NO SIGNIFICANT RISK LEVEL (NSRL) FOR THE PROPOSITION 65 CARCINOGEN CHLOROETHANE

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SUMMARY OF FINDINGS

The cancer potency of chloroethane was estimated from dose-response data of uterine tumors among female mice exposed by inhalation (NTP, 1989). The cancer potency estimate corresponds to the upper 95 percent confidence bound on the linear term of the multistage model fit to cancer dose-response data in experimental animals. The potency derivation takes into account body size differences between humans and experimental animals. The Proposition 65 "no significant risk level" (NSRL) is defined in regulation as the daily intake level posing a 10^{-5} lifetime risk of cancer. The cancer potency estimate and corresponding NSRL are given in Table 1.

Table 1. Cancer Potency and NSRL for Chloroethane

Chemical	Cancer Potency $(mg/kg\text{-}day)^{-1}$	NSRL (μg/day)
Chloroethane	0.0047	150

INTRODUCTION

This report describes the derivation of a cancer potency value and no significant risk level for chloroethane (CAS number 75-00-3, molecular weight 64.5). Chloroethane was listed on July 1, 1990 as a chemical known to the State to cause cancer under Proposition 65 (California Health and Safety Code 25249.5 *et seq*.). Chloroethane is used as an intermediate in the manufacture of pharmaceuticals, plastics, dyes, and tetraethyllead, as a solvent, as a topical anesthetic and chilling agent, as an industrial refrigerant, and as a blowing agent in the production of polystyrene foam (NTP, 1989; IARC, 1999). Chloroethane has been detected in ambient air (IARC, 1999), and in sources of drinking water (ATSDR, 1989).

This document discusses the studies available for cancer dose-response assessment, and summarizes the derivation of the cancer potency estimate and NSRL. A description of the methodology used is provided in the Appendix.

STUDIES SUITABLE FOR DOSE-RESPONSE ASSESSMENT

The carcinogenicity of chloroethane was investigated in a series of four studies, in which chloroethane was administered via inhalation to rats and mice of both sexes (NTP, 1989). No

other carcinogenicity studies of chloroethane were identified (IARC, 1999). Female mice were identified as the most sensitive sex and species for purposes of deriving the cancer potency.

Groups of 50 male and 50 female F344/N rats were dosed via inhalation with chloroethane six hours per day, five days per week at either zero or 15,000 ppm for 102 weeks (NTP, 1989). Among the male rats, increased incidences of the following skin tumors were observed in the treated group, as compared to none observed in the controls: trichoepithelioma (1/50), sebaceous gland adenomas (1/50) and basal cell carcinoma (3/50). The combined incidence of these morphologically similar skin tumors was statistically significant when compared to controls ($p=0.016$, logistic regression test). In female rats, three of fifty treated animals were observed with rare malignant astrocytomas of the brain as compared to 0/49 among controls ($p>0.05$).

Groups of 50 male and 50 female B6C3F_1 mice were dosed via inhalation with chloroethane six hours per day, five days per week at either zero or 15,000 ppm for 100 weeks (NTP, 1989). In treated male mice, an increased incidence of alveolar/bronchiolar adenomas and carcinomas (combined) was observed (10/48 compared to 5/50 among controls, $p=0.008$ by logistic regression test). However, the study in male mice was considered inadequate because of reduced survival in the exposed group (NTP, 1989). Among female mice, a highly significant increase in the incidence of uterine carcinomas of endometrial origin was observed in dosed female mice (see Table 2). A single uterine carcinoma was observed in the control group, but NTP concluded that this was not of endometrial origin and was morphologically distinct from uterine tumors observed in treated female mice. The majority of the treated female mice died as a result of the uterine carcinomas. NTP concluded there was clear evidence for carcinogenicity in the female mouse.

Table 2. Incidence of Uterine Endometrial Carcinoma in Female B6C3F$_1$ Mice Treated with Chloroethane by Inhalation (NTP, 1989)

Administered[1] Concentration (ppm)	Average Dose[2] (mg/kg-day)	Tumor Incidence[3]	Statistical significance[4]
0	0	0/46	--
15 000	8 486	43/49	$p < 0.001$

1 Chloroethane was administered 6 hours per day, 5 days per week, for 100 weeks.

2 Lifetime average dose is calculated as described in the Appendix.

3 Number of tumor-bearing animals/effective number of animals (effective number is the number of animals alive at week 67, the first occurrence of uterine tumors in either of the two groups). Note that NTP reports overall rates in their summary tables; the effective rates presented here were determined using the individual animal data for female mice reported in Appendix D of the NTP report.

4 Results of pairwise comparison using the Fisher Exact Test.

APPROACH TO DOSE-RESPONSE ANALYSIS

Chloroethane is mutagenic in bacteria (Araki *et al*., 1994; IARC, 1999) and genotoxic in Chinese hamster ovary cells (Ebert *et al*., 1994). Several reports suggest that absorption via inhalation and skin contact are significant in some occupational or therapeutic contexts (U.S. EPA, 1981; ATSDR, 1989). Morgan *et al*. (1970) reported that humans (number and body weights not presented) who inhaled [^{38}Cl]chloroethane (administered amount reported as "approximately 5 mg"), exhaled 30 percent of the administered dose in one hour. No information was located on the fractional absorption of chloroethane by mice. *In vitro* studies have shown that the genotoxic carcinogen acetaldehyde is formed as a result of oxidative cytochrome P450-dependent metabolism of chloroethane, while the formation of glutathione conjugates has been demonstrated in rats and mice *in vivo* (IARC, 1999).

The positive findings of genotoxicity, taken together with information on the metabolism of chloroethane, are strongly suggestive of a genotoxic mode of action. There is insufficient information on the precise mechanism of carcinogenicity to permit the development of a biologically based model for cancer potency estimation.. The absence of absorption data in rodents precludes the use of a pharmacokinetic correction for absorption between mice and humans, and there are insufficient data to support other pharmacokinetic adjustments. Therefore, the default approach (i.e., a linearized multistage model and interspecies scaling) has been applied. The approach is described in detail in the Appendix.

DOSE-RESPONSE ASSESSMENT

The female mouse was the most sensitive species/sex tested by the NTP in its carcinogenicity studies of chloroethane. A cancer potency estimate was derived for chloroethane based on administered dose, using the female mouse uterine carcinoma data summarized in Table 2 (NTP, 1989). A cancer potency estimate of 0.0047 $(\text{mg/kg-day})^{-1}$, which includes adjustments for the shortened study duration (100 versus 104 weeks) and rodent-human differences in body size, is obtained.

NO SIGNIFICANT RISK LEVEL

The NSRL for Proposition 65 is the intake associated with a lifetime cancer risk of 10^{-5}. The cancer potency estimate for female mouse uterine carcinomas was used to calculate the NSRL for chloroethane (150 μg/day).

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR, 1989). *Toxicological Profile for Chloroethane*. PB90-181264. U.S. Public Health Service in collaboration with the U.S. Environmental Protection Agency.

American Conference of Governmental Industrial Hygienists (ACGIH, 1986). *Documentation of the Threshold Limit Values and Biological Exposure Indices*. Fifth Edition. Federal ID No. 31-1142148, Cincinnati, Ohio.

Araki A, Noguchi T, Kato F, Matsushima T (1994). Improved method for mutagenicity testing of gaseous compounds by using a gas sampling bag. *Mutat Res* **307**:335-344.

Ebert R, Fedtke N, Certa H, Weigand H-J, Regnier J-F, Marshall R, Dean SW (1994). Genotoxicity studies with chloroethane. *Mutat Res* **322**:33-44.

Gold LS, Zeiger E (1997). *Handbook of Carcinogenic Potency and Genotoxicity Databases.* CRC Press, Inc., Boca Raton.

International Agency for Research on Cancer (IARC, 1999). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* Volume 71: 1345-1349. *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide.* IARC, Lyon France.

Morgan A, Black A, Belched DR (1970). The excretion in breath of some aliphatic halogenated hydrocarbons following administration by inhalation. *Ann Occup Hyg* **13**:219-233.

National Toxicology Program (NTP, 1989). *Toxicology and carcinogenesis studies of chloroethane (CAS No. 75-00-3) in F344/N rats and B6C3F$_1$ mice (inhalation studies).* Technical Report Series No. 346. NIH Publication No. 90-2801. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

Rao GN (Rao, 1990). Personal communication (letter) to Sara Hoover (Reproductive and Cancer Hazard Assessment Section, California Department of Health Services) conveying information from the files of the NTP, September 28.

U.S. Environmental Protection Agency (U.S. EPA, 1981*). Chemical Hazard Information Profile Draft Report. Chloroethane (CAS No. 75-00-3).* Office of Toxic Substances, U.S. EPA, Washington, D.C.

APPENDIX: DEFAULT METHODOLOGY USED TO DERIVE THE NSRL FOR CHLOROETHANE

Procedures for the development of Proposition 65 NSRLs are described in regulation (California Code of Regulations, Title 22, Sections 12701 and 12703). Consistent with these procedures, the specific methods used to derive the NSRL for chloroethane are outlined in this Appendix.

A.1 Cancer Potency as Derived from Animal Data

"Multistage" polynomial

For regulatory purposes, the lifetime probability of dying with a tumor (p) induced by an average daily dose (d) is often assumed to be (CDHS, 1985; U.S. EPA, 1987; Anderson *et al.*, 1983):

$$p(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \cdots + q_j d^j)] \qquad (1)$$

with constraints,

$$q_i \geq 0 \text{ for all i.}$$

The q_i are parameters of the model, which are taken to be constants and are estimated from the data. The parameter q_0 represents the background lifetime incidence of the tumor. The parameter q_1, or some upper bound, is often called the cancer potency, since for small doses it is the ratio of excess lifetime cancer risk to the average daily dose received. For the present discussion, cancer potency will be defined as q_1^*, the upper 95% confidence bound on q_1 (CDHS, 1985), estimated by maximum likelihood techniques. When dose is expressed in units of mg/kg-day, the parameters q_1 and q_1^* are given in units of $(\text{mg/kg-day})^{-1}$. Details of the estimation procedure are given in Crump (1981) and Crump *et al.* (1977). To estimate potency in animals (q_{animal}) from experiments of duration T_e, rather than the natural life span of the animals (T), it is assumed that the lifetime incidence of cancer increases with the third power of age:

$$q_{animal} = q_1^* \bullet (T/T_e)^3 \qquad (2)$$

Following Gold and Zeiger (1997) and the U.S. Environmental Protection Agency (U.S. EPA, 1988), the natural life span of mice and rats is assumed to be two years, so that for experiments lasting T_e weeks in these rodents:

$$q_{animal} = q_1^* \bullet (104/T_e)^3 \qquad (3)$$

To estimate risk at low doses, potency is multiplied by average daily dose. The risk estimate obtained is referred to by the U.S. EPA (Anderson *et al.*, 1983) as "extra risk", and is equivalent to that obtained by using the Abbott (1925) correction for background incidence.

Calculation of the lifetime average dose

The lifetime average dose in units of mg/kg-day was calculated for each of the relevant dose groups, based on the dose level, duration and regimen described in the experiments above. In this case, an average body weight of 0.036 kg for the female $B6C3F_1$ mice in the NTP chloroethane studies was obtained directly from NTP (Rao, 1990). The default inhalation rate for female mice of 0.03 L/min cited by Gold and Zeiger (1997) was also used in the calculation. Briefly, the air concentration of chloroethane in units of ppm was converted to units of mg/m^3 by multiplying by 2.64 (mg/m^3)/ppm (the conversion factor for chloroethane). This number was multiplied by the inhalation rate for mice (0.03 L/min =0.0432 m^3/day) (Gold and Zeiger, 1997), divided by an average body weight for female $B6C3F_1$ mice of 0.036 kg (Rao, 1990), multiplied by 6/24 to account for the 6 hour per day exposure, and then multiplied by 5/7 to account for the 5 day per week exposure, to obtain the lifetime average daily dose in units of mg/kg-day.

A.2 Interspecies Scaling

Once a potency value is estimated in animals following the techniques described above, human potency is estimated. As described in the California risk assessment guidelines (CDHS, 1985), a dose in units of milligram per unit surface area is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Under this assumption, scaling to the estimated human potency (q_{human}) can be achieved by multiplying the animal potency (q_{animal}) by the ratio of human to animal body weights (bw_h/bw_a) raised to the one-third power when animal potency is expressed in units $(mg/kg\text{-}day)^{-1}$:

$$q_{human} = q_{animal} \bullet (bw_h / bw_a)^{1/3} \qquad (4)$$

A.3 Risk-Specific Intake Level Calculation

The intake level (I, in mg/day) associated with a cancer risk R, from exposure is:

$$I = \frac{R \bullet bw_h}{q_{human}} \qquad (5)$$

where bw_h is the body weight, and q_{human} the theoretical cancer potency estimate for humans.

Daily intake levels associated with lifetime cancer risks above 10^{-5} exceed the no significant risk level for cancer under Proposition 65 (Title 22 California Code of Regulations, Section 12703). Thus for a 70 kg person, the NSRL is given by:

$$NSRL = \frac{10^{-5} \bullet 70kg}{q_{human}} \qquad (6)$$

APPENDIX REFERENCES

Abbott WS (1925). A method of computing the effectiveness of an insecticide. *J Econ Entomol* **18**:265-267.

Anderson EL and the U.S. Environmental Protection Agency Carcinogen Assessment Group (1983). Quantitative approaches in use to assess cancer risk. *Risk Analysis* **3**:277-295.

California Department of Health Services (CDHS, 1985). Guidelines for Chemical Carcinogen Risk Assessment and Their Scientific Rationale. California Department of Health Services, Health and Welfare Agency, Sacramento, CA.

Crump KS (1981). An improved procedure for low-dose carcinogenic risk assessment from animal data. *J Environ Path Toxicol* **52**:675-684.

Crump KS, Guess HA, Deal LL (1977). Confidence intervals and test of hypotheses concerning dose-response relations inferred from animal carcinogenicity data. *Biometrics* **33**:437-451.

Gold LS, Zeiger E (1997). *Handbook of Carcinogenic Potency and Genotoxicity Databases.* CRC Press, Inc., Boca Raton.

Rao GN (Rao, 1990). Personal communication (letter) to Sara Hoover (Reproductive and Cancer Hazard Assessment Section, California Department of Health Services) conveying information from the files of the NTP, September 28.

U.S. Environmental Protection Agency (U.S. EPA, 1987). The Risk Assessment Guidelines of 1986. Office of Health and Environmental Assessment, Washington D.C. EPA/600/8-87/045.

U.S. Environmental Protection Agency (U.S. EPA, 1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Health and Environmental Assessment, Washington D.C. EPA/600/6-87/008.