic fuel production is expected to be another major source of quinoline in the environment (CHIP, 1983).

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CARCINOGENICITY DATA SUMMARY: 5-CHLORO-*o*-TOLUIDINE AND ITS HYDROCHLORIDE

5-Chloro-*o*-toluidine and its hydrochloride salt (C.I. Azoic Diazo Component 32; 5-chloro-2-methylaniline; CAS No. 95-79-4) are used as dyes for cotton, silk, and nylon. This aromatic amine is also used as a chemical intermediate in the synthesis of other dyes. 5-Chloro-*o*-toluidine has not been reviewed by IARC, although the structurally-related compound 4-chloro-*o*-toluidine has been reviewed and classified as a group 2A carcinogen by IARC in 1990.

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to 5-chloro-*o*-toluidine hydrochloride were found in recent literature searches performed by OEHHA. Occupational studies of workers exposed to 4-chloro-*o*-toluidine suggest an increased risk of bladder cancer associated with exposure to this structurally related chemical, however (IARC, 1990).

Animal bioassays

1. Mouse long-term feeding studies (78 weeks + an additional 13 week observation period): NCI, 1979. A significant increase in hemangiosarcomas was observed in both males (1/20 controls; 11/50 low-dose group; 37/48 high-dose group) and females (0/20 controls; 6/50 low-dose group; 22/43 high-dose group). The incidences of hepatocellular carcinomas and combined hepatocellular adenomas and carcinomas were also significantly increased in both males (carcinomas: 4/20, 19/50, 25/47; combined adenoma/carcinoma: 4/20, 20/50, 27/47) and females (carcinomas: 0/20, 19/50, 26/43; combined adenoma/carcinoma: 0/20, 21/50, 31/43). The NCI concluded that the chemical "was carcinogenic to $B6C3F_1$ mice, inducing hemangiosarcomas and hepatocellular carcinomas in both males and females."

2. Rat long-term feeding studies (78 weeks + additional 26 week observation period): NCI, 1979. Although no statistically significant increases in treatment-related tumors were observed, a significant positive association was observed in male rats between dose and the incidence of adrenal pheochromocytomas (0/20; 2/49; 7/48; Cochran-Armitage test, $p = 0.019$).

Other relevant data

5-Chloro-*o*-toluidine binds to hemoglobin *in vivo* in female Wistar rats, and to a lesser extent in female $B6C3F_1$ mice following oral administration (Birner and Neumann, 1988). The chemical did not induce unscheduled DNA synthesis in primary cultured rat hepatocytes exposed *in vitro* (Yoshimi *et al*, 1988). 5-Chloro-*o*-toluidine hydrochloride is structurally related to 4-chloro-*o*-toluidine, which has been classified by IARC as a 2A carcinogen (IARC, 1990). The results of a computerized analysis of structure-activity relationships based on a set of rules generated by US EPA experts (Oncologic, version 1.0) finds that 5-chloro-*o*-toluidine is of high-to-moderate concern (i.e., the highest level of concern noted for chemicals which are not included in the database of carcinogenicity bioassay results from which the program rules are derived).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **HIGH** level of **carcinogenicity concern** over 5-chloro-*o*-toluidine and 5-chloro-*o*-toluidine hydrochloride since hemangiosarcomas, a relatively uncommon tumor, were observed in high incidence in both male and female mice. In addition, hepatocellular carcinomas (and carcinomas/adenomas combined) were increased in both sexes of the mouse. Although 5-chloro-*o*-toluidine tested negative in the female rat and the findings in the male rat were equivocal, this may be due to the fact that the maximum tolerated dose may not have been reached in this study. The concern is reinforced by the structural similarity with 4-chloro-*o*-toluidine, a known carcinogen, and by the results of a computerized analysis of structure-activity

relationships based on a set of rules generated by US EPA experts (Oncologic, version 1.0), which predicts that 5-chloro-*o*-toluidine is of high-to-moderate concern.

There is a **MEDIUM** level of **concern over the extent of exposure** since 5-chloro-*o*-toluidine and 5-chloro-*o*-toluidine hydrochloride are produced in the U.S. (U.S. production levels reported by U.S. EPA's 1990 TSCA Inventory Update: 57,378 lbs.) and are imported into the U.S. (4.8 E+07 g were imported in 1975). Readily absorbed by the skin or by inhalation, exposure is thought to be limited primarily to workers in the chemical and dye manufacturing and textile industries (NCI, 1979). Releases to the environment may occur during manufacture, and indeed, 5-chloro-*o*-toluidine has been detected in tap water drawn from the Rhine in the Netherlands (HSDB).

References

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CARCINOGENICITY DATA SUMMARY: 2,4,5-TRIMETHYLANILINE

2,4,5-Trimethylaniline (CAS number 137-17-7) was formerly manufactured in the US as an intermediate for the dye Ponceau 3R, formerly used in foods and cosmetics. The hydrochloride (CAS number 6334-11-8) is expected to be toxicologically equivalent. No evidence of 2,4,5-trimethylaniline manufacture in the US since the 1960s was found, but it is unclear whether it might be present in imported products, or as an environmental contaminant in areas of former manufacture or storage. 2,4,5-Trimethylaniline was tested by the National Cancer Institute in 1979 and reviewed by IARC in 1982. The National Cancer Institute found that 2,4,5-trimethylaniline was carcinogenic for male and female F344 rats and female $B6C3F_1$ mice. On the other hand IARC concluded that the evidence of carcinogenicity was inadequate in humans and limited in animals (group 3 carcinogen). The bioassay results are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to 2,4,5-trimethylaniline were found in an earlier search by IARC (1982) or more recently by OEHHA.

Animal bioassays

1. Rat long-term diet studies: NCI, 1979. Hepatocellular carcinomas and neoplastic nodules, and lung adenomas and carcinomas were observed in both males and females. The dose-related trend for liver tumors was significant ($P < 0.001$, Cochran-Armitage trend test) in both males (controls 1/19; 200 ppm 6/50; 800 ppm 20/50) and females (controls 0/20; 200 ppm 12/49; 800 ppm 27/50), and for the lung tumors in females. Incidences of liver tumors relative to controls were significant ($P < 0.01$, Fisher Exact test) for liver tumors in high-dose males and in females at both high and low doses. The incidences of lung tumors in females (controls 0/20; 200 ppm 3/43; 800 ppm 11/50) were also statistically significant ($P < 0.01$, Fisher Exact test). Although NCI reported that the abundance of the major component of the test material was < 99.9 % by gas chromatography, and provided other identity data, IARC (1982) asserted that the purity of the test compound had not been established and noted the identification of at least one impurity. Also the design of this study, one of the early series conducted by NCI, is not consistent with the protocol later established as a standard by the National Toxicology Program. The control groups were small (20 animals initially), and the test animals were housed in the same room as animals exposed to several other potentially carcinogenic test materials.

2. Rat long-term diet study (males only): Weisburger, 1978. Incidence of subcutaneous fibromas and fibrosarcomas, and of liver tumors, was elevated in the low-dose group, but this result was statistically significant ($P < 0.025$) only relative to a pooled control group. Tumor incidences in the matched controls, pooled controls, low dose, and high dose groups, respectively, were as follows: fibromas and fibrosarcomas 4/22, 18/111, 6/17, 1/25; liver tumors 2/22, 2/111, 3/17, 2/25.

3. Mouse long-term diet studies: NCI, 1979. Hepatocellular carcinomas were observed in both male and female mice. The dose-related trend for liver tumors was significant (controls 0/20; 50 ppm 18/49; 100 ppm 40/50; $P < 0.001$, Cochran-Armitage trend test) in females. Incidences relative to controls were significant ($P < 0.01$, Fisher Exact test) for liver tumors in females at both high and low doses. In males incidences were elevated in both dose groups (controls 5/20; 50 ppm 26/50; 100 ppm 27/50), but the statistical significance was lower ($P < 0.05$) due to the high background incidence of this tumor. Incidences of hemangiosarcomas were also somewhat increased in female mice (controls 0/20, 50 ppm 11/49, 100 ppm 7/50). Although NCI reported that the abundance of the major component of the test material was < 99.9 % by gas chromatography, and provided other identity data, IARC (1982) asserted that the purity of the test compound had not been established and noted the identification of at least one impurity. Also the design of this study, one of the early series conducted by NCI, is not consistent with the protocol later established as a standard by the National Toxicology Program. The matched control groups were small (20 animals initially), and the test animals were housed in the same room as animals exposed to several other potentially carcinogenic test materials.

4. Mouse long-term diet studies: Weisburger, 1978. Liver and lung tumors were observed in both males and females. Incidences of these tumors in both males and females were statistically significant (at least $P < 0.05$) relative to a pooled control group. Tumor incidences in the matched controls, pooled controls, low dose, and high dose groups, respectively, were as follows. Hepatomas; males, 3/18, 7/99, 9/14, 19/21; females, 0/20, 1/102, 6/15, 14/22. Lung tumors; males, 5/18, 24/99, 11/14, 10/21; females, 6/20, 32/102, 11/15, 12/22. Survival was poor in the high-dose groups of both sexes, and IARC (1982) noted that this and the limited detail provided in the published report made it difficult to evaluate the study.

Other relevant data

2,4,5-Trimethylaniline was found to be mutagenic in the *Salmonella* reverse mutation assay, but did not induce strand breaks in the DNA of Chinese hamster V79 cells *in vitro*. (Zimmer *et al.*, 1980). 2,4,5-Trimethylaniline is structurally related to other anilines which induce liver tumors, such as the liver carcinogen Ponceau 3, a dye made from trimethylaniline mixtures.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **HIGH** level of **toxicological concern** over 2,4,5-trimethylaniline since carcinogenicity has been observed in both sexes of two species; rat and mouse. However, both the studies by NCI and, especially, those by Weisburger, have their limitations. The early NCI studies for the Carcinogenesis Testing Program (now the National Toxicology Program) were smaller and more limited in design than the standard bioassay now used, although clear results in some such studies have been accepted as reliable. The NCI found as follows: "It is concluded that under the conditions of this bioassay, 2,4,5-trimethylaniline was carcinogenic for male and female F344 rats and female B6C3F_1 mice …" On the other hand IARC (1982) described the overall evidence of carcinogenicity in animals as limited. They did not state their reasons for this divergence of opinion in detail, although it is clear that the study design, results and reporting of the Weisburger *et al.* (1978) study are such that this study is of value as supporting evidence only. The concern is reinforced by the observation of mutagenicity in a short-term test. Structure-activity comparisons with other anilines also support the level of concern; the dye Ponceau 3R, which was made from trimethylaniline mixtures, was identified as a liver carcinogen and its registrations for food and cosmetic uses were withdrawn.

There is a **LOW** level of **concern over the extent of exposure.** Although 2,4,5-trimethylaniline is no longer manufactured in bulk and is not naturally abundant it was extensively used at one time (IARC, 1982), and some residual exposure may occur.

References

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CARCINOGENICITY DATA SUMMARY: CARBARYL

Carbaryl (1-naphthyl N-methyl carbamate; Sevin; CAS No. 63-25-2) is a broad spectrum carbamate pesticide used primarily for agricultural purposes. Indoor and outdoor homeowner uses and livestock and poultry uses account for greater than 50% of the usage in the U.S. Carbaryl was reviewed by IARC in both 1976 and 1987. IARC concluded that there was no data available on the evidence of carcinogenicity in humans, and that there was inadequate evidence in animals (group 3 carcinogen). However, the IARC review did not included the Hazelton Laboratory studies submitted to US EPA and the California Department of Pesticide Regulation (CDPR) in 1993. Carbaryl was reviewed by US EPA in 1994. US EPA concluded that carbaryl is carcinogenic to animals and classified it as a Group C (possible human carcinogen) (US EPA, 1994). The studies reviewed by IARC, as well as the additional data available, are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

One case-control study by Davis *et al*. (1993) reported significant positive associations for several different pesticide uses, including carbaryl use in the garden or orchard (OR 2.4, CI 1.1 - 5.6) with risk for childhood brain cancer vs. childhood cancers other than brain. The data from this study are too limited to form the basis for an evaluation of the carcinogenicity of carbaryl to humans because of the small study size, the limited nature of the exposure data, and the fact that an association of brain cancer with exposure to carbaryl was observed in comparison with the "other childhood cancers" group, but not in comparison with the "non-cancer friend" group (i.e., age matched controls).

Animal bioassays

1. Rat long-term feeding studies (104 weeks): Hazelton Laboratory, 1993, submitted to CDPR (1993). Statistically significant increases in urinary bladder transitional cell papillomas and carcinomas were seen in high-dose males and females and statistically significant positive trends for transitional cell carcinomas, papillomas, and combined tumors were observed in both sexes. Statistically significant increases in thyroid adenomas and combined adenomas/carcinomas were seen in high-dose male rats, as was a statistically significant positive trend for thyroid follicular cell adenomas and combined adenomas/carcinomas. Statistically significant increases in liver adenomas and foci were seen in high-dose females, as was a significant positive trend for liver adenomas (US EPA, 1994). The highest dose tested was considered by the US EPA's Carcinogenicity Peer Review Committee to be excessively high due to decreased body weight gains and alteration in hematology and clinical chemistry (US EPA, 1994). The next dose level was a factor of 5 lower than the high dose.

2. Mouse long-term feeding studies (104 weeks): Hazelton Laboratory, 1993, submitted to CDPR (1993). In males, statistically significant increases in hemangiosarcomas were observed in the second-highest dose group, and in combined hemangiomas/hemangiosarcomas in the two highest dose groups. A statistically significant increase in combined renal tubular cell adenomas/carcinomas was observed in high-dose males and significant positive trends in renal tubule cell adenomas, carcinomas, and combined adenomas/carcinomas were seen in males. In females, a statistically significant increase in hemangiosarcomas was seen in the high-dose group as well as significant positive trends for hemangiosarcomas and combined hemangiomas/hemangiosarcomas. Statistically significant increases in hepatocellular adenomas and combined adenomas/carcinomas were seen in high-dose females, as well as significant positive trends for hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas (US EPA, 1994). The highest dose tested was considered by the US EPA's Carcinogenicity Peer Review Committee to be excessively high due to significantly decreased body weight gain during week 13, significant decrease in choline esterase activity, and signs of toxicity in the kidney, bladder and spleen (US EPA, 1994). The next dose level was a factor of 8 lower than the high dose.

3. Rat long-term gavage studies (22 months): Andrianova and Alekseev, 1970. This study was judged inadequate by IARC (1976), due to high mortality.

4. Mouse long-term gavage, followed by feeding studies (3 weeks gavage + 74 weeks diet): Innes *et al*., 1969. No treatment-related tumors were observed.

5. Rat long-term feeding studies (104 weeks): Carpenter *et al*., 1961. No treatment-related tumors were observed.

Other relevant data

Carbaryl has tested positive in several, but not all of the various *in vitro* short-term genotoxicity assays reported to date. It was negative in several standard plate *Salmonella* reverse mutation assays, but was positive in one *Salmonella* assay which included a pre-incubation step with carbaryl. Carbaryl was negative in yeast recombination assays and gene conversion assays, and equivocal for alterations in human sperm morphology and sex-linked lethal mutations in *Drosophila melanogaster*. Carbaryl was mutagenic in a gene mutation assay with cultured Chinese hamster V79 cells, clastogenic in Chinese hamster fibroblasts, induced chromosomal aberrations in Chinese hamster ovary cells, and inhibited mitosis and spindle fiber formation in cultured human embryonic fibroblasts (IARC, 1987).

Carbaryl has the potential to be transformed in the stomach to N-nitrosocarbaryl, a proven mutagen and carcinogen in rats following oral or subcutaneous administration (Davis *et al*., 1993). N-nitrosocarbaryl interacts with human DNA *in vitro*, forming alkali-sensitive bonds (IARC, 1987).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM HIGH** level of **carcinogenicity concern** over carbaryl since evidence of carcinogenicity has been observed in multiple organs and multiple species at multiple sites: in rats, neoplasia of the thyroid (male), liver (female), and urinary bladder (male and female); in mice, neoplasia of the liver (male), kidney (male), and vascular system (male and female). The extensive tumor findings in high-dose animals were discounted by US EPA, since the highest dose tested in both species was considered to be excessively high (US EPA, 1994). However, no clear mechanistic explanation was provided to account for the tumorigenicity. The next doses were a factor of 8 lower for mice and 5 lower for rats. Significant positive trends were observed at lower doses for each of the elevated tumor types in the mouse and the rat. It is noteworthy that the incidence of a relatively uncommon tumor type, i.e., combined hemangiomas/hemangiosarcomas, was significantly increased relative to controls in the second-highest dose group of male mice, as well as in the highest dose group. IARC in its early evaluations (1976; 1987) did not review the data from the Hazelton bioassays. Both the US EPA and the United Kingdom's Department of Health have reviewed these studies. The US EPA concluded that exposure to carbaryl is an animal carcinogen, and classified it as a group C (possible human) carcinogen (US EPA, 1994). The UK Department of Health concluded that carbaryl is a potential human carcinogen (Anon., 1995). The concern is reinforced by the observations of genotoxicity in short-term tests and by the potential for carbaryl to be transformed to a mutagenic and carcinogenic metabolite. The California Department of Pesticide Regulation assigned carbaryl a "high" priority for risk assessment on 1/28/94 based on excessive use and potential for carcinogenicity.

There is a **HIGH** level of **concern over the extent of exposure** since carbaryl is used as an insecticide on a wide range of food crops, and has been detected in foods and drinking water (IARC, 1987). In 1982, annual production in the U.S. was estimated to be between 35,059,500 - 44,982,000 lbs. In California in 1993, 786,395 pounds. were reportedly used in 11,818 applications on various crops (CDPR, 1995), while in 1995 usage doubled to 1,454,820 pounds (CDPR, 1996). Exposure may occur by inhalation or dermal absorption in either the occupational setting or the home environment. A 1983 NIOSH survey estimated that 16,544 workers were exposed in 2,381 facilities across the US (NIOSH, 1994). Exposure may also occur in the general population by ingestion of residues on food; the average daily intake of carbaryl for

adults during the period 1980-1984 was estimated to be 0.12 - 0.032 µg/kg (Gartrell *et al*., 1985; 1986; Gunderson, 1988).

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CARCINOGENICITY DATA SUMMARY: HYDRALAZINE AND ITS HYDROCHLORIDE

Hydralazine (1-Hydrazinophthalazine; CAS number 86-54-4; usually formulated as the monohydrochloride, CAS number 204-20-1) is a synthetic compound widely used as a drug for the treatment of hypertension. Hydralazine was reviewed by IARC in both 1980 and 1987. IARC concluded that the evidence of carcinogenicity was inadequate in humans and limited in animals (group 3 carcinogen). The IARC review did not include the mouse study of Drozdz et al. (1987), the Hazleton Laboratory (1985) studies in rats, or the DNA adduct formation studies of Mathison et al. (1994). These results, in addition to the studies reviewed by IARC, are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

Two studies suggested an association between hydralazine exposure and human cancer. Both of these involved small numbers of patients exposed to hydralazine, and did not completely exclude possible confounding factors or selection bias. Two other studies failed to find such an association. IARC reviewed this epidemiological evidence and judged it to be inadequate (IARC, 1980; 1987). In a recent literature search OEHHA did not identify additional epidemiologic studies.

Animal bioassays

1. Rat long-term (104 weeks) gavage studies: Hazelton Laboratories, 1985. Sprague-Dawley rats received 15, 30 or 60 mg/kg hydralazine HCl by gavage in water. Significant increases in the incidences of benign liver neoplastic nodules were reported in the high-dose males (4/20, compared to 1/51 in controls) and in the mid- (4/28) and high-dose (5/25), compared to 0/48 in controls) females. Significant mortality was observed at the high-dose level, so the dose given to these groups was reduced during the second and third week of the study. The study authors diagnosed the liver lesions as benign tumors. In the males an increased incidence of testicular interstitial cell tumors was noted in the high-dose group. Increased interstitial cell hyperplasia was also noted, both in this dose group and, within certain defined time periods during the second half of the study, at the two lower doses. The testicular tumors were diagnosed as benign, and described as similar to spontaneous lesions of this type. (This study was not reviewed by IARC (1980, 1987).)

2. Mouse lifetime drinking water studies: Toth, 1978. Swiss mice received 0.125% hydralazine HCl in drinking water. Increased incidences of lung adenoma and adenocarcinoma were noted; 30/50 (60%) of treated females *vs.* 18/50 (36%) of female controls, and 23/50 (46%) of treated males *vs.* 13/50 (26%) of male controls developed lung tumors. Limitations of the study design and analysis, and low purity of the test compound (93% rather than the USP standard of 98%) were noted by IARC (1980). This was the only animal bioassay reviewed by IARC (1980) in reaching their conclusion that evidence for carcinogenicity was limited.

3. Mouse lifetime drinking water studies: Drozdz *et al.*, 1987. Swiss mice received 0.312% hydralazine HCl in drinking water. Increased incidences of lung adenoma and adenocarcinoma were noted; 33/60 (55%) of treated females *vs.* 10/50 (20%) of female controls, and 26/60 (43%) of treated males *vs.* 8/50 (16%) of male controls. Increased incidences of malignant lymphoma, angioma or angiosarcoma at various sites and hepatoma were noted in both exposed groups, but the authors were unwilling to conclude that they were dose related due to the small number of tumors involved. (This study was not reviewed by IARC (1980; 1987).)

Other relevant data

Hydralazine was found to be a mutagen in the *Salmonella* reverse mutation assay in several tests. A bacterial DNA damage assay was positive. A sister chromatid exchange (SCE) test in human lymphocytes *in* vitro was positive, but an SCE test in the Chinese hamster *in vivo* was negative. A cell transformation assay in BALB/3T3 cells *in vitro* was negative. Two DNA repair tests, using rat or rabbit hepatocytes, were

positive, although various other DNA repair tests *in vitro* were negative. Genetic toxicity results with hydralazine have been reviewed by IARC (1980; 1987) and Ciba-Geigy (1986).

Various studies have shown that hydralazine causes formation of DNA adducts *in vivo* and *in vitro* (Mathison *et al.*, 1994). A well established side effect of use of hydralazine in some patients, especially those receiving high doses, is drug-induced lupus erythematosus. This is an auto-immune condition associated with the appearance of anti-nuclear or anti-DNA antibodies (IARC, 1980).

Hydralazine appears to cause formation of oxidative radicals, and reduces the activity of superoxide dismutase in the lungs of mice (Drozdz *et al.*, 1987).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM HIGH** level of **carcinogenicity concern** over hydralazine since lung adenomas and adenocarcinomas were observed in separate studies in both sexes of the mouse, and benign liver neoplastic nodules were observed in both sexes of the rat. IARC (1980) concluded that there was limited evidence in animals based on the findings of lung tumors in males and females by Toth (1978); the mouse study of Drozdz *et al.* (1987) and the Hazelton Laboratory (1985) studies in rats were not reviewed by IARC. A more recent review by IARC (1987) did not refer to any additional animal data beyond that included in the earlier review. The concern raised by the findings in the rat is reduced by the conclusion of the study authors that the liver and testicular tumors were benign. The concern is reinforced by the observations of mutagenicity and induction of DNA damage in short-term tests, and the identification of lupus erythematosus, an autoimmune syndrome associated with DNA damage or modification, as a possible side effect in humans treated with hydralazine.

There is a **HIGH** level of **concern over the extent of exposure** since hydralazine is widely used as a drug for the treatment of essential hypertension and also hypertension during pregnancy. NIOSH (1983) has estimated that some occupational exposure to hydralazine occurs in the United States.

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CARCINOGENICITY DATA SUMMARY: HYDROQUINONE

Hydroquinone (1,4-benzenediol; *p*-hydroxyphenol; CAS No. 123-31-9) is used as an antioxidant in the rubber industry, as a developing agent in black and white photography, as a polymerization inhibitor for vinyl acetate, as a stabilizer in paints, varnishes, motor fuels, and oils, as an intermediate in the chemical manufacturing industry, and as a skin bleaching agent in cosmetic products. Hydroquinone has been detected in tobacco smoke. IARC reviewed hydroquinone in 1977 and concluded that the evidence for carcinogenicity was inadequate in humans and animals (group 3). Two studies of possible carcinogenicity of hydroquinone in rats and mice (NTP, 1989; Shibata *et al.*,1991) have found some evidence of carcinogenicity. Studies reviewed by IARC and these additional studies are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to hydroquinone were reported in an earlier review by IARC (1977).. A mortality study of workers exposed to hydroquinone found no association between hydroquinone exposure and cancer (Pifer et al., 1995). A study of "lithographers" exposed to hydroquinone and other chemicals used in the printing industry found an increase in the incidence of malignant melanoma (Nielsen et al., 1996). A study of workers exposed to hydroquinone in photographic processing found no association with cancer (Friedlander et al., 1982).

Animal bioassays

1. Rat long-term feeding studies (104 weeks): Shibata *et al.*, 1991. A statistically significant increase in the incidence of renal tubular cell adenomas was observed in males (controls 0/30; treated 14/30). A significant increase in tumor incidence at any site was not reported in females.

2. Mouse long-term feeding studies (104 weeks): Shibata *et al.*, 1991. A nonstatistically significant increase in the incidence of renal tubular cell adenomas was observed in males (controls 0/28; treated 3/30). A statistically significant increase in hepatocellular adenomas was observed in males (controls 6/28; treated 14/30). A significant increase in tumor incidence at any site was not reported in females.

3. Rat long-term gavage studies (104 weeks): NTP, 1989; Kari *et al.,* 1992. A statistically significant dose-related increase in the incidence of mononuclear cell leukemia was observed in low- and high-dose females (9/55; 15/55; 22/55). NTP concluded that there was "some evidence of carcinogenic activity of hydroquinone in female F344/N rats." A statistically significant increase in the incidence of renal tubular cell adenomas was observed in high-dose males (0/55; 4/55; 8/55). NTP concluded that there was "some evidence of carcinogenic activity of hydroquinone in male F344/N rats."

4. Mouse long-term gavage studies (104 weeks): NTP, 1989; Kari *et al.,* 1992. A statistically significant dose-related increase in the incidence of hepatocellular tumors (adenomas and carcinomas combined) was observed in low- and high-dose females (3/55; 16/55; 13/55). NTP concluded that there was "some evidence of carcinogenic activity of hydroquinone in female $B6C3F_1$ mice."

5. Mouse long-term pellet implantation studies (25 weeks): Boyland *et al.*, 1964. Following implantation in the bladder of cholesterol pellets containing either hydroquinone, or no hydroquinone, a statistically significant increase in the incidence of bladder carcinoma was observed in mice that had received the hydroquinone-containing pellets (6/19) vs. the control group (5/77).

Other relevant data

Hydroquinone was not mutagenic in the *Salmonella* reverse mutation assay; equivocal in the *Drosophila* sex-linked recessive lethal mutation test, and positive in the mouse lymphoma assay. There is extensive evidence for the clastogenicity of hydroquinone in mammalian cells, both *in vitro* and *in vivo*. It induces sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells and micronuclei,

and chromosomal loss and breakage in mouse bone marrow cells *in vivo*. Hydroquinone induces unscheduled DNA synthesis (UDS) in rat liver cultures. Hydroquinone induces DNA adduct formation in mouse bone marrow cells and HL-60 promyelocytic leukemic cells (Chen and Eastman, 1995) and in human bone marrow cells *in vitro* (Levay *et al*., 1993). Hydroquinone did not produce detectable DNA adducts in kidney tissues following oral administration to male and female F344 rats (English et al., 1994a); however, oral administration of 50 mg/kg/day appeared to increase the rate of renal tubule cell division in male F344 rats but not in male Sprague-Dawley rats or female F344 rats (English et al., 1994b). Hydroquinone is one of the DNA-reactive metabolites of benzene, a known human carcinogen.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM HIGH** level of **carcinogenicity concern** over hydroquinone. Two carcinogenicity studies in male rats have observed an increased incidence of renal tubular cell adenomas, one study in female rats has observed a dose-related increase in the incidence of mononuclear cell leukemia, and studies in mice have reported an increased incidence of hepatocellular adenomas in males, and of hepatocellular adenomas and carcinomas (combined) in females. The concern is reinforced by the induction of UDS, by the numerous observations of clastogenicity both *in vivo* and *in vitro* in mammalian (and human) cells, and by the formation of DNA adducts in both mouse and human cells *in vitro*. Further reinforcing this level of concern is the fact that hydroquinone is a DNA-reactive metabolite of benzene, a known human carcinogen.

There is a **HIGH** level of **concern over the extent of exposure** since hydroquinone is used in the chemical, rubber, and polymer manufacturing industries, and in the photographic developing business (IARC, 1977; NTP, 1989). Hydroquinone is used in certain cosmetic products, and has been detected in tobacco smoke (IARC, 1977; NTP, 1989). U.S. annual production in 1990 was estimated to be 53,000,000 lbs. In 1994, 1,250 lbs. were reported released by the U.S. TRI. NIOSH (1994) estimated that 381,000 U.S. workers were exposed to hydroquinone in 1993.

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CARCINOGENICITY DATA SUMMARY: VINYL ACETATE

Vinyl acetate (CAS No. 108-05-4) "is used in the production of a wide range of polymers, including polyvinyl acetate, polyvinyl alcohol, polyvinyl acetals, ethylene-vinyl acetate copolymers and polyvinyl chloride-vinyl acetate copolymers, which are widely used in the production of adhesives, paints and food packaging" (IARC, 1995). Vinyl acetate was reviewed by IARC in 1995. IARC concluded that the evidence of carcinogenicity was inadequate in humans and limited in animals, but classified the chemical as a group 2B carcinogen, based on "other relevant data". The studies reviewed by IARC are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

One occupational cohort study of men exposed to numerous chemicals (Waxweiler *et al*., 1981) and one nested case-control study in a cohort of workers exposed to numerous chemicals (Ott *et al*., 1989) have found no association between vinyl acetate exposure and cancer. In reviewing these studies, IARC (1995) concluded that "the available data were too limited to form the basis for an evaluation of the carcinogenicity of vinyl acetate to humans."

Animal bioassays

1. Rat long-term drinking water studies (100 weeks + 30 weeks observation): Lijinsky and Reuber, 1983. A statistically significant increase in the incidence of liver neoplastic nodules was observed in high-dose females (0/20; 0/20; 6/20); a nonsignificant increase was observed in males (0/20; 4/20; 2/20). Statistically significant increases in the incidences of uterine polyps (0/20; 3/20; 5/20), uterine adenocarcinomas (0/20; 1/20; 5/20), and thyroid c-cell adenomas (0/20; 2/20; 5/20) were also observed in females. This study was considered inadequate by IARC (1995) due to small group sample size and degradation of the test chemical, leading to inaccurate dosing of the treated groups under the experimental conditions of the study.

2. Rat long-term inhalation studies (104 weeks): Bogdanffy *et al.*, 1994a. A statistically significant increase in the incidence of nasal tumors (benign and malignant) was observed in high-dose males (0/59; 1/59; 7/59); a nonsignificant increase in squamous cell carcinoma of the nasal cavity was observed in high-dose females (0/60; 0/60; 4/59).

3. Mouse long-term inhalation studies (104 weeks): Bogdanffy *et al*., 1994a. No treatment-related tumors were observed in either male or female mice.

4. Rat *in utero* and long-term drinking water studies (*in utero* + 104 weeks): Bogdanffy *et al*., 1994b. No treatment-related tumors were observed in either male or female rats.

Other relevant data

"Vinyl acetate is rapidly metabolized by esterases in human blood and animal tissues to acetaldehyde and acetic acid. Vinyl acetate induced sperm abnormalities and sister chromatid exchange in rodents exposed *in vivo*; micronuclei were induced in bone marrow but not in meiotic cells. No DNA binding was seen in rat hepatocytes. In human lymphocytes *in vitro*, vinyl acetate produced chromosomal aberrations, micronuclei, sister chromatid exchange and DNA cross-links. It enhanced viral transformation and sister chromatid exchange in mammalian cells *in vitro*, and it induced DNA-protein cross-links in rat nasal epithelial cells *in vitro*. Vinyl acetate did not induce mutations in bacteria but induced DNA-protein cross-links in plasmid DNA. The primary metabolite of vinyl acetate, acetaldehyde, is genotoxic in a wide range of assays" (IARC, 1995).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM HIGH** level of **carcinogenicity concern** over vinyl acetate. Although IARC (1995) determined that there was inadequate evidence in humans and limited evidence in experimental animals, the agency classified vinyl acetate as a Group 2B carcinogen based on "other relevant data." This classification is based on the following: "(1) Vinyl acetate is rapidly transformed into acetaldehyde in human blood and animal tissues. (2) There is sufficient evidence in experimental animals for the carcinogenicity of acetaldehyde (IARC, 1987). Both vinyl acetate and acetaldehyde induce nasal cancer in rats after administration by inhalation. (3) Vinyl acetate and acetaldehyde are genotoxic in human cells *in vitro* and in animals *in vivo*" (IARC, 1995). In the absence of the "other relevant data" IARC would have placed the chemical in Group 3.

There is a **HIGH** level of **concern over the extent of exposure** since vinyl acetate is a high volume industrial chemical with widespread uses (IARC, 1995). U.S. annual production was 2,800,000,000 lbs. in 1993. The Vinyl Acetate Toxicology Group, Inc. reports that vinyl acetate is not currently produced commercially in California (VATG, 1996), however, significant quantities are imported into the state. In 1987 16 facilities in California reported processing or otherwise using vinyl acetate; maximum amounts of vinyl acetate reported to be on site at each of these facilities ranged from 100 to 9,999,000 pounds (ATSDR, 1992). California TRI data indicate that approximately 50,000 pounds of vinyl acetate are released annually in the state (48,012 pounds released in 1994, including 30,358 pounds release to the air; 53,195 pounds released in 1993, including 33,261 pounds released to the air). NIOSH (1994) estimated that in 1983 129,024 workers were potentially exposed to vinyl acetate during production and operation by inhalation and dermal routes. The level of concern is supported by the detection of vinyl acetate in wastewater effluents, cigarette smoke, coal smoke, and emissions from new carpets, and its release from food packaging during heating in a microwave oven (IARC, 1995).

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CARCINOGENICITY DATA SUMMARY: 5-NITRO-ORTHO-TOLUIDINE

5-Nitro-*o*-toluidine (2-amino-4-nitrotoluene; 2-methyl-5-nitroaniline; CAS No. 99-55-8) is used as a precursor for the synthesis of a number of dyes and pigments. It is also used in the textile industry for *in situ* dyeing. It is a metabolite of 2,4-dinitrotoluene. 5-Nitro-*o*-toluidine was reviewed by IARC in 1990. IARC concluded that there was no data available on the evidence of carcinogenicity in humans and that the evidence in animals was limited (group 3 carcinogen). Since the IARC (1990) review, IARC modified its criteria on the use of mechanistic data in evaluating carcinogenicity data (IARC, 1992). Mechanistic information that has become available since the IARC review in 1990 are described below.

Carcinogenicity Data available:

Epidemiological studies

IARC (1990) noted that no data on long-term effects of human exposure to 5-nitro-*ortho*-toluidine have been reported, and OEHHA did not find epidemiological data in a recent literature search.

Animal bioassays

1. Rat long-term feed studies (78 weeks + 30-31 weeks observation): NCI, 1978. Fischer 344 rats were fed 0.005% or 0.01% 5-nitro-*ortho*-toluidine in the diet. Increased incidences of hepatocellular carcinoma in male rats were not statistically significant relative to the control, but a significant positive dose-related trend in tumor incidence was found (control, 0/47; low-dose, 0/41; high-dose, 3/46). No increased tumor incidences were seen in the females.

2. Mouse long-term feed studies (78 weeks + 20 weeks observation): NCI, 1978. A statistically significant increase in the incidence of hepatocellular carcinoma was seen in both male and female $B6C3F_1$ mice (control, low-dose and high dose incidences: males - 12/50, 12/44, 29/45; females - 2/47, 7/46, 20/45). In addition, there was an increase in the combined incidence of hemangiomas and hemangiosarcomas in male mice and an increased incidence in hemangiosarcomas in female mice. NCI considered these tumors "to be associated with compound administration, since they rarely occur in untreated $B6C3F_1$ mice."

3. Mouse ip (16 week) screening studies: Maronpot *et al.,* 1986. In a lung-tumor induction screening study in strain A mice, incidences of lung tumors were 11%, 18%, 30%, and 6% in vehicle control, low-dose, mid-dose and high-dose groups, respectively. In a similar study in A/J mice, a treatment- related effect was not seen among surviving animals.

Other relevant data

5-Nitro-*ortho*-toluidine was found to be mutagenic both with and without metabolic activation in the *Salmonella* reverse mutation assay (IARC, 1990). The chemical also formed hemoglobin adducts *in vitro* (Zwirner-Baier *et al*., 1994). The results of a computerized analysis of structure-activity relationships based on a set of rules generated by US EPA experts (Oncologic, version 1.0) finds that 5-nitro-*o*-toluidine is of high-to-moderate concern (*i.e.,* the highest level of concern noted for chemicals which are not included in the database of carcinogenicity bioassay results from which the program rules are derived).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM HIGH** level of **carcinogenicity concern** over 5-nitro-*ortho*-toluidine since evidence of carcinogenicity has been observed in both sexes of $B6C3F_1$ mice and a significant trend in the incidence of hepatocellular carcinomas was found in male rats. No tests in other species have been reported. On the basis of the bioassay data NCI concluded the substance was carcinogenic to male and female $B6C3F_1$ mice; IARC (1990) found limited evidence for carcinogenicity of the chemical in experimental animals; however, information on structure-activity relationships and hemoglobin binding were not included in this evaluation. The concern is reinforced by the observations of mutagenicity in short-term tests, hemoglobin binding activity, and structural similarity to known carcinogens, as indicated by the Oncologic computer program.

There is a **MEDIUM** level of **concern over the extent of exposure.** The compound is an intermediate in the production of pigments and azo dyes It is a metabolite of 2,4-dinitrotoluene. It is present in waste water effluent from munitions plants and sites, and dye and polyurethane manufacturing facilities. In 1990, use of greater than 25,000 lbs was reported to US EPA TSCA (Sherlock, 1995). There is the potential for occupational exposure.

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CARCINOGENICITY DATA SUMMARY: ACROLEIN

Acrolein (2-propenal; CAS No. 107-02-8) is produced in the chemical industry by the oxidation of propylene. It is also produced as a photochemical oxidation product, and by the combustion of fossil fuels, wood, paper, cooking oils, and vegetable material such as tobacco. Acrolein has been identified as a natural product of certain plant species. The major use of acrolein is for the synthesis of acrylic acid for acrylate polymer products. It is used as an intermediate in the manufacture of glycerol, polyurethane, and methionine. It is used as an aquatic herbicide and as a rodenticide, and is also used for the control of algae and bacteria. The US EPA has classified acrolein as a group C carcinogen (US EPA, 1994). Acrolein was reviewed by IARC in 1995. IARC concluded that the evidence of carcinogenicity was inadequate in humans and inadequate in animals (group 3 carcinogen). The IARC review did not include the original data from the studies reported by Parent *et al.* (1991; 1992). These original study data, in addition to the data reviewed by IARC, are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

One nested case-control study in a cohort of workers exposed to numerous chemicals reported two cases of non-Hodgkin's lymphoma, one case of multiple myeloma and three cases of lymphatic leukemia in individuals exposed to acrolein (Ott *et al*., 1989). In reviewing this study, IARC (1995) concluded that "the available data were inadequate to form the basis for an evaluation of the carcinogenicity of acrolein to humans."

Animal bioassays

1. Rat long-term gavage studies (102 weeks): Submitted to CDPR in 1989 and published as Parent *et al*., 1992. Parent *et al.* (1992) reported that no treatment-related tumors were observed in either sex. Based on the published report, IARC (1995) reached an identical conclusion. Upon review of the data from this series of gavage studies submitted as a requirement for the continued use of acrolein as a pesticide in California, the California Department of Pesticide Regulation (CDPR, 1994) concluded that a dose-related increase in pancreatic acinar cell tumors (adenomas and carcinomas) was observed in treated males. CDPR (1994) further concluded that the increased incidences in pancreatic acinar cell tumors in acrolein-treated males was higher than that of the laboratory's historical controls.

2. Mouse long-term gavage studies (18 months): Submitted to CDPR in 1989 and published as Parent *et al*., 1991. High early mortality was observed in all groups and attributed to gavage-related accidents. Parent *et al*. (1991) reported that no treatment-related tumors were observed in either sex. CDPR (1994) concluded that this study was unacceptable for evaluation, due to high early mortality and the late addition of mice to the study as replacements for those that succumbed to gavage-related accidents.

3. Rat long-term drinking water studies (104 weeks + 28 weeks additional observation): Lijinsky and Reuber, 1987; Lijinsky, 1988. The authors reported a nonsignificant increase in the incidence of adrenal cortical adenomas in female rats (controls 1/20; high-dose group 5/20). IARC (1995) noted the lack of a dose-related effect, and the small group size (n = 20).

4. Hamster long-term inhalation studies (52 weeks + 29 weeks additional observation): Feron and Kruysse, 1977. No treatment-related tumors were observed. IARC (1995) noted the short exposure period and the small group size (n = 18).

Other relevant data

"Acrolein induced both somatic and germinal mutations in insects and DNA mutation and DNA damage in bacteria. In cultured mammalian cells acrolein induced gene mutation, sister chromatid exchange and DNA damage; weak induction of chromosomal aberrations was observed in one study. In single studies, acrolein did not induce DNA damage in rats or dominant lethal mutations in mice treated *in vivo*" (IARC, 1995).

Acrolein inhibits DNA synthesis *in vivo* and *in vitro* and forms DNA adducts *in vitro* and *in vivo*. A short-term initiation/promotion assay in rats indicates that acrolein initiates bladder carcinogenesis (Cohen *et al.*, 1992). One of the metabolites of acrolein is glycidaldehyde, which is carcinogenic to mice after skin application and to mice and rats after subcutaneous injection (IARC, 1987). Acrolein is a potent irritant and cytotoxicant, causing intense eye and respiratory irritation in humans, which may serve to limit the amount of exposure.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** over acrolein since evidence of carcinogenicity has been observed only in male rats in one study (submitted to CDPR and published as Parent *et al.*, 1992). Upon review of the original study data, which was not provided in Parent *et al*. (1992) or available to IARC (1995), CDPR (1994) concluded that acrolein induced a significant, dose-related increase in pancreatic acinar cell tumors in male rats. Three additional studies in mice, rats, and hamsters are considered either non-positive, or inadequate for evaluation due to one or more of the following: high early mortality, small numbers of animals tested, and short exposure period. There is a need for additional adequate long-term studies in animals; acrolein is scheduled to be tested in toxicity and carcinogenesis studies by the National Toxicology Program (NTP, 1995). The level of concern is reinforced by the observations of mutagenicity and genotoxicity in numerous short-term tests, and by the fact that it is metabolized to a known animal carcinogen. The level of concern is tempered by acrolein's potent irritant properties (IARC, 1995).

There is a **HIGH** level of **concern over the extent of exposure** since acrolein occurs naturally in foods and is formed during the combustion of fossil fuels, wood, and tobacco and during the heating of cooking oils (IARC, 1995). Acrolein is a widespread atmospheric pollutant which is listed by the California Air Resources Board as a Toxic Air Contaminant. Acrolein is also used extensively as a chemical intermediate and as an herbicide to control weeds in irrigation canals, a rodenticide to control squirrel populations, and as a slimicide to control algae and bacteria (IARC, 1995; CDPR, 1994). U.S. annual production in 1990 was estimated to be 60,000,000 lbs. (Cohen *et al*., 1992). In California, agricultural use was reported as 227,000 lbs. for 1992 and 300,000 lbs. for 1993 (CDPR, 1995).

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CARCINOGENICITY DATA SUMMARY: CHLOROACETALDEHYDE

Chloroacetaldehyde (CAS No. 107-20-0) is an intermediate in the manufacture of 2-aminothiazole and other chemicals. It is a by-product of drinking water chlorination and has also been used to facilitate bark removal from trees, and as a fungicide. The available data are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to chloroacetaldehyde are available.

Animal bioassays

1. Long-term drinking water study in male $B6C3F_1$ mice: Daniel *et al.*, 1992. Significantly increased incidences of hepatocellular tumors included 31% carcinoma and 8% adenoma compared to control incidences of 10% and 5% respectively. Preneoplastic lesions (hyperplastic nodules) were observed in 8% of the treated mice.

Other relevant data

Daniel *et al*. (1992) reported numerous measures of the genotoxicity of chloroacetaldehyde. These genotoxic effects include mutagenicity in *Salmonella* and mammalian cells, induction of aneuploidy in yeast, formation of DNA adducts and induction of DNA strand breaks in human lymphocytic cells. Chloroacetaldehyde was also observed to be a potent inhibitor of DNA synthesis.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** regarding chloroacetaldehyde based on the carcinogenic effects observed in male $B6C3F_1$ mice as described above. Although only one sex of one species was tested, there is extensive genotoxicity data in both bacterial and mammalian cells that support the bioassay findings. In addition, chloroacetaldehyde is a major metabolite of vinyl chloride, a carcinogen listed under Proposition 65, and has been considered one of the likely proximate carcinogens involved in the carcinogenicity of vinyl chloride.

There is a **HIGH** level of **concern over the extent of exposure** to chloroacetaldehyde since there is the potential for widespread exposure to the general public as a result of formation of chloroacetaldehyde as a reaction product from chlorination of drinking water (Daniel *et al.*, 1992). It has also been suggested that the reaction of vinyl chloride monomer and chlorine is a possible source of chloroacetaldehyde in drinking water (Ando and Sayato, 1984). There is further concern due to potential occupational exposure (NIOSH, 1974; RTECS, 1995) and its use as a fungicide (HSDB, 1995).

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CARCINOGENICITY DATA SUMMARY: C.I. DISPERSE YELLOW 3

C.I. Disperse Yellow 3 (N-(4-[(2-hydroxy-5-methylphenyl) azo] phenyl)-acetamide; CAS No. 2832-40-8) is a monoazo pigment dye used to color nylon, polyvinyl chloride and acrylic fibers, wools, furs, cellulose acetate, polystyrene and other thermoplastics. This compound was selected for evaluation as a result of a search of NCI/NTP summary data indicating positive bioassay findings, and information suggesting the potential for high exposures of some occupational subgroups. C.I. Disperse Yellow 3 was reviewed by IARC in 1990. IARC concluded that there was no data available on the evidence of carcinogenicity in humans and that the evidence in animals was limited (group 3 carcinogen). Literature searches did not identify any critical studies published subsequent to the IARC (1990) evaluation. The results of a structure-activity analysis performed by OEHHA, in addition to the studies reviewed by IARC, are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to C.I. Disperse Yellow 3 were found by IARC (1990) or in subsequent literature searches by OEHHA.

Animal bioassays

1. Rat long-term feeding studies (103 weeks + 2 weeks observation): NTP, 1982. A significant increase in neoplastic liver nodules was observed in low- and high-dose males (1/49 controls; 15/50 low-dose group; 10/50 high-dose group). Five rare stomach tumors were observed in treated males (0/49; 4/50; 1/50); NTP noted that a relationship between the stomach tumors and treatment could not be clearly established, while IARC (1990) concluded that the stomach tumors were possibly related to treatment. No treatment-related tumors were observed in females.

2. Mouse long-term feeding studies (103 weeks + 2 weeks observation): NTP, 1982. A significant increase in hepatocellular adenomas was observed in low- and high-dose females (0/50 controls; 6/50 low-dose group; 12/50 high-dose group). A nonsignificant increase in hepatocellular carcinomas was observed in females (2/50; 4/50; 5/50). A significant increase in malignant lymphoma was observed in high-dose females, as was a significant dose-related trend ($p < 0.05$) (10/50; 16/50; 19/50). Due to the historical variability in the control incidence of malignant lymphoma in female mice, NTP concluded that the observed increase in malignant lymphoma was not clearly related to treatment; IARC (1990) concluded that this increase was possibly treatment-related. A significant increase in the incidence of alveolar/bronchiolar adenomas was observed in high-dose males (2/50; 6/49; 9/49), but neither NTP nor IARC (1990) considered these tumors to be treatment-related.

Other Relevant data

C.I. Disperse Yellow 3 was mutagenic in both the presence and absence of metabolic activation in the *Salmonella* reverse mutation assay and in cultured mouse lymphoma cells (IARC, 1990). C.I. Disperse Yellow 3 induced unscheduled DNA synthesis (UDS) in primary cultured rat hepatocytes and sister chromatid exchanges (SCEs) in Chinese hamster ovary (CHO) cells (IARC, 1990). C.I. Disperse Yellow 3 did not induce chromosomal aberrations in CHO cells (IARC, 1990). These positive results are in agreement with the observation that amino azo dyes are generally genotoxic. As an azo dye, C.I. Disperse Yellow 3 also has the potential to be metabolically transformed to aromatic amines, many of which have been shown to possess carcinogenic activity. A computer program that analyzes structure-activity relationships based on a set of rules generated by US EPA experts (Oncologic, version 1.0) predicts that C.I. Disperse Yellow 3 is of moderate concern.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** over C.I. Disperse Yellow 3 since evidence of carcinogenicity has been observed in the male rat and the female mouse. The concern is tempered by the lack of a clear association between treatment with the chemical and the development of malignant tumors. IARC (1990) classified this chemical as a group 3 carcinogen. Evidence of genotoxic activity in short-term tests, combined with structural similarities to other genotoxicants, and with chemicals known to be metabolically transformed to carcinogenic aromatic amines support the level of concern.

There is a **HIGH** level of **concern over the extent of exposure** since there is potentially widespread exposure to C.I. Disperse Yellow 3 due to its widespread use in clothing, hosiery, carpets, and thermoplastics (NTP, 1982), although its availability for absorption from these materials would appear unlikely. C.I. Disperse Yellow 3 has been produced in significant quantities since the 1940's. U.S. production in 1980 was 1,860,000 lbs. NIOSH estimated that 18,958 workers were potentially exposed in 359 U.S. facilities in 1983 (NIOSH, 1994). C.I. Disperse Yellow 3 has been found in wastewater and river mud samples taken from rivers that receive wastewater from carpet dyeing facilities (IARC, 1990).

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CARCINOGENICITY DATA SUMMARY: CLOMIPHENE AND ITS SALTS

Clomiphene (CAS No. 911-45-5) is a pharmaceutical agent used to treat infertility in women. Treatment with clomiphene stimulates ovulation, apparently as a result of increased concentrations of gonadotropins. Clomiphene has also been used in men to treat oligospermia. Clomiphene was reviewed by IARC in both 1979 and 1987. IARC concluded that the evidence of carcinogenicity was inadequate in humans and inadequate in animals (group 3 carcinogen). The IARC review did not include the epidemiology studies of Rossing *et al.* (1994), Whittemore *et al.* (1992), Harris *et al*., (1992), or the numerous case reports discussed by Spirtas *et al.* (1993). These results, in addition to the studies reviewed by IARC, are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

A recent case-cohort study (Rossing *et al*., 1994) suggested that prolonged use of clomiphene may increase the risk of ovarian tumors. The study followed 3,837 women who had been evaluated for infertility. Eleven developed ovarian tumors classified as invasive or borderline malignant, compared with an expected number of 4.4 (standardized incidence ratio, 2.5; 95% CI, 1.3 - 4.5). Nine of the women in whom ovarian tumors developed took clomiphene. The study found that increased risk was associated with clomiphene treatment for one year or more (relative risk, 11.1; 95% CI 1.5 - 82.3).

An analysis of 12 case-control studies of ovarian cancer found that the risk of invasive epithelial tumors was increased among women who had used fertility drugs (Whittemore *et al*., 1992). In another study, risks were also increased for borderline epithelial ovarian tumors among women who had used fertility drugs (Harris *et al*., 1992). These studies were limited by small numbers and by the lack of information on specific fertility drugs prescribed.

A number of cases of ovarian cancer in women treated with fertility drugs have been reported in the literature and to the Food and Drug Administration (Spirtas *et al*., 1993).

Animal bioassays

1. Neonatal rat subcutaneous injection study: Clark and McCormack, 1977. Multiple reproductive tract abnormalities were noted in Sprague-Dawley rats treated with clomiphene citrate (10-500 μg, single s.c. injection at 1 day). These included hilus-cell tumors of the ovary and tumors of the uterus. The authors noted that although uterine tumors were observed in only a few animals, the observation period in the study was limited to a maximum of 100 days, and the incidence of these tumors may increase considerably in older rats. IARC (1979) noted the incomplete reporting of the experiment.

Other relevant data

No studies of short-term genetic toxicity tests of clomiphene were located in the literature. Epidemiological evidence suggests that any factor which reduces the number of times a woman ovulates (*e.g.* late menarche, use of oral contraceptives, number and duration of intervals without ovulation due to pregnancy and lactation, early menopause) reduces the risk of ovarian cancer (Spirtas *et al.*, 1993). This is presumed to be because suppression of ovulation reduces the injury and repair of the ovarian epithelium. By analogy, any effect which promotes ovulation might be expected to increase the incidence of ovarian cancer. An alternative theory suggests that elevated levels of pituitary gonadotropins directly increases the risk of ovarian cancer.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** over clomiphene since an association between exposure to clomiphene and ovarian cancer has been observed in a case-cohort study of women. This concern is reinforced by the findings of a meta-analysis of 12 case-control studies, which suggests that

women treated with fertility drugs, including clomiphene, are at increased risk for ovarian cancer. Numerous case reports further support this. One limited animal bioassay in female rats provides additional support for this level of toxicological concern.

There is a **HIGH** level of **concern over the extent of exposure** since it is widely prescribed as a treatment for infertility in women, and since therapeutic dose levels are high (50-100 mg/day) (IARC, 1979). In 1991 there were an estimated 731,000 prescriptions for clomiphene citrate in the US, increased from 390,000 prescriptions in 1973 (Wysowski, 1993).

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CARCINOGENICITY DATA SUMMARY: COUMARIN

Coumarin (CAS No. 91-64-5) is a member of a large class of naturally occurring compounds. It is widely used in perfumes and cosmetics as a fragrance and has potential application as a flavor-enhancer in food and tobacco. IARC reviewed this compound in 1976 and concluded that the evidence of carcinogenicity was limited in animals (group 3 carcinogen). The Food and Drug Administration and the National Cancer Institute nominated coumarin for testing by the National Toxicology Program (NTP) because of its widespread use. The results of this NTP bioassay are described below.

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to coumarin are available.

Animal bioassays

1. Long-term gavage studies in F344/N rats: NTP, 1993. NTP found some evidence of the carcinogenic activity of coumarin based on increased incidences of renal tubule adenomas in male rats. Marginal increases in these tumors were seen in female rats.

2. Long-term gavage studies in $B6C3F_1$ mice: NTP, 1993. NTP reported clear evidence of the carcinogenic activity of coumarin in female mice based on increased incidences of alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and hepatocellular adenomas. In male mice, there were increased incidences of alveolar/bronchiolar adenomas which NTP considered to provide some evidence of carcinogenic activity. Marginal increases in the incidences of squamous cell papillomas of the forestomach in both males and females were also observed.

Other relevant data

Coumarin was shown to be mutagenic in *Salmonella* TA100 with S9 (NTP, 1993). It was also found to induce SCEs in CHO cells (without S9), as well as chromosomal aberrations in CHO cells (with S9). NTP has also tested 3,4-dihydrocoumarin, a metabolite of coumarin and reported kidney tumors in male rats and liver tumors in female mice.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** regarding coumarin based on carcinogenic effects observed in male F344/N rats and $B6C3F_1$ mice as described above. The NTP concluded that there was clear evidence of the carcinogenic activity of coumarin in female mice based on neoplasms in the lung and the liver. The incidences of pulmonary neoplasms (benign or malignant combined) in high-dose male and female mice were well above the highest incidence observed in NTP historical controls. Further, focal renal hyperplasia (a lesion considered to be preneoplastic) was observed in dosed rats with incidences generally paralleling the incidences of renal neoplasms. The level of concern is also supported by the positive results in short-term tests for mutagenicity and genotoxicity, and by the observation that a metabolite of coumarin induced neoplasms in the male rat kidney and the female mouse liver.

There is a **HIGH** level of **concern over the extent of exposure** to coumarin. In addition to being widely used in perfumes, soap, other related household products, coumarin is also used as an odor-masking agent that may be found in paints, insecticides, and plastics (NTP, 1993). In 1990, NIOSH (NTP, 1993) estimated that approximately 240,000 workers are potentially exposed. The annual production of coumarin in the US is reported to be over 1 million lbs/yr (TSCA, 1990).

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CARCINOGENICITY DATA SUMMARY: NITROFURANTOIN

Nitrofurantoin (CAS No. 67-20-9) is used extensively to treat and to prevent lower urinary-tract infections in humans. This compound was evaluated by the IARC in 1990. IARC concluded that evidence of carcinogenicity was inadequate in humans and limited in animals (group 3 carcinogen). No additional information was identified by OEHHA since the IARC review. Studies reviewed by IARC are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

One study found an association between nitrofurantoin use and the incidence of cancers of the female genital tract and nervous system (IARC, 1990). A recent literature search by OEHHA did not identify any additional epidemiologic studies.

Animal bioassays

1. Rat long-term feed studies: NTP, 1989. A statistically significant increase in the incidence of renal tubular cell adenomas was seen in males (control, 3/50; 1,300 ppm, 11/50; 2,500 ppm, 19/50). Also, uncommon osteosarcomas of the bone and neoplasms of the subcutaneous tissue were observed in high-dose male rats. On the basis of these findings NTP concluded that this provided some evidence of carcinogenicity in the male F344 rat. No significant increases in tumor incidence were found in treated female Fischer 344 rats.

2. Female rat long-term feeding study: Wang *et al.,* 1984. Female Sprague Dawley rats received 1880 ppm nitrofurantoin in the diet for 104 weeks. Mammary fibroadenomas were observed in 9/12 treated animals compared to 2/11 controls.

3. Mouse long-term feed studies: NTP, 1989. Statistically significant increases in the incidences of ovarian tubular adenomas, benign mixed cell tumors, and granulosa cell tumors were observed in female mice, and NTP consequently concluded that there was clear evidence for carcinogenicity in the female. No significant increases in tumor incidence were seen in male $B6C3F_1$ mice given nitrofurantoin. Feed concentrations were 0, 1300 or 2500 ppm for both male and female studies.

4. Mouse long-term feed studies: Ito *et al.*, 1983. No increases in tumor incidence were seen in groups of male and female BDF_1 mice given 750 or 3,000 ppm nitrofurantoin in feed for 104 weeks.

5. Mouse long-term feed studies: Butler *et al.,* 1990. A significant increase in the incidence of malignant lymphomas was seen in male Swiss mice given 200 ppm nitrofurantoin in the diet for 22 months ($p=0.014$). A non-statistically significant decrease in the incidence of these tumors was seen in females receiving this dose.

6. Female mouse intermediate-term feed study: Stitzel *et al.,* 1989. The incidence of reproductive tract tumors was not elevated in female mice fed nitrofurantoin at 0, 350 or 500 ppm in the diet for 64 weeks. This experiment was too short in duration to observe late occurring tumors.

Other relevant data

Nitrofurantoin was mutagenic to *Salmonella typhimurium* and *Escherichia coli* and induced DNA strand breaks, unscheduled DNA synthesis, and sister chromatid exchanges in mice (IARC, 1990).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** over nitrofurantoin based on the findings by the NTP of renal tubular cell adenomas in the male rat and ovarian tumors in female mice, malignant lymphomas in male mice (Butler et al., 1990), and mammary fibroadenomas in female rats (Wang *et al*.,

1984). The level of concern is reinforced by the observations of mutagenicity and genotoxicity in short-term tests. On the basis of the bioassay data, IARC (1990) found the evidence for carcinogenicity of the chemical in experimental animals was limited. OEHHA did not identify information in recent literature searches that indicate this evaluation should be reconsidered.

There is a **HIGH** level of **concern over the extent of exposure** based on the extensive use of this drug to treat and prevent lower urinary tract infections. The recommended dosage is 200-400 mg per day by mouth for the treatment of infections. When administered chronically as a preventive for urinary tract infections, the recommended dosage is 50-100 mg/day. Sales in the U.S. of nitrofurantoin were 9,300 kg in 1986 (NTP, 1989).

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CARCINOGENICITY DATA SUMMARY: OZONE

Ozone (CAS No. 10028-15-6) is formed naturally in the stratosphere by photodissociation of oxygen. It is also formed in the lower atmosphere as a result of interaction between ultraviolet radiation and atmospheric pollutants, and it is produced in welding arcs and by electrical discharges in general. Ozone is used as a disinfectant for air and water; for bleaching textiles, oils, and waxes, and in organic syntheses (NTP, 1994).

Carcinogenicity Data available:

Epidemiological studies

No studies of the long-term effects of human exposure to ozone have been reported which provide an adequate assessment of the potential for carcinogenic effects.

Animal bioassays

1. Mouse long-term inhalation studies (105 weeks): NTP, 1994. The "incidences of alveolar/bronchiolar adenoma or carcinoma (combined) were marginally increased in 0.5 and 1.0 ppm males (0 ppm 14/50; 0.12 ppm 13/50; 0.5 ppm 18/50; 1.0 ppm 19/50) and were increased in 1.0 ppm females (6/50; 7/50; 9/49; 16/50)."

2. Mouse long-term inhalation studies (130 weeks): NTP, 1994. The "incidences of alveolar/bronchiolar adenoma or carcinoma (combined) were marginally increased in exposed males (0 ppm 16/49; 0.5 ppm 22/49; 1.0 ppm 21/50) and in exposed females (6/50; 8/49; 12/50)."

3. Rat long-term inhalation studies (105 weeks): NTP, 1994. No treatment-related tumors were observed in either male or female rats.

4. Rat long-term inhalation studies (125 weeks): NTP, 1994. No treatment-related tumors were observed in either male or female rats.

5. Rat long-term inhalation study (105 weeks ozone + NNK for the first 20 weeks): NTP, 1994. Male rats were exposed to ozone for 105 weeks and injected 3 times weekly for the first 20 weeks with 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK). "The administration of ozone did not affect the occurrence of pulmonary neoplasms or nonneoplastic lesions in rats administered NNK."

6. Rat long-term inhalation studies (13 months): Ichinose and Sagai, 1992. Rats were exposed to low levels of ozone (i.e., 0.05 ppm). No treatment-related tumors were observed in either male or female rats.

7. Hamster long-term inhalation studies: Witschi *et al.*, 1993. No ozone treatment-related effects were observed in hamster lungs.

8. Mouse lung adenoma inhalation study (103 hr/wk for 6 months + additional observation for 5 months): Hassett *et al.*, 1985. Female strain A/J mice were exposed to ozone starting in week 8 of life. Other treatment groups, in addition to untreated controls, include animals treated with a single i.p. injection of urethane in week 7 of life, and animals treated with a single i.p. injection of urethane plus ozone exposure. A statistically significant increase in the mean number of lung tumors per animal was observed in the ozone-treated group (0.85) as compared with the untreated controls (0.60) (Chi square analysis, $p < 0.005$). No significant difference in the mean number of lung tumors per animal was observed in the urethane + ozone group (2.68) vs. the urethane only group (2.95).

9. Mouse lung adenoma inhalation study (102 hr/wk for the first week of 6 consecutive months + additional observation for 3 months): Hassett *et al.*, 1985. Female strain A/J mice were exposed to ozone starting in week 8 of life. Other treatment groups, in addition to untreated controls, include

animals treated with six i.p. injections of urethane (once a month for 6 months), and animals treated with (six) i.p. injections of urethane immediately following each week of exposure to ozone for 6 months. A statistically significant increase in the mean number of lung tumors per animal was observed in the ozone-treated group (0.64) as compared with the untreated controls (0.20) (Chi square analysis, $p < 0.005$), and in the urethane + ozone group (10.30) vs. the urethane only group (7.91) ($p < 0.005$).

Other relevant data

Ozone is genotoxic in a variety of *in vitro* and *in vivo* tests. *In vitro*, ozone induced gene mutations *in E. coli* and *S. typhimurium*, dominant lethal mutations in *D. melanogaster*, chromosomal aberrations in cultured human lymphocytes and fibroblasts, and sister chromatid exchanges in Chinese hamster V79 cells and human lymphocytes. *In vivo*, ozone induced chromosomal aberrations in lymphocytes of Chinese hamsters and in pulmonary macrophages of F344 rats (NTP, 1994).

In the long-term inhalation studies conducted in rats by NTP (1994), increased incidences of ozone-induced metaplasia occurred in the nose and lung of rats exposed to 0.5 or 1.0 ppm ozone for two years, and in the nose, larynx, and lung of rats exposed to 0.5 or 1.0 ppm ozone for an additional six months in the lifetime studies. Metaplasia is thought to be one step in the continuum of pathologic changes which lead to neoplasia, although no increases in the incidences of neoplasms of the nose, larynx or lung were observed in these studies (see above, NTP, 1994). Similar increases in the incidence of ozone-induced metaplasia were observed in the long-term inhalation studies conducted in mice by NTP (1994). As noted above, these increases in metaplasia observed in the mouse studies were accompanied by marginal increases in the incidences of alveolar/bronchiolar adenomas and carcinomas (NTP, 1994).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** over ozone since there is "some evidence of carcinogenic activity in female mice", "equivocal evidence of carcinogenic activity in male mice", and "no evidence of carcinogenic activity for male and female rats" (NTP, 1994). This level of concern is reinforced by the evidence of carcinogenic activity in strain A/J mice (Hassett *et al*., 1985) and by the observations of genotoxicity in a variety of *in vitro* systems and in two *in vivo* test systems. The observations of metaplasia, but not dysplasia in both rats and mice in long-term inhalation studies (NTP, 1994) provide additional support for this level of concern.

There is a **HIGH** level of **concern over the extent of exposure** since ozone is a widespread air contaminant; the US EPA (1986) estimates that greater than 115 million people in the U.S. are exposed to concentrations higher than the current standard (i.e., 0.12 ppm) each year. Concentrations in large cities such as Los Angeles typically range from 0.2 - 0.5 ppm during the summer, and have reached as high as 1.0 ppm (US EPA, 1986).

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CARCINOGENICITY DATA SUMMARY: PENTACHLOROANISOLE

Pentachloroanisole (CAS No. 1825-21-4) is a widespread environmental contaminant from the breakdown of chlorinated aromatic compounds. The Food and Drug Administration and the National Institute of Environmental Health Sciences nominated pentachloroanisole for testing by the NTP because of its wide distribution in the environment and in human foods. The results of this NTP bioassay are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to pentachloroanisole are available.

Animal bioassays

1. Long-term gavage studies in F344/N rats: NTP, 1993. Significantly increased incidences of benign pheochromocytomas of the adrenal medulla were observed in male rats. Marginally increased incidences of benign pheochromocytomas of the adrenal medulla were reported in female rats. On the basis of these findings NTP concluded that there was some evidence of carcinogenicity in the male rat and equivocal evidence of carcinogenicity in the female rat.

2. Long-term gavage studies in $B6C3F_1$ mice: NTP, 1993. Significantly increased incidences of benign pheochromocytomas of the adrenal medulla and hemangiosarcomas of the liver were observed in male mice, and NTP consequently concluded that there was some evidence of carcinogenic activity in these animals. No evidence of carcinogenicity was reported in female mice.

Other relevant data

Pentachloroanisole was found to be mutagenic in *Salmonella typhimurium* strains TA98 and TA1537 in the absence of S9. It was also found to be positive in the mouse lymphoma assay in the presence of S9 and induced SCEs in CHO cells *in vitro* (with and without S9) (NTP, 1993). NTP reported that some species can metabolize pentachloroanisole to pentachlorophenol in assays *in vitro* and *in vivo*. In NTP diet studies with pentachlorophenol, adrenal gland medullary pheochromocytomas and hepatocellular carcinomas or carcinomas/adenomas were observed in male and female $B6C3F_1$ mice. Also in the pentachlorophenol studies, circulatory system hemangiosarcomas were observed in female mice. (Pentachlorophenol is listed as a carcinogen under Proposition 65.)

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** regarding pentachloroanisole based on the increased incidence of benign pheochromocytomas of the adrenal medulla in male F344/N rats and male $B6C3F_1$ mice, hemangiosarcomas in male mice and no evidence of carcinogenicity in female mice, as described above. Concern is strengthened by the observations of bacterial mutagenicity and by the metabolism of pentachloroanisole to pentachlorophenol, a known carcinogen which induces pheochromocytomas of the adrenal medulla, hepatocellular adenomas and carcinomas, and hemangiosarcomas in mice.

There is a **HIGH** level of **concern over the extent of exposure**. Although pentachloroanisole is not manufactured commercially, it occurs as a result of environmental degradation of structurally related, ubiquitous chlorinated aromatic compounds such as pentachlorophenol, a known carcinogen currently listed under Proposition 65 (NTP, 1993). NTP (1993) states that "its presence as an environmental contaminant is widespread" and that it "is probably derived from ubiquitous related chlorinated aromatic compounds, especially pentachlorophenol". NTP also notes that "Pentachloroanisole was nominated for toxicity and carcinogenicity testing by the Food and Drug Administration and NIEHS because its wide distribution in the environment and in human foods presents a potential for low-level human exposure through drinking water and through food."

References

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CARCINOGENICITY DATA SUMMARY: TRIFLURALIN

Trifluralin (CAS No. 1582-09-8) is an herbicide for grasses and broadleaf weeds. Trifluralin was reviewed by IARC in 1991. IARC concluded that the evidence of carcinogenicity was inadequate in humans and limited in animals (group 3 carcinogen). However, their review included only the NCI (1978) rat and mouse studies and the mouse studies by Francis et al. (1991). The studies by Emmerson et al. (1980) and Eli Lilly (1966) were not considered. US EPA has posted a series of reviews and actions relating to trifluralin (USEPA, Federal Register) and IRIS currently lists trifluralin as a Class C - possible human carcinogen.

Carcinogenicity data available:

Epidemiological studies

1. Population-based case-control study: Hoar, 1986. This study of white males in an agricultural setting found an elevated odds ratio for non-Hodgkin's lymphoma among farmers exposed to trifluralin, among other herbicides (OR 12.5, 95% CI 1.6-116.1). However, these other significant chemical exposures confound the analysis with respect to trifluralin.

Animal bioassays

1. Mouse long-term diet studies (treated 78 weeks + additional 12 weeks observation): NCI, 1978. Significant increases in hepatocellular carcinomas and alveolar and bronchial adenomas were seen in female mice receiving 0, 2740 or 5192 ppm in the diet. A small increase in relatively rare forestomach carcinomas seen in low-dose female mice (4/45 versus 0/60 in pooled controls) was also considered treatment-related. Increased tumor incidences in male mice were not significant. The NCI concluded that "technical grade trifluralin is a carcinogen in female $B6C3F_1$ mice…" This study used technical grade trifluralin, later found to be contaminated with N-nitroso-n-propylamine (NDPA).

2. Rat long term diet studies (treated 78 weeks + additional 33 weeks observation): NCI, 1978. No increase in tumors was observed in male or female rats.

3. Rat diet studies: Emmerson *et al.*, 1980 (This series of studies has not been published in the open literature, but was submitted to and reviewed by CDFA [1990], and is cited by US EPA, with a summary in IRIS). Technical grade trifluralin with <0.01 ppm of NDPA was administered to both sexes of Fischer 344 rats at 0, 813, 3250 or 6500 ppm in diet. Uncommon transitional cell carcinomas of the renal pelvis epithelium were increased in all treated groups of males, reaching significance in the high-dose group. Dose-dependent increases in tumors of the bladder or renal pelvis transitional epithelium were observed in both sexes (males: 0/60, 3/59, 4/60, 7/60; females: 0/60, 0/60, 1/60, 5/60). In addition, thyroid follicular adenomas and carcinomas were significantly increased in high-dose male rats.

4. Mouse long-term diet studies (2 years): Francis *et al.*, 1991. Technical grade trifluralin with < 0.01 NDPA was administered at 0, 563, 2250, or 4450 in diet to males and female $B6C3F_1$ mice. No evidence of oncogenicity was observed, although the high dose resulted in significantly decreased body weight gains.

5. Rat long-term diet studies (2 years): Eli Lilly, 1966, as reported in US EPA 1986 Peer Review of Trifluralin. In groups of 25 of each sex, Sprague-Dawley rats were administered 0, 200, 1000, or 2000 ppm trifluralin in the diet. "The CAG concluded that this study showed no evidence of carcinogenicity and that the study was an adequate basis for safety evaluation."

IARC (1991) reviewed the published data on trifluralin and concluded that there was limited evidence of carcinogenicity in animals (group 3). However, since they do not, as a matter of policy, review studies which have only been submitted for product registration purposes and not otherwise published, their review included only the NCI (1978) rat and mouse studies and the mouse studies by Francis *et al.* (1991). Neither

the positive study by Emmerson *et al.* (1980), nor the non-positive result obtained by Eli Lilly (1966) was considered. US EPA currently classifies trifluralin as a Class C - possible human carcinogen.

Other relevant data

Trifluralin was negative in the dominant lethal test in rats and in assays for SCEs and induction of reverse mutations in *Salmonella* (CDFA, 1990), however, it induced aneuploidy in *Neurospora crassa*, and yielded mixed results in aneuploidy tests in *Drosophila* (IARC, 1991). Trifluralin is structurally related to ethalfluralin, which produces mammary gland fibroadenomas in female rats (IRIS).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** over trifluralin. Concern is due to dose-dependent increases in the incidences of tumors of the transitional epithelium of the bladder and renal pelvis in male and female F344 rats, and significant increases in thyroid follicular tumors in males. Similar observations were not made in studies in other strains of rats. It is noteworthy that in the positive study, the number of animals observed with renal calculi increased substantially with increasing dose; they were found in the majority of high-dose animals. There was a positive bioassay in female mice at three tumor sites, but the study is compromised by contamination with N-nitroso-n-propylamine and was considered unacceptable by CDFA (1990). A follow-up study with a sample of greater purity did not find an effect under similar circumstances. The level of concern is reinforced by the possible (but unproven) association with lymphoma among exposed farmers and the structural similarity to the animal tumorigen ethalfluralin. The single positive observation of genotoxicity in short-term tests neither adds nor detracts from the level of concern.

There is a **HIGH** level of **concern over the extent of exposure** to trifluralin. It is used on a large number of California crops; 1,404,088 lbs were applied in 1993 (DPR, 1995). Most usage is on cotton and alfalfa, indicating that, like other agricultural chemicals, occupational exposures are possible. The general public may consume food crops treated with trifluralin, especially tomatoes, carrots and grapes, and could be additionally exposed by dermal and inhalation routes from lawn products (HSDB). Trifluralin may also bioaccumulate in fish (HSDB).

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CARCINOGENICITY DATA SUMMARY: ACETOXIME

Acetoxime (acetone oxime; 2-propanone oxime; CAS No. 127-06-0) is widely used as a starting material for organic synthesis. It is also used in oil paints and coatings as an anti-skinning agent.

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to acetoxime have been reported.

Animal bioassays

1. Rat long-term drinking water studies (18 months + observation until death): Mirvish *et al.*, 1982. Acetoxime was administered at a concentration of 1,000 ppm in drinking water to groups of male and female MRC-Wistar rats for 18 months. Surviving animals were then observed without further exposure until death occurred. For male rats, the incidence of hepatocellular neoplasms was 12/15 in treated animals as compared with 0/23 in controls. For females, the incidences were 3/16 and 0/20 in treatment and control groups, respectively. All of the hepatocellular tumors were classified as adenomas with the exception of a carcinoma found in a dosed male. In addition, acetoxime produced a significant increase in the number of hyperplastic liver nodules in Wistar and MRC-Wistar rats.

Other relevant data

In short-term studies, acetoxime was not mutagenic in *Salmonella typhimurium* strains TA98, TA100 or TA2637 and it was not mutagenic in *E. coli* strain WP2 uvrA/pKM101 either with or without metabolic activation (Araki *et al.*, 1986). Acetoxime produced 8-hydroxyguanine in hepatic DNA following oral or i.p. administration to male Sprague-Dawley and F344 rats (Hussain *et al.*, 1990). The pattern of modified nucleosides produced in rat liver is qualitatively similar to the pattern produced by the known rat liver carcinogen 2-nitropropane. Both acetoxime and 2-nitropropane are metabolized in the liver to propane 2-nitronate, the proximate carcinogenic metabolite of 2-nitropropane (Kohl *et al.*, 1992). A computer program that analyzes structure-activity relationships based on a set of rules generated by US EPA experts (Oncologic, version 1.0) finds that acetoxime is of moderate carcinogenicity concern.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** over acetoxime since it produces liver tumors in male rats and it is metabolized to propane 2-nitronate, the active metabolite of the animal liver carcinogen 2-nitropropane. No tests in other species have been reported. A computer program that analyzes structure-activity relationships based on a set of rules generated by US EPA experts (Oncologic, version 1.0) predicts that acetoxime is of moderate concern.

There is a **MEDIUM** level of **concern over the extent of exposur**e to acetoxime. It is used in oil paints, with many containing 0.1-0.4% acetoxime and other similar oximes (Mirvish *et al.*, 1982; Kohl *et al.*, 1992); therefore artists are likely to represent a highly exposed subpopulation. It is used as starting material in organic syntheses and as an anti-skinning agent in oil paints and coatings. Exposure to acetoxime is likely to occur by inhalation due to its high volatility (Mirvish *et al.*, 1982). The reported level of U.S. production in 1990 is 70,000 lbs. (Sherlock, 1995).

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CARCINOGENICITY DATA SUMMARY: 2,6-DICHLORO-*p*-PHENYLENEDIAMINE

2,6-Dichloro-*p*-phenylenediamine (CAS No. 609-20-1) is a chemical intermediate in dye and resin manufacture. It is also a metabolite of the fungicide 2,5-dichloronitroaniline. The compound was identified as being of potential concern because of the suggestive findings in bioassays by the NTP published in the early 1980's. IARC (1985) reviewed 2,6-dichloro-*p*-phenylenediamine and concluded that there was limited evidence of carcinogenicity in animals (group 3). Literature searches were performed to identify additional data which have become available since the IARC review. These new findings include a structure-activity analysis and several tests for mutagenicity which are briefly described below.

Carcinogenicity data available:

Epidemiological Studies

No studies of the effects of long-term human exposure have been reported.

Animal Bioassays

1. Mouse diet studies (treated 103 weeks + additional 8 weeks observation): NTP, 1982. Increased incidences of liver tumors were observed in both male and female mice. There was a statistically significant trend in the incidence of hepatocellular adenomas with increasing dose in males; the increase in the high-dose group was also significant (4/50, 7/50, 15/50). In female mice, incidence of liver carcinomas exhibited a significant dose-related trend, although no single dose group had a significant increase. When the incidences of carcinomas and adenomas in females were taken together, the trend with dose was again significant as was the increase in the high-dose group (6/50, 6/50, 16/50).

2. Rat diet studies (103 weeks): NTP, 1982. No evidence of carcinogenicity in rats of either sex was observed.

Other relevant data

2,6-Dichloro-*p*-phenylenediamine was positive in the mouse lymphoma forward mutation assay (McGregor *et al.*, 1988), and showed equivocal results in a mammalian cell transformation assay (Hatch *et al*., 1986; Tu *et al.*, 1986). Mutagenicity in 3 strains of *Salmonella typhimurium* has also been reported (HSDB). A computer program that analyzes structure activity relationships based on a set of rules generated by US EPA experts (Oncologic, version 1.0) finds 2,6-dichloro-*p*-phenylenediamine to be of high-moderate carcinogenicity concern, the highest predictive level of concern possible. Only known carcinogens will be reported as having a high level of concern.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogencity concern** over 2,6-dichloro-*p*-phenylenediamine due to the observed liver tumors in mice of both sexes. NTP found that the compound "was carcinogenic for male and female $B6C3F_1$ mice". Based on the NTP bioassay results, IARC (1985) concluded that there is limited evidence of carcinogenicity in animals. The level of concern of medium is reinforced by the structure-activity analysis results of the Oncologic computer program, and mutagenic activity *in vitro*.

There is a **MEDIUM** level of concern over the **extent of exposure** to 2,6-dichloro-*p*-phenylenediamine. The major potential for exposure is as a metabolite of the fungicide 2,6-dichloro-4-nitroaniline, also called dicloran. In 1993, 42,922 lbs of dicloran were used on a variety of California crops (DPR, 1995). The USFDA Total Diet Studies estimated an adult ADI of 0.047 ug/kg-day in 1982 (HSDB). Dicloran is listed on the EPA TSCA inventory (1993). In addition to exposure to dicloran as a food residue, NIOSH estimated 3,580 workers were potentially exposed in 1972-1974. Although IARC and HSDB report that 2,6-dichloro-*p*-phenylenediamine is no longer produced in the US, one manufacturer of the compound was found listed in a 1996 chemical manufacturers directory.

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CARCINOGENICITY DATA SUMMARY: CHLOROFLUOROMETHANE

Chlorofluoromethane (Halocarbon 31; CAS number 593-70-4) occurs as an impurity in commercial grades of dichlorofluoromethane (Halocarbon 21). This compound was identified for review because of positive bioassay data. Chlorofluoromethane was reviewed by IARC in 1986. IARC concluded that the evidence of carcinogenicity was inadequate in humans and limited in animals (group 3 carcinogen). No more recent information on the evidence for carcinogenicity of the agent identified by the literature searches conducted. However, a new structure-activity analysis is now available. These results, in addition to the study reviewed by IARC, are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to chlorofluoromethane were available to IARC (1986) or identified in subsequent literature searches by OEHHA.

Animal bioassays

1. Rat long-term gavage study: Longstaff *et al.*, 1984. Squamous cell carcinoma and fibrosarcoma of the stomach were reported in 92% of exposed males and 94% of exposed females: Background incidence of these lesions in both sexes was 1%. The study authors were unable to determine whether the sites of origin of the tumors were in the forestomach only or in both forestomach and glandular stomach.

Other relevant data

Chlorofluoromethane was found to be a highly active mutagen in the *Salmonella* reverse mutation assay, and to induce transformation of BHK21 cells *in vitro* (Longstaff *et al.*, 1984). A computerized analysis of structure-activity relationships based on a set of rules generated by US EPA experts (Oncologic, version 1.0) finds that chlorofluoromethane is of high-to-moderate concern. (This is the highest level of concern noted for chemicals which are not included in the database of carcinogenicity bioassay results from which the program rules are derived.)

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** over chlorofluoromethane since evidence of carcinogenicity has been observed in both sexes of the rat in the one available study. In this single dose-level study, carcinogenic effects were observed at the site of application. Although the study was smaller and more limited in design than the standard bioassay, the extremely high level of incidence relative to controls of a relatively uncommon tumor is noteworthy. No tests in other species have been reported. The concern is reinforced by the observations of mutagenicity and cell transforming ability in short-term tests, and by the results of a computerized analysis of structure-activity relationships based on rules generated by US EPA experts (Oncologic, version 1.0), which predicts that chlorofluoromethane is of high-to-moderate concern (*i.e.*, the highest level of concern possible on chemicals which have not been included in the program's database).

There is a **LOW** level of **concern over the extent of exposure** since chlorofluoromethane is not manufactured in bulk or naturally abundant, although it occurs as an impurity in a commodity chemical (IARC, 1986). NIOSH (1983) estimated that 2,703 workers were potentially exposed to chlorofluoromethane, but levels were probably low since this compound is only present as an impurity. IARC (1986) characterized the exposure potential as limited.

References

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CARCINOGENICITY DATA SUMMARY: MERCURIC CHLORIDE

Mercuric chloride (CAS No. 7487-94-7) is used in the production of other mercury compounds. It is also used as a catalyst in the production of vinyl chloride and as a fungicide. Mercuric chloride was reviewed by IARC in 1993. IARC concluded that the evidence for carcinogenicity was inadequate in humans and limited in animals (group 3). A literature search by OEHHA did not reveal critical studies not reviewed by IARC.

Carcinogenicity Data available:

Epidemiological studies

IARC (1993) concluded "There is inadequate evidence in humans for the carcinogenicity of mercury and mercury compounds." A recent literature search by OEHHA did not find additional recent epidemiological studies not reviewed by IARC.

Animal bioassays

1. Mouse drinking water study (lifetime): Schroeder and Mitchner, 1975. Groups of 54 male and 54 female Swiss mice were given drinking water containing either 0 or 5 ppm of mercuric chloride starting at 20 days of age. No significant increase in the incidence of tumors was found in treated animals of either sex, but there was a non-significant increase in the incidence of lymphoma and leukemia (combined) in treated females.

2. Mouse gavage study (two years): NTP, 1993. Groups of 60 male and 60 female B6C3F_1 mice were given mercuric chloride at a rate of 0, 5, or 10 mg/kg body weight by gavage on 5 days per week for 103-104 weeks. No statistically significant increases in tumor incidence were seen in treated animals, but 2 of 49 high-dose males were found with renal tubular-cell adenomas, and one with adenocarcinomas. No renal adenomas or carcinomas were seen in controls or dosed females. The NTP concluded that there was equivocal evidence of carcinogenic activity in mice and no evidence in females based on these findings.

3. Rat gavage study (two years): NTP, 1993. Groups of 60 male and 60 female Fischer 344/N rats were given mercuric chloride by gavage at a rate of 0, 2.5, or 5 mg/kg body weight on 5 days per week for 103-104 weeks. In treated males, there was a dose-related increase in the incidence of squamous-cell papillomas of the forestomach (controls, 0/50; low dose, 3/50; high dose, 12/50) and of follicular-cell carcinomas of the thyroid (controls, 1/50; low dose, 2/50; high dose, 6/50). The NTP concluded that there was some evidence of carcinogenicity in the male and equivocal evidence in the females based on these findings.

Following review of the above studies, IARC (1993) concluded that "There is limited evidence in experimental animals for the carcinogenicity of mercuric chloride."

Other relevant data

IARC (1993) stated that mercuric chloride induced DNA damage, chromosomal aberrations, and sister chromatid exchange.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** for human exposure to mercuric chloride based on the observations of thyroid tumors in rats and DNA damage in short-term tests.

There is a **LOW** level of **concern over the extent of exposure**. The compound is used in the production of other mercury compounds, and is used as a catalyst in the production of vinyl chloride and as a fungicide and wood preservative. There is not widespread exposure to the general population, although it is expected

that small numbers of people may be occupationally exposed. In 1990, use of 11,840 pounds was reported to US EPA TSCA (Sherlock, 1995).

References

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CARCINOGENICITY DATA SUMMARY: 2-NITRO-*P*-PHENYLENEDIAMINE

2-Nitro-*p*-diphenylamine (1,4-diamino-2-nitrobenzene, CAS No. 5307-14-2) is used as an ingredient in cosmetic products for dyeing hair. This compound was identified for review because of positive findings in the early bioassay by the National Cancer Institute (NCI) and the potential for direct and repeated exposures through its use as a hair dye. IARC (1993) reviewed 2-nitro-*p*-phenylenediamine and concluded that the evidence for carcinogenicity was inadequate in humans and limited in animals (group 3).

Carcinogenicity Data available:

Epidemiological studies

No data on carcinogenic effects of human exposure to 2-nitro-*p*-diphenylamine were available to IARC (1993) or discovered in a more recent literature search by OEHHA.

Animal bioassays

1. Rat long-term feed studies: NCI, 1979. No statistically significant increases in tumor incidence were seen in male or female Fischer 344/N rats fed 2-nitro-*p*-diphenylamine at 550 or 1,100 ppm for 78 weeks and then observed for an additional 27 weeks (NCI, 1979).

2. Mouse long-term feed studies: NCI, 1979. A statistically significant increase in the incidence of hepatocellular adenomas or carcinomas was seen in female but not in male $B6C3F_1$ mice fed a diet containing 2-nitro-*p*-diphenylamine (control 1/20, low-dose 10/49, high-dose 17/48).

Other relevant data

2-Nitro-*p*-diphenylamine was found to be mutagenic both with and without metabolic activation in *Salmonella typhimurium, Escherichia coli*, and L5178Y cells, but not in *Neurospora crassa* (IARC, 1993). A computerized analysis of structure-activity relationships using rules generated by US EPA experts (Oncologic, version 1.0) predicts that the level of carcinogenicity concern is moderate for this compound.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** over 2-nitro-*p*-diphenylamine since evidence of carcinogenicity has been observed in female $B6C3F_1$ mice. The concern is reinforced by the observations of mutagenicity in short-term tests. On the basis of the NCI oral carcinogenicity studies IARC (1993) found limited evidence in experimental animals for the carcinogenicity of the compound. A computerized analysis of structure-activity relationships (Oncologic) predicts that 2-nitro-*p*-diphenylamine is of moderate concern.

There is a **LOW** level of **concern over the extent of exposure** based on the use of this lipid soluble compound in hair dyes (brunette shades) which may be used continuously for several years (possibly even decades). A large segment of the US population over 40 years of age uses hair dyes: approximately half of all women in the US dye their hair (Seligson, 1993) and consumer sales of men's hair dyes have increased 4-fold between 1986 and 1995 (Wallenstein, 1995). The reported U.S. annual usage of 2-nitro-*p*-diphenylamine is only 150 kilograms (IARC, 1993).

References

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CARCINOGENICITY DATA SUMMARY: SEMICARBAZIDE HYDROCHLORIDE

Semicarbazide hydrochloride (carbamylhydrazine hydrochloride, CAS No. 563-41-7) is used as a chemical reagent and is synthesized and available commercially in the US. IARC reviewed this compound in 1976, and found that there was limited evidence of carcinogenicity in animals (group 3). A literature review was conducted to identify studies not evaluated by IARC. The results of these studies are briefly described below.

Carcinogenicity data available:

Epidemiological studies

No studies of long term exposure in humans have been reported.

Animal bioassays

1. Drinking water studies in female Swiss mice ("lifetime"): Toth *et al.*, 1975. 0.0625% semicarbazide hydrochloride was administered in drinking water for life resulting in increased incidence of lung and vascular tumors in treated females. 50% of treated females developed lung adenomas and adenocarcinomas, compared with 21 % of controls. The incidence of vascular tumors, including angiomas of the liver and angiosarcomas, rose from a control incidence of 5% to 18% in the treated group. 0.0625% semicarbazide hydrochloride administered in drinking water for life was also associated with an increase in lung tumors in male mice. The incidence rose from 23% in controls to 30% in the treated group

2. Diet study in mice (7 months): Mori *et al.*, 1960. Female mice were fed 0.1% semicarbazide hydrochloride in diet. Six of 8 survivors had lung tumors, compared with 1 of 20 controls.

3. Diet study in rats (104 week): Weisburger *et al*., 1981. Male and female Charles River CD rats were fed diets containing 500 ppm for 78 weeks or 1000 ppm for 32 weeks. Treatment-related increases in tumor incidences were not observed. However, the authors noted that "In males, the number of survivors was so small that induction of any late occurring tumors could have gone undetected."

Other relevant data

This compound is a hydrazine derivative; hydrazines have been found to induce lung and/or vascular tumors in animal studies. Semicarbazide hydrochloride is mutagenic in *Drosophila* (cited in TOMES), and induced chromosome aberrations and non-disjunction in cultured grasshopper cells (cited in RTECS).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **MEDIUM** level of **carcinogenicity concern** regarding semicarbazide hydrochloride. Two tumor sites were seen, and for lung tumors an increased incidence was observed in both sexes. Both target sites for semicarbazide hydrochloride are consistent with results from studies of other hydrazines; this consistency lends support to the level of concern. This concern is reinforced by the observation of mutagenicity *in vitro.*

There is a **LOW** level of **concern over the extent of exposure** to semicarbazide hydrochloride. Current information on exposure was not available. IARC (1974) notes that the compound has been used as a chemical reagent in the qualitative determination of aldehydes and ketones, and in the isolation of hormones and certain fractions of essential oils. NIOSH (1983) estimated that 2815 employees in 41 US facilities were exposed in 1983. The identification of a low level of concern is based on the presumption that, as in the past, there is likely to be very little exposure to the general public.

References

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CARCINOGENICITY DATA SUMMARY: ACETAMINOPHEN

Acetaminophen (CAS No. 103-90-2) (otherwise known as Paracetamol; systematic name N-(4-hydroxyphenyl)-acetamide) is a widely used analgesic and antipyretic drug. It is available without prescription and commonly used by a large number of people, including children (since it is considered preferable to aspirin in view of the latter compound's rare induction of Reye's syndrome in febrile children and adolescents). Acetaminophen was reviewed by IARC in 1990, and was tested by the National Toxicology Program in 1993. IARC concluded that the evidence of carcinogenicity was inadequate in humans and limited in animals (group 3 carcinogen). The IARC review did not include the non-positive results of the NTP bioassays in rats and mice. These results, in addition to the studies reviewed by IARC, are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

A series of three case-control studies examined possible associations between urinary tract cancer and acetaminophen use. In these studies, cases were classified as controls (no acetaminophen use), regular use (cumulative consumption of at least 0.1 kg) or higher exposure (cumulative consumption of at least 1 kg). A significantly increased risk of ureteral cancer was observed in regular acetaminophen users, but there was no further increase in this risk for the subgroup with higher exposure. Three other studies found no association between acetaminophen use and cancer at any urinary tract site. Results were adjusted for smoking, but not for exposure to phenacetin, a known carcinogen formerly used as an analgesic. IARC (1990) found the human evidence for carcinogenicity of acetaminophen to be inadequate.

Animal bioassays

1. Rat long-term diet studies: NTP, 1993. No evidence of carcinogenicity was found in male F344/N rats given 0, 600, 3000 or 6000 ppm acetaminophen in the diet for 103 weeks. An increased incidence of mononuclear cell leukemia was observed in female rats. The incidence in the highest dose group (48%, compared to 18% in the control group) and the positive dose-related trend were statistically significant. NTP (1993) noted however that the spontaneous incidence of mononuclear cell leukemia in rats is high and variable, and that the increased incidence was not associated with increased mortality. In view of these considerations, and the lack of response in male rats, they concluded that this result provided equivocal evidence of carcinogenicity in the female rat.

2. Mouse long-term diet studies: NTP, 1993. No evidence of carcinogenicity was found in male or female $B6C3F_1$ mice given 0, 600, 3000 or 6000 ppm acetaminophen in the diet for 103 weeks.

3. Rat long-term diet studies: Flaks *et al.*, 1985. Male and female Leeds rats were fed 0, 5000 or 10000 ppm acetaminophen in the diet. Incidences of liver neoplastic nodules (characterized by IARC as benign) and bladder tumors (papillomas and a few carcinomas) were increased in rats of both sexes. The incidences of liver neoplastic nodules were: males, control 0/40, low-dose 1/48, high-dose 9/45; females, control 0/40, low-dose 0/49, high-dose 10/49. The incidences of bladder tumors were: males, control 0/40, low-dose 0/48, high-dose 5/45 papillomas and 1/49 carcinoma; females, control 0/40, low-dose 4/49 papillomas and 1/49 carcinoma, high-dose 0/49. Hyperplasia and calculi were also noted in the bladders of treated rats, but there was no relationship between the presence of calculi and the appearance of either tumors or hyperplasia.

4. Rat long-term diet study: Johansson, 1981. Groups of 30 male SPF Sprague-Dawley rats were fed 0 or 5350 ppm acetaminophen in the diet for 117 weeks. No significant differences in tumor incidences or survival rates were noted, although bladder papillomas or tumors were observed in 4/30 exposed rats, *vs.* 2/30 controls.

5. Rat long-term diet study: Hiraga and Fujii, 1985. Groups of 50 Fischer 344 rats were fed acetaminophen in the diet for 104 weeks, then observed for a further 26 weeks. Males received 0, 4500

or 9000 ppm, while females received 0, 6500 or 13000 ppm. Survival at 104 weeks was 86-90% in males and 80-82% in females. No significant increases in tumor incidences were seen in any group.

6. Rat Short-term diet study: Maruyama *et al.*, 1990. Groups of 13 Fischer 344 rats were fed 0, 4500 ppm or 9000 ppm acetaminophen in the diet for a period of 25 weeks following feeding of choline supplemented, basal or choline-deficient diets for 27 weeks. Non-neoplastic lesions were observed in the liver associated with both choline deficiency and acetaminophen treatment, but no significant increase in tumor incidence was associated with acetaminophen treatment.

7. Mouse long-term diet studies: Flaks and Flaks, 1983. Groups of 60 male and 60 female IF strain mice were fed 0, 5000 or 10000 ppm acetaminophen in the diet for 18 months. Significant increases of liver tumors (including carcinomas) were observed in male and female IF mice. Severe toxicity, including liver necrosis, body weight depression and early mortality, was observed in animals receiving 10000 ppm acetaminophen in the diet. This dose caused hepatotoxicity in hale the males, as well as early lethality. A group receiving 5000 ppm acetaminophen showed neither the carcinogenic nor the toxic effects. The incidences of liver adenomas and carcinomas (combined) were: males, control 1/50, low-dose 1/54, high-dose 20/23; females, control 0/48, low-dose 0/57, high-dose 9/47.

8. Mouse long-term diet studies: Amo and Matsuyama, 1985. Groups of 50 - 55 male and female $B6C3F_1$ mice were fed 3000 or 6000 ppm acetaminophen in the diet for 134 weeks. No differences were observed between incidences of tumors at any site in control *vs.* exposed mice.

9. Mouse long-term diet study: Hagiwara and Ward, 1986. Groups of 60 and 120 male $B6C3F_1$ mice were fed 5000 or 10000 ppm acetaminophen in the diet for 70 weeks. Survival was poor in the high- dose group, with severe hepatotoxicity commonly found in mice that died. No increases in the incidences of neoplasms were found.

Other relevant data

Some studies of co-administration of acetaminophen with known carcinogens were reviewed by IARC (1990). One study (Tsuda *et al.*, 1984) showed an increased incidence of preneoplastic renal lesions in Fischer 344 rats treated with a single injection of N-nitrosoethyl-N-hydroxyethylamine followed by up to 70 weeks exposure to diet containing 5000 or 10000 ppm acetaminophen. Five other series of studies examining promotion of tumors or preneoplastic lesions in liver, kidney and other tissues of rats, mice or hamsters were negative.

Acetaminophen at high doses causes liver and kidney toxicity in animals and humans. Liver damage is a potentially fatal side-effect of severe accidental or suicidal overdose with acetaminophen. It is exacerbated by concurrent exposure to alcohol. Initial signs of liver and/or kidney toxicity such as elevated serum transaminase levels may appear after use at therapeutic doses or moderate over-use, especially when this is combined with alcohol consumption (IARC, 1990). The liver and kidney damage are considered to be the result of a minor (5-10%) metabolic pathway involving cytochrome P-450 activation. This generates a reactive intermediate (postulated to be a quinoneimine), which interacts with tissue proteins and undergoes glutathione conjugation (IARC, 1990).

Acetaminophen does not induce gene mutations in the standard *Salmonella* reverse mutation assay, in *Escherichia coli* or in Chinese hamster V79 cells *in vitro*, or *in vivo* in *Drosophila*. Sister chromatid exchanges and chromosomal effects (aberrations, micronuclei) were observed in several mammalian cell test systems *in vitro*, including one study with human lymphocytes. Studies of chromosomal effects in mammals *in vivo* were negative apart from one report (Tsuruzaki *et al.*, 1982) of aneuploidy induction in 12-day rat embryos after maternal treatment with acetaminophen. Another study reported no embryo or fetotoxic effects after oral treatment of rats.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **LOW** level of **carcinogencity concern** over acetaminophen. Although carcinogenic effects were observed in two studies (Flaks *et al*., 1985; Flaks and Flaks, 1983), these effects occurred only at high doses at which significant toxicity was also noted. Several other studies had non-positive outcomes. IARC (1990) determined that the evidence for carcinogenicity in experimental animals was limited, and the evidence in humans was inadequate. This judgment preceded the non-positive results of the NTP bioassays in rats and mice. It is plausible that high dose hepatotoxicity is the mode of action for the observation of liver tumorigenicity. Acetaminophen is metabolized to a reactive intermediate that is detoxified by conjugation with glutathione. High dose levels may lead to the depletion of hepatic glutathione, resulting in hepatotoxicity.

There is a **HIGH** level of **concern over the extent of exposure** since acetaminophen is a widely used over-the counter medication. (IARC, 1990; NTP, 1993).

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CARCINOGENICITY DATA SUMMARY: BENZYL ACETATE

Benzyl acetate (acetic acid phenylmethyl ester; CAS No. 140-11-4) occurs naturally in some flowers, fruits, and essential oils. It is used as a fragrance in soaps, perfumes and cosmetics, as a synthetic flavoring agent in food (e.g., gum, candy, gelatin, ice cream, beverages, baked goods), as a solvent for cellulose acetate and nitrate, resins, oils, lacquers, polishes and printing inks, and in varnish removers. Benzyl acetate was reviewed by IARC in 1986. IARC concluded that there was no data available on the evidence of carcinogenicity in humans and that the evidence was limited in animals (group 3 carcinogen). The IARC review did not include the mouse studies of NTP (1993), the rat studies of NTP (1993) and Longnecker *et al*. (1990), or the short-term genotoxicity studies reported by NTP (1993). These results, in addition to the studies reviewed by IARC, are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to benzyl acetate have been reported (IARC, 1986).

Animal bioassays

1. Mouse long-term gavage studies (103 weeks): Abdo *et al*., 1985; NTP, 1986. Early mortality was observed in all female groups, and was due to the occurrence of genital tract infections. A statistically significant dose-related increase in the incidence of hepatocellular adenomas was observed in both males (0/50; 5/49; 13/50, test for trend $p < 0.001$) and females (0/50/; 0/50; 6/50, test for trend $p = 0.002$) after adjusting for age. A statistically significant increase in the incidence of hepatocellular adenomas and carcinomas (combined) was observed in high-dose males (10/50; 18/49; 23/50) and high-dose females (1/50; 0/50; 10/50) after adjusting for age, as well as significant positive trends with increasing doses in both sexes. A statistically significant increase in the incidence of squamous-cell papillomas of the forestomach was observed in high-dose males (3/49; 3/48; 9/49) and high-dose females (0/50; 0/50; 4/48) after adjusting for age. The incidences of these tumors in the high-dose animals were higher than the historical corn oil gavage control rates in this laboratory. A significant positive trend for squamous-cell papillomas and carcinomas (combined) of the forestomach was also observed in males.

2. Rat long-term gavage studies (103 weeks): Abdo *et al*., 1985; NTP, 1986. A statistically significant increase in acinar-cell adenomas of the pancreas was observed in both low- and high-dose males, after adjusting for age (22/50; 27/50; 37/49). Significant positive trends in preputial gland cystadenocarcinomas (0/50; 0/50; 3/50), all adenocarcinomas (0/50; 1/50; 4/50) and adenocarcinomas and carcinomas (combined) (1/50; 1/50; 6/50) were observed in males, at $p < 0.05$. A nonsignificant increase in the incidence of clitoral gland tumors (adenomas and carcinomas combined) was observed (2/50; 0/50; 5/50) in females.

3. Mouse long-term feeding studies (103 weeks): NTP, 1993. No treatment-related increases in tumors were observed. NTP (1993) noted the contrast in these results with those of the gavage study in mice (NTP, 1986), and suggested that the difference in the dose levels used (highest dose: gavage, 1,000 mg/kg/day; feed, 360 mg/kg/day) might have played a role in the different study outcomes.

4. Rat long-term feeding studies (103 weeks): NTP, 1993. No treatment-related increases in tumors were observed. The highest dose administered was similar to that used in the earlier gavage study (feed - 510 and 575 mg/kg/day were received by high-dose male and female groups, respectively, as compared to gavage - 500 mg/kg/day).

5. Rat long-term feeding study (104 weeks, males only): Longnecker *et al*., 1990. A low, but statistically significant increase in the incidence of carcinoma *in situ* of the pancreas ($p = 0.04$) was observed in the high-dose group (3/25) vs. the control group (0/25). No increase in the incidence of pancreatic adenomas was observed (controls 10/50; 11/50 high-dose group). The authors concluded that benzyl acetate had no initiating activity, but might have had a weak promoting effect on the growth of

spontaneous pre-neoplastic foci in the male rat pancreas. [The small size of the treatment groups (n = 25) and the histopathological examination of only pancreatic tissue is noted.]

Other relevant data

Benzyl acetate was negative in several short-term tests for mutagenicity and genotoxicity (e.g., *Salmonella* reverse mutation assay, *Bacillus subtilis* assay, sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, unscheduled DNA synthesis in rat liver primary cell cultures following *in vitro* or *in vivo* administration) (IARC, 1986). Benzyl acetate was mutagenic in the mouse lymphoma assay in the presence of metabolic activation (IARC, 1986). IARC (1986) concluded that there was inadequate evidence of the genotoxicity of benzyl acetate. Additional short-term tests have also been negative (e.g., sister chromatid exchanges and chromosomal aberrations in mouse bone marrow cells, sex-linked recessive lethal germ cell mutations in *D. melanogaster*, micronuclei in mouse bone marrow and peripheral blood) (NTP, 1993).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **LOW** level of **carcinogenicity concern** over benzyl acetate. In gavage studies (NTP, 1986) an increased incidence of acinar cell adenomas of the pancreas was observed in male rats, but well-conducted follow-up feeding studies by NTP (1993) did not confirm this finding. There was "some evidence of carcinogenicity in mice" since increased incidences of hepatocellular adenomas and squamous cell neoplasms of the forestomach were observed in males and females (NTP, 1986). Evaluating the gavage studies, IARC (1986) found this evidence suggestive and concluded that "there is limited evidence of carcinogenicity" in experimental animals. Feeding studies in rats by Longnecker *et al*. (1990) provide additional support for IARC's conclusion. NTP more recently conducted long-term feeding studies in rats and mice and concluded that under the conditions present in the feeding studies, there was "no evidence of carcinogenic activity" (NTP, 1993). Failure to observe tumors in the same species/strains in the later NTP studies reduces the overall toxicological concern. The low level of concern is reinforced by the lack of mutagenic and genotoxic activity in the majority of short-term tests conducted to date.

There is a **HIGH** level of **concern over the extent of exposure** since there is widespread human exposure by ingestion, skin application, and inhalation through the wide use of benzyl acetate in foods, perfumes, and other consumer goods (NTP, 1986; 1993). NIOSH estimated that 161,626 U.S. workers were exposed to benzyl acetate in 1983 (NIOSH, 1994). U.S. annual production in 1990 was estimated to be 3,000,000 lbs.

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CARCINOGENICITY DATA SUMMARY: BUTYL BENZYL PHTHALATE

Butyl benzyl phthalate (CAS number 85-68-7) is a synthetic substance used as a plasticizer for plastics (in particular, polyvinyl chloride). It is also used as a dispersant and carrier. Butyl benzyl phthalate was reviewed by IARC in 1982, and was tested by the National Toxicology Program in 1995. IARC found inadequate evidence of carcinogenicity in animals and insufficient evidence for evaluation in humans. The more recent NTP study found some evidence of carcinogenic activity of butyl benzyl phthalate in the male F344 rat and equivocal evidence of carcinogenic activity in the female rat These results, in addition to the studies reviewed by IARC, are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

Although there are some occupational studies of irritation, neurotoxicity and reproductive effects, no data on possible carcinogenic effects of human exposure to butyl benzyl phthalate have been reported (NTP, 1995; IARC, 1982).

Animal bioassays

1. Rat long-term diet studies: NTP, 1995. Fischer 344/N rats were fed diets containing butyl benzyl phthalate for 103 weeks. Males received 0, 3,000, 6,000 or 12,000 ppm while females received 0, 6,000, 12,000 or 24,000 ppm. The incidence of pancreatic acinar cell adenoma or carcinoma was increased in the 12,000 ppm males only (3/50 in controls, 2/49 low-dose, 3/50 mid-dose, 11/50 high-dose). Focal hyperplasia of the pancreatic acinar cells was also increased in this group. Transitional cell papillomas were observed in the urinary bladders of two high-dose females, and one control female, but in no other groups. Transitional epithelial cell hyperplasia of the kidney and urinary bladder were also observed in high-dose females. NTP (1995) determined that these results showed some evidence of carcinogenicity in male rats, and equivocal evidence in female rats.

2. Rat long-term diet studies: NTP, 1982. Fischer 344/N rats were fed diets containing 0, 6,000 or 12,000 ppm butyl benzyl phthalate for 103 weeks. Severe early mortality occurred in both dosed groups of male rats, and this section of the study was abandoned without further examination. In the exposed females, an increased incidence of mononuclear cell leukemia was noted in the high-dose group only (7/49 in controls, 7/49 low-dose, 18/49 high-dose). This increase was statistically significant and also larger (at 37%) than the incidence of this tumor in historical controls, although this historical incidence is high and somewhat variable (females, mean 11%, range 8-15%; males, mean 17%, range 9-24%). NTP (1982) concluded from these data that butyl benzyl phthalate was "probably" carcinogenic to female rats, but was unable to reach a conclusion about its effects in male rats.

3. Mouse long-term diet studies: NTP, 1982. Male and female B6C3F_1 mice were fed diets containing 0, 6,000 or 12,000 ppm butyl benzyl phthalate for 103 weeks. No carcinogenic effects were observed.

4. Mouse intraperitoneal injection study: Theiss *et al.*, 1977. In this study, which used the mouse lung adenoma "accelerated bioassay" protocol, no increases in lung adenomas were observed in male Strain A mice receiving 24 intraperitoneal doses of up to 800 mg/kg butyl benzyl phthalate.

Other relevant data

Butyl benzyl phthalate has been tested in various genetic toxicity assays, including the *Salmonella* reverse mutation assay, other assays in bacteria and *Saccharomyces cerevisiae*, and various mutation or cytogenetic tests in mammalian cells. In all the tests *in vitro*, the results were negative (IARC, 1982; NTP, 1995). A recessive lethal test *in vivo* in *Drosophila melanogaster* was negative, but weak induction of sister chromatid exchanges, and chromosome aberrations at a single time point only, were reported *in vivo* in mice (NTP, 1995).

A related compound, di(2-ethylhexyl)phthalate, is a rodent hepatocarcinogen and is listed as a carcinogen under Proposition 65. There is an ongoing debate over the extent to which observations of hepatocarcinogenicity in rodents by phthalates and other peroxisome-proliferation inducing agents are applicable to non-rodent species such as humans. Butyl benzyl phthalate appears to have only weak peroxisome proliferation inducing activity (NTP, 1995). It causes thymic and testicular atrophy in rodents.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **LOW** level of **carcinogenicity concern** over butyl benzyl phthalate, based on the equivocal carcinogenic responses in the female rat and the suggestive evidence in the male rat observed in the recent NTP (1995) studies. The observations in the male rat involved tumors with variable background incidence, and results statistically above background were obtained only at the highest dose level. Mononuclear cell leukemia was noted in the high-dose male rats in an earlier NTP (1982) study. The sites of tumor appearance in the male rat were not concordant in the two NTP studies. Available studies in the mouse were nonpositive. There are no clear observations of mutagenicity, cytogenetic effects or cell transforming ability in short-term tests. IARC (1982) found inadequate evidence of carcinogenicity in animals.

There is a **HIGH** level of **concern over the extent of exposure** since butyl benzyl phthalate is manufactured in bulk and occurs ubiquitously as an ingredient in consumer products and as an environmental contaminant (IARC, 1982; NTP, 1995). Butyl benzyl phthalate has been commercially produced in the United States since 1946, and annual production was estimated at 80 million pounds per year in 1978. U.S. FDA has approved butyl benzyl phthalate as a plasticizer in food contact materials. As a result of this use, food product levels of butyl benzyl phthalate between 0.5 and 53 mg/kg have been reported. Occupational exposure studies indicated that 68,488 workers were potentially exposed to benzyl butyl phthalate in 1972-74, and 331,840 in 1981-1983. (Production and exposure statistics are quoted from NTP [1995], who cite a variety of primary sources.) Persistence in the environment appears to be moderate: Although subject to biodegradation, the rate of input appears to be sufficient to produce measurable levels in many surface water bodies and drinking water supplies (IARC, 1982; NTP, 1995). According to reports cited by NTP (1995), water samples from a range of US sources showed a mean level of 9 µg/l, and one study in New Orleans found 0.08 to 1.8 µg/l in drinking water. NTP (1995) estimates that all consumers are exposed to butyl benzyl phthalate to some extent.

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CARCINOGENICITY DATA SUMMARY: DECABROMOBIPHENYL OXIDE

Decabromobiphenyl oxide (CAS No. 1163-19-5) is a widely used flame retardant for plastics (e.g., components in electrical and electronic equipment) and other materials (e.g., textiles) for which long-term flame retardant properties are desirable. This compound was identified as a result of a CCRIS (Chemical Carcinogenesis Research Information System) database search, and information suggesting a potential for high exposure concern. IARC reviewed this compound in 1990 and found that there was limited evidence of carcinogenicity in animals (group 3). The results of the studies reviewed, as well as from a new structure-activity analysis are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to decabromobiphenyl oxide were identified by IARC (1990) or in a more recent literature search by OEHHA.

Animal bioassays

1. Long-term diet study in F344/N rats: NTP, 1986. Significantly increased incidences of neoplastic nodules of the liver were observed in male and female rats. However, the incidence of hepatocellular carcinomas was low in all groups and characterized by NTP as not compound-related. Since benign rather than malignant tumors were observed, NTP considered these results to indicate some, rather than clear, evidence of carcinogenicity.

2. Long-term diet study in $B6C3F_1$ mice: NTP, 1986. Increased incidences of hepatocellular adenomas/carcinomas, and thyroid follicular cell adenomas/carcinomas were observed in male mice. NTP considered this to be equivocal evidence of carcinogenicity due to the early loss of control animals and the lack of a statistically significant effect at the high dose. No evidence of carcinogenicity was reported in female mice. Increased incidences of several nonneoplastic lesions were observed, most notably thyroid gland follicular cell hyperplasia in male mice.

3. Long-term diet study in Sprague-Dawley rats: Kociba *et al*., 1975. No significant differences in the number of rats developing tumors (total number of tumors or specific type of tumors) were observed between control and treated animals.

Other relevant data

Decabromobiphenyl oxide was not found to be mutagenic in several strains of *Salmonella* (with or without S9), or mouse lymphoma assays. It also did not induce SCEs or chromosomal aberrations in CHO cells *in vitro*. (NTP, 1986) A computerized analysis of structure-activity relationships (Oncologic) based on rules generated by US EPA experts predicts decabromobiphenyl oxide to be of "moderate" concern.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **LOW** level of **carcinogenicity concern** regarding decabromobiphenyl oxide. NTP concluded that there was "some evidence" of carcinogenicity in rats due to increases in the same tumor type in both males and females. Oncologic, a computer analysis of structure-activity relationships generated by US EPA experts, predicts that decabromobiphenyl oxide is of moderate concern. IARC (1990) concluded that there was limited evidence of carcinogenicity in animals.

There is a **HIGH** level of **concern over the extent of exposure** to decabromobiphenyl oxide. This is a widely used, high production volume flame retardant. US annual production is estimated to be up to 50 million pounds (TSCA, 1990) and TRI release data reports over 170,000 pounds were released in the U.S. in 1993. Human exposure occurs in the course of manufacture and use; the Brominated Flame Retardants

Industry Panel estimates that "the greatest potential for occupational exposure or dispersive types of releases (to air or water) occurs at the site of polymer formulation, and not at the level of the persons using the formulation or finished article" (Spurlock, 1996). According to the Panel, decabromobiphenyl oxide is produced in only two locations within the U.S., neither of which is in California (Spurlock, 1996). The Panel reports that decabromobiphenyl oxide typically enters California in either formulated resin systems (e.g., thermoplastics, thermosets, or coatings/adhesives) or as finished articles; a lesser amount enters the state as the pure chemical (Spurlock, 1996). The 1994 TRI data for California reported releases of decabromobiphenyl oxide at four separate locations; 350 pounds were reported as released to the air and 250 pounds were reported as released to publicly operated treatment works (Spurlock, 1996). The Panel was not aware of any uses of decabromobiphenyl oxide in polymer formulations for making food contact articles or in components (pipes, valves, etc.) of drinking water systems, nor was the Panel aware of any uses in its commercial form by the general public (Spurlock, 1996).

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CARCINOGENICITY DATA SUMMARY: EUGENOL

Eugenol (2-methoxy-4-(2-propenyl)-phenol; CAS No. 97-53-0) occurs naturally and is widely distributed in plants as a component of essential oils (e.g., cloves, cinnamon, fennel, jasmine, basil, tobacco leaf phenol). It is widely used as a flavoring agent in foods and as a fragrance, an analgesic in dental materials and nonprescription drugs, an insect attractant and a chemical intermediate. The concern over the chemical arose because of the potential for high exposure. Eugenol was reviewed by IARC in 1985 and 1987. IARC concluded that there was no data available on the evidence of carcinogenicity in humans and that the evidence was limited in animals (group 3 carcinogen). The IARC review did not include the promotion study of Imaida *et al*. (1990), or the genotoxicity data of Allavena *et al.* (1992) and Howes *et al*. (1991). These results, in addition to the studies reviewed by IARC, are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

IARC (1987) noted that no data on long-term effects of human exposure to eugenol have been reported; also, a more recent literature search by OEHHA did not identify epidemiological studies.

Animal bioassays

1. Mouse long-term feeding studies (103 weeks): NTP, 1983. A nonsignificant increase in hepatocellular adenomas was seen in males (4/50; 13/50; 10/49) and females (0/50; 4/49; 3/49). A nonsignificant increase in hepatocellular carcinomas was seen in males (10/50; 20/50; 9/49) and females (2/50; 3/49; 6/49). No dose-related trend in the incidence of combined hepatocellular adenomas and carcinomas was observed in males, although a statistically significant increase was observed in the low-dose group compared to controls ($p = 0.004$). A dose-related trend ($p = 0.02$) in the incidence of combined hepatocellular adenomas and carcinomas was observed in females, and a statistically significant increase was observed in the high-dose group compared to controls ($p = 0.02$). NTP (1983) concluded that the evidence of carcinogenicity in these studies was equivocal.

2. Rat long-term feeding studies (103 weeks): NTP, 1983. A positive trend in the incidence of (benign) endometrial stromal polyps was observed with increasing dose ($p = 0.02$) in females (6/40; 6/50; 16/50). No other treatment-related tumors were observed in males or females. NTP (1983) concluded, based on these results, that eugenol was not carcinogenic in F344 rats of either sex.

3. Mouse long-term feeding studies (12 months + 8 months additional observation): Miller *et al*., 1983. No treatment-related tumors were observed. IARC (1985) noted the short duration of the experiment.

4. Mouse long-term gavage studies (5 weeks + 13 months additional observation): Miller *et al*., 1983. No treatment-related tumors were observed. IARC (1985) noted the short treatment and the short duration of the experiment.

5. Mouse long-term topical application study (3x/week for 63 weeks): Van Duuren *et al*., 1966. No treatment-related tumors were observed. IARC (1985) noted the small number of animals per group ($n = 20$) and the short duration of the experiment.

Other relevant data

Eugenol was not mutagenic in *E. coli*, equivocal in the *Bacillus subtilis* DNA repair assay, negative for mutations and gene conversion in *Saccharomyces cerevisiae*, and tested both positive and negative in various *Salmonella* reverse mutation assays. Eugenol induced chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells *in vitro*. IARC (1985) concluded that the evidence for the genetic activity of eugenol in short-term tests was inadequate. More recent short-term test data contribute to the overall evidence that eugenol is unlikely to have significant carcinogenic activity (Allavena *et al*., 1992; Howes *et al*., 1990). However, eugenol is structurally similar to the animal liver carcinogen

safrole. Eugenol is metabolized by rat liver epithelial cell cultures to 2',3'-epoxyeugenol, which is mutagenic in the *Salmonella* reverse mutation assay and induces benign skin tumors in mice following topical application. In a study of the effect of treatment of eugenol during the promotional phase of tumor development in rats pretreated with 1,2-dimethylhydrazine and 1-methyl-1-nitrosourea, eugenol enhanced the development of forestomach hyperplasia and papilloma but decreased the incidence kidney nephroblastomas (although the results were not statistically significant) (Imaida *et al*., 1990).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **LOW** level of **carcinogenicity concern** over eugenol since long-term feeding studies have reported equivocal results in mice, and no evidence of carcinogenicity in rats. Specifically, a dose-response relationship was not observed for the induction of tumors (liver adenomas and carcinomas) in male mice, and in females, the induction of tumors (liver adenomas and carcinomas) was only observed in the high-dose group. Consideration of other relevant information, including that published since the IARC review, does not add to this concern.

There is a **HIGH** level of **concern over the extent of exposure** since eugenol is a naturally occurring substance, with widespread distribution in plants and widespread use in foods (e.g., sweets, baked goods), alcoholic beverages, chewing gum, and mouthwashes (IARC, 1985). NIOSH (1994) estimated that 72,961 U.S. workers in 53 industries were exposed to eugenol in 1983. U.S. annual production in 1984 was estimated to be 360,000 lbs. Eugenol has been detected in U.S. municipal wastewater treatment effluent (IARC, 1985).

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CARCINOGENICITY DATA SUMMARY: ISOPHORONE

Isophorone (CAS No. 78-59-1) is used as a solvent for vinylic resins, printing inks, lacquers, adhesives, nitrocellulose resins, finishes, and a variety of fats, oils and gums. It is used in the formulation of pesticides and herbicides, and as a chemical intermediate. It occurs naturally in cranberries in trace amounts. Isophorone was reviewed by US EPA in 1992. US EPA concluded that there was no data available on the evidence of carcinogenicity in humans and that the evidence in animals was limited (group C, possible human carcinogen). Literature searches did not identify any critical studies published subsequent to the US EPA (1992) evaluation. The studies reviewed by US EPA are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

US EPA (1992) found no data on long-term effects of human exposure to isophorone, and neither did OEHHA in a more recent literature search.

Animal bioassays

1. Rat long-term gavage studies: NTP, 1986; Bucher *et al*., 1986. A statistically significant increase in renal tubular cell adenomas and adenocarcinomas was observed in the high-dose males by life table analysis (0/50 controls; 3/50 low-dose group; 3/50 high-dose group). A statistically significant increase in carcinoma of the preputial gland was also seen in high-dose males (0/49; 0/46; 5/44). NTP concluded that the findings of renal tubular cell and preputial gland tumors provide some evidence of carcinogenicity in the male rat. The US EPA (1992) considered this as equivocal evidence of carcinogenicity, after concluding that the increased incidence of renal tumors in the male rat were the result of an interaction between isophorone and the male rat specific protein α-2μ-globulin. No treatment-related tumors were observed in female rats.

2. Mouse long-term gavage studies: NTP, 1986; Bucher *et al.*, 1986. A statistically significant increase in the incidence of liver adenomas and carcinomas combined (18/48 controls; 18/50 low-dose group; 29/50 high-dose group) and mesenchymal tumors of the integumentary system (6/48; 8/50; 14/50) was observed in high-dose males. A nonsignificant increase in the incidence of malignant lymphomas was observed in low-dose males (8/48; 18/50; 5/50). Survival was so low in both the treated and control groups that both the NTP and the US EPA consider the results in male mice to be equivocal (NTP, 1986; US EPA, 1992). No treatment-related tumors were observed in female mice.

Other relevant data

Isophorone tested positive in the mouse lymphoma assay and induced sister chromatid exchanges in cultured Chinese hamster ovary cells (CHO) in the absence of metabolic activation. Isophorone was negative in the *Salmonella* reverse mutation assay (± metabolic activation) and did not induce chromosomal aberrations in cultured CHO cells, nor did it induce unscheduled DNA synthesis in primary cultures of rat hepatocytes.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **LOW** level of **carcinogenicity concern** over isophorone. There are no data in humans. There are some suggestive findings of carcinogenicity in animals, primarily from small increases in the incidence of preputial gland tumors in the male rat in one study. The kidney tumors observed in male rats in this study may be associated with α-2μ-globulin, and the US EPA concluded that they were of questionable relevance to humans.

There is a **HIGH** level of **concern over the extent of exposure** since isophorone is a widely used solvent and chemical intermediate (NTP, 1986). U.S. annual production was 6,891,540 lbs. in 1990. In 1991, 327 lbs. were reported to be released into the atmosphere in California. Isophorone has been detected in U.S.

municipal water supplies, and in oysters and fish (ATSDR, 1989). In 1988, NIOSH estimated that 37,469 workers were exposed to isophorone. Inhalation and dermal contact are the most likely routes for occupational exposures, while drinking isophorone-contaminated water is the most probable route of exposure for the general population (ATSDR, 1989).

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US Environmental Protection Agency (US EPA, 1992). Integrated Risk Information System.

CARCINOGENICITY DATA SUMMARY: NAPHTHALENE

Naphthalene (CAS number 91-20-3) occurs naturally in crude oil, and is also manufactured from coal tar. It is also formed as a combustion product, particularly from combustion of fuel oil and gasoline. It is used in chemical manufacturing, as an insecticide and insect repellent, vermicide, and antiseptic; some of these uses result in its appearance in consumer products. It has been reported as a contaminant of tap water and fresh water fish. Naphthalene was tested by the National Toxicology Program in 1992. The NTP studies found some evidence for carcinogenicity via inhalation in female mice, but no evidence in male mice. These results are briefly described below.

Carcinogenicity Data available:

Epidemiological studies

An unexpectedly high incidence of laryngeal and other cancers was noted in two reports on workers exposed to naphthalene, and naphthalene exposure was found for some cases in a small case-control study (studies cited by NTP, 1992). It is not clear whether these studies have any relevance to possible human carcinogenic effects of naphthalene since there may have been substantial confounding effects from other carcinogens in the workplace and from cigarette smoking.

Animal bioassays

1. Mouse long-term inhalation studies: NTP, 1992. Mice of both sexes were exposed to 0, 10 or 30 ppm naphthalene vapor for 6 h daily, 5 days per week for 104 weeks. No increase in tumor incidence was observed in males. A significantly increased incidence of alveolar/bronchiolar adenomas, and a single alveolar/bronchiolar carcinoma, were observed in the high-dose females. On the basis of these findings the NTP concluded that there was some evidence of carcinogenic activity in females, and no evidence in males.

2. Studies in rats: Schmähl, 1955. Three small long-term (>1000 days) studies in BD I, II or III rats using subcutaneous or intraperitoneal injection with, or dietary incorporation of, naphthalene in oil did not result in any increase in tumors. The study is seriously limited: Small numbers of animals were used and the study was without controls.

3. Short term A/J mouse inhalation study: Adkins *et al.*, 1986. Daily 6-h exposures of Strain A/J mice to 30 ppm naphthalene for 6 months caused a statistically significant increase in the number of adenomas per mouse lung.

4. Rabbit dermal study: Bogdat'eva and Bid, 1955. No carcinogenic activity was observed at levels which induced systemic toxicity.

5. Mouse bladder implantation study: Boyland *et al.*, 1964. Carcinoma incidence was similar to that caused by implantation of inert materials.

6. Several early studies using various routes of exposure were non-positive: Bloch, 1922 (mice, skin painting); Kennaway, 1930 (mice, skin painting); Kennaway and Heiger, 1930 (mice, skin painting); Fitzhugh and Buschke, 1949 (rats, diet). However, a study in rats by Knake (1956) using subcutaneous injection found some sarcomas, as did a study by the same author using skin painting of mice with naphthalene dissolved in benzene. These studies are described in PHS 149 (DHHS, 1994 and earlier).

Other relevant data

Naphthalene has been found to be negative in the *Salmonella* reverse mutation assay by numerous investigators. Various studies of gene mutation potential in other systems *in vivo* and *in vivo* have also found negative results with naphthalene. NTP (1992) examined the genetic toxicity of naphthalene and found negative results in the *Salmonella* reverse mutation assay but significant increases in sister chromatid exchanges and chromosome aberrations in Chinese hamster ovary cells *in vitro*. Metabolism of naphthalene

in various species is postulated to occur via an epoxide intermediate: the observed metabolites include naphthol, various diols and quinones and conjugates of these products. Some of the metabolites have been observed to react with cellular macromolecules and cause DNA damage *in vitro*. One metabolite, 1,4-naphthoquinone, was reported to induce skin tumors in a skin-painting assay (Takizawa, 1940).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **LOW** level of **carcinogenicity concern** over naphthalene. No clear evidence of carcinogenicity has been observed in rats or mice. Some evidence for carcinogenicity was found in female mice, but no evidence in similarly treated male mice. Most of the other studies did not find significant carcinogenic activity, although it is hard to draw any definite conclusion from the early studies which were limited by number of animals, duration of treatment, survival and in some cases, lack of control groups.

There is a **HIGH** level of **concern over the extent of exposure** since naphthalene appears to be widely distributed in the environment. Although it does not appear to be very environmentally persistent, there are sufficient natural and artificial sources to result in its presence as a contaminant in many media, including drinking water with a range of reported concentrations from 1 ng/l to 1 µg/l. Some residues in freshwater fish have been noted, including a range of 0.1- 3.4 µg/kg in Boston. U.S. production of naphthalene in 1984 was 280 million pounds. [Environmental levels and production data are taken from NTP (1992), who cite a number of primary sources]. Occupational exposures are reported to be significant, affecting an estimated 112,696 workers in 1981-83, especially in the petroleum and coal products industries (NIOSH, 1990). It is also a component of various consumer products (NTP, 1992).

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CARCINOGENICITY DATA SUMMARY: PROPYL GALLATE

Propyl gallate (CAS No. 121-79-9) is used as an antioxidant to stabilize cosmetics, food-packaging material, and foods containing fats. It is also found in hair grooming products, pressure-sensitive adhesives, lubricating oil additives, and transforming oils. This compound was selected for testing by NTP because of widespread human exposure through its use as a food additive and because the available carcinogenicity data was considered to be inadequate. Propyl gallate is regulated as Generally Recognized as Safe (GRAS) by the US FDA (see 21 CFR 184.1660 for use in human foods and 21 CFR 582.1660 for use in animal feed).

Carcinogenicity Data available:

Epidemiological studies

No data on long-term effects of human exposure to propyl gallate are available.

Animal bioassays

1. Long-term diet study in F344/N rats: NTP, 1982. Significantly increased incidences of preputial gland tumors, pancreatic islet-cell tumors, and adrenal gland pheochromocytomas were observed in low-dose (6000 ppm) male rats. Rare brain tumors were found in two low-dose (6000 ppm) female rats. NTP concluded that the compound "was not considered to be carcinogenic for F344/N rats, although there was evidence of an increased proportion of low-dose male rats with preputial gland tumors, islet-cell tumors of the pancreas, and pheochromocytomas of the adrenal glands; rare tumors of the brain occurred in two low dose females".

2. Long-term diet study in $B6C3F_1$ mice: NTP, 1982. Significantly increased incidences of malignant lymphoma were observed in male mice in the high-dose group (12000 ppm) as compared to concurrent controls, as well as a positive trend with increasing dose ($p<0.014$). However, the high-dose incidence was not statistically significant when compared to the historical rate. Liver adenomas in female mice occurred with a statistically significant positive trend, with the incidence in the high-dose group being significantly higher than that in controls. However, since the incidences of hepatocellular adenomas or carcinomas (combined) were similar in control and dosed groups, the increased incidence of hepatocellular adenomas in the high-dose group was not considered to be related to propyl gallate administration. NTP concluded that the compound "was not considered to be carcinogenic for $B6C3F_1$ mice of either sex, although the increased incidence of malignant lymphoma in male mice may have been related to dietary administration of propyl gallate".

Other relevant data

Propyl gallate was not found to be mutagenic in *Salmonella* strains TA98, 100, 1535 or 1537 (with or without metabolic activation).

Preliminary evaluation of carcinogenicity and exposure data:

There is a **LOW** level of **carcinogenicity concern** regarding propyl gallate based on the results of the NTP bioassay in F344/N rats and $B6C3F_1$ mice as described above. Propyl gallate was not clearly carcinogenic to rats or mice under the conditions of the studies. However, NTP reported that there was evidence of an increased proportion of low-dose male rats with various tumors (see above) and an increased incidence of malignant lymphomas in male mice that may have been related to dietary administration of propyl gallate.

There is a **HIGH** level of **concern over the extent of exposure** to propyl gallate. Widespread human exposure occurs through food; approximately 150,000 lbs. were used in food in the US in 1970 (NTP, 1982). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an acceptable daily intake (ADI) of 0-1.4 mg/kg body weight in 1993 (Behling, 1996). In 1973 the Select Committee on GRAS Substances estimated that the maximum daily intake values for propyl gallate were 0.054 mg/kg body weight for infants 0-5 months of age, 0.4 mg/kg body weight for infants 6-11 months of age, 0.495

mg/kg body weight for infants 12-23 months of age, and 0.235 mg/kg body weight for individuals 2-65+ years of age (Behling, 1996). NIOSH (1983) estimated that over 36,000 workers were exposed in 16 US industries in 1983. Propyl gallate is listed on the TSCA inventory, however current production figures are not available. Although not currently manufactured in California, propyl gallate is widely used in California's food processing industries (Behling, 1996).

References

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CARCINOGENICITY DATA SUMMARY: CHLORAMBEN

Chloramben (CAS # 133-90-4) is a grass and broadleaf weed herbicide used on soybeans and a variety of other crops. The National Cancer Institute selected this chemical for testing because of the potential for human exposure through it use as a herbicide.

Carcinogenicity data available:

Epidemiological studies

No studies of effects of long-term exposure in humans have been reported.

Animal bioassays

1. Mouse long-term diet studies (treated 80 weeks + additional 11-12 weeks observation): NCI, 1977. NCI reported that chloramben was carcinogenic in female $B6C3F_1$ mice: hepatocellular carcinomas were significantly increased (historical controls for hepatocellular carcinomas in female mice average 2.3%) in a dose-related trend (3%, 15%, and 20%; p= 0.004). The increased incidence was significant in high-dose females vs. pooled controls. The dose-related trend for these tumors was significant in male mice (13%, 33%, 29%; p = 0.029), but only the incidence in the low-dose group was significantly increased when compared to pooled controls. With regard to these findings in male mice, the NCI noted that "the incidence of hepatocellular carcinoma was considered to be only marginally associated with the administration of chloramben because of the variations in the spontaneous incidence of this lesion in male mice encountered at this laboratory."

2. Rat long-term diet studies (treated 80 weeks + additional 32-33 weeks observation): NCI, 1977. No evidence of carcinogenicity in Osborne-Mendel rats of either sex was observed. (Significant elevation of hemangiomas was observed in low-dose male rats, when compared with pooled controls, but since the tumor did not occur at a significantly higher incidence in the high-dose group than in the pooled control group, the lesion was considered not to be compound related by the NCI.

Other relevant data

Chloramben causes chromosomal aberrations in cultured CHO cells, but not in mouse bone marrow studies *in vitro*. DPR noted that bone marrow may not be a target tissue for chloramben (DPR, 1986). A computer program that analyzes structure-activity relationships based on a set of rules generated by US EPA experts (Oncologic, version 1.0) predicts that chloramben is of low-moderate carcinogenicity concern.

Preliminary evaluation of carcinogenicity and exposure data:

There is a **LOW** level of **carcinogenicity concern** over chloramben, due to the increased incidence of liver carcinoma in female mice, the marginal association between treatment and tumorigenicity in male mice, and no evidence of significant carcinogenic activity in male or female rats This level of concern is reinforced by the observation of clastogenicity in cultured mammalian cells, and by the results of a computerized analysis of structure-activity relationships (Oncologic), which predicts that chloramben is of low-to-moderate concern.

There is a **LOW** level of **concern over the extent of exposure** to chloramben. According to the 1993 Pesticide Use Report (DPR, 1995) chloramben was used on asparagus and bean crops. However, in 1993 there were only 2 applications, totaling 65 lbs, of ammonium salts of chloramben. Workers may be exposed by dermal or inhalation routes, and the general public could be exposed through drinking water in addition to food residues (HSDB).

References

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Hazardous Substances Data Bank (HSDB, 1995). National Library of Medicine.

CARCINOGENICITY DATA SUMMARY: ETHYL PARATHION (PARATHION)

Ethyl parathion (CAS # 56-38-2) is an organophosphate pesticide used on a variety of food crops. Ethyl parathion was reviewed by IARC in 1983. IARC concluded that there were no data available on the evidence of carcinogenicity in humans and that the evidence was inadequate in animals (group 3 carcinogen). The IARC review did not include rat studies performed by Biodynamics, Inc. (1984) and the Bayer Institute of Toxicology (as summarized by DPR in 1986 and 1990, respectively), or the mouse studies of the Southern Research Institute (as summarized by DPR in 1991). These results, in addition to the studies reviewed by IARC, are briefly described below.

Carcinogenicity data available:

Epidemiological studies

No studies of the long-term effects of human exposure to ethyl parathion have been reported which provide an adequate assessment of its potential for carcinogenic effects. One study, cited in IARC (1983) reported 30 cancer deaths in 316 men exposed to a variety of herbicides, insecticides and fungicides including ethyl parathion, but since data on individual pesticides were not collected, no conclusion can be drawn from this study. No additional epidemiological studies were identified in a recent literature search by OEHHA.

Animal bioassays

1. Rat long-term diet studies (80 weeks with 32-33 weeks additional observation): NCI, 1979. Two dose groups of each sex of Osborne-Mendel rats were exposed to ethyl parathion in diet. In both sexes, there was a significant positive trend of combined adenoma and carcinoma of the adrenal cortex. When compared to pooled controls, the incidence in high-dose groups was significant. Significant positive trends with increasing dose of pancreatic islet cell carcinoma and thyroid follicular cell adenoma in males were also noted. This study used only 10 control animals per sex/species, necessitating the use of pooled controls for analysis. NCI (1979) concluded that "In male and female Osborne-Mendel rats receiving parathion in their diet, there was a higher incidence of cortical tumors of the adrenal than in pooled or historical controls, suggesting that parathion is carcinogenic to this strain of rat."

2. Mouse long-term diet studies (62-80 weeks, with additional observation until 90 weeks): NCI, 1979. Ethyl parathion in diet was administered to two dose groups of each sex of $B6C3F_1$ mice. No evidence for oncogenicity was seen in mice of either sex.

3. Rat long-term diet studies (2 years): Biodynamics, Inc., 1984. This study in Sprague Dawley rats used three dose levels, reaching the MTD. There was no unequivocal evidence of treatment-related carcinogenic response. A slightly increased incidence of thyroid follicular adenomas was noted in high-dose males, which was slightly greater than the incidence in laboratory historical controls. Because the natural incidence is variable, Biodynamics noted that it is unclear whether these tumors were compound related. DPR (1986) indicated the study was "unacceptable" (for registration purposes) due to unexplained early deaths in some treated animals.

4. Rat long-term diet studies (26 months): Bayer Institute of Toxicology, 1987, as cited by DPR, 1990. Parathion in diet was administered at three dose levels to Wistar rats. An increasing trend with dose of pancreatic exocrine tumors in male rats was observed. Although the number of tumor-bearing animals was low (0, 0, 1, 3 with increasing dose), historical control data from Bayer shows that no exocrine pancreatic tumors were noted in either sex in 11 studies of 2000 total animals (DPR, 1991). A non-significant increase in pancreatic islet cell adenomas was also observed. DPR termed this study "acceptable".

5. Mouse long-term diet studies (18 months): Southern Research Institute, 1991, as summarized by DPR, 1991. Male and female $B6C3F_1$ mice received 0, 60, 100, or 140 ppm in feed. "A possible adverse

effect is noted for systemic malignant lymphoma in males with incidences of 0/50, 0/50, 2/50, 4/50 with increasing dose and a positive trend test of p = 0.008 -- these incidences are within historical control values" DPR (1991).

Other relevant data

As summarized by IARC (1983), "no evidence has been found that parathion is mutagenic".

Preliminary evaluation of carcinogenicity and exposure data:

There is a **LOW** level of **carcinogenicity concern** over ethyl parathion. Tumors of the rat adrenal cortex were seen at levels higher than in historical controls in both sexes in the NCI studies; however, technical limitations of these studies hinder interpretation of the significance of these findings. In addition, the possible induction of pancreatic tumors in rats is supported by the results of the Bayer study in a different strain. Finally, small increases in the incidence of thyroid follicular cell adenomas were observed in two bioassays in male rats of different strains.

There is a **LOW** level of **concern over the extent of exposure** to ethyl parathion because most of the uses of the pesticide in California have been voluntarily cancelled by the registrant since 1992, the volume currently applied is low, and there is a continued trend toward decreased use in California. In 1992 33,887 pounds were applied, decreasing to 4,665 lbs. in 1993 (DPR, 1993; 1994). Humans are exposed to parathion primarily during field application and in formulation of the insecticide. Dermal exposure is considered the most important during pesticide application; parathion and other organophosphates are well absorbed through the skin. The general public may be exposed to parathion by dermal and inhalation exposure from spray drift onto adjacent areas during application, parathion brought into the households of workers, and through dietary intake of residues.

References

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