New Jersey Drinking Water Quality Institute

Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water

September 26, 1994

Appendix A

Health-Based Maximum Contaminant Level Support Documents and Addenda

SUBMITTED TO:

State of New Jersey
Department of Environmental Protection

APPENDIX A

HEALTH-BASED MAXIMUM CONTAMINANT LEVEL (MCL)

SUPPORT DOCUMENTS AND ADDENDA

RECOMMENDATION FOR HEALTH-BASED MCL FOR CHLOROBENZENE

Background

The current New Jersey Health-based MCL for chlorobenzene is 4.5 ug/L (NJDWQI, 1987). The risk assessment is based on the No Adverse Effect Level (NOAEL) for effects observed in a subchronic study in dogs (Monsanto, 1977). Chlorobenzene was classified as a Group C carcinogen (possible human carcinogen) because of an increased incidence of liver nodules observed in male rats in a chronic bioassay (NTP, 1985), and an additional uncertainty factor of 10 was applied to the NOAEL from the Monsanto study because of the classification as Group C. At the time the New Jersey risk assessment was developed, USEPA (1985) had also classified chlorobenzene as a Group C carcinogen in proposed drinking water regulations. Additionally, an uncertainty factor of 3 was applied by New Jersey because of the small number of dogs utilized in the Monsanto study (4 dogs per sex per dose level).

Subsequent to the adoption of the New Jersey A-280 standards, USEPA revised its carcinogenicity classification for chlorobenzene to Group D (no evidence for carcinogenicity) (USEPA, 1989). This was based on close reexamination of the data on neoplastic liver nodules and carcinomas in the male rats in the NTP study.

The final USEPA MCLG of 100 ug/L (rounded from 139 ug/L) for chlorobenzene is based on the same study and NOAEL as is the New Jersey Health-based MCL (USEPA, 1991) of 4.5 ug/L. The 30 fold difference results from the application of the additional uncertainty factors of 10 and 3 by New Jersey (discussed above) which were not utilized by USEPA.

Evaluation

The Lists and Levels Subcommittee evaluated the basis for the application of the two uncertainty factors discussed above during its April and July 1992 meetings.

Regarding the additional uncertainty factor of 3 because of small number of experimental animals, in a subchronic study involving dogs it is desirable that 6-8 animals be used per sex per dose group (Mosberg and Hayes, 1989) while in the Monsanto study, 4 dogs were used. Additionally, not more than 10% of high dose animals should die during the study (Mosberg and Hayes, 1989), while in the Monsanto study 50% of the high dose animals died. After considering this information, the Lists and Levels Subcommittee decided that the additional uncertainty factor of 3 remains warranted, and recommended keeping it in place in the New Jersey Health-based MCL.

Regarding the carcinogenicity classification of chlorobenzene, the Lists and Levels Subcommittee considered the data from the NTP study, as well as general USEPA recommendations for risk assessment of rat liver lesions (1986). The classification as Group C was

based on the increased incidence of neoplastic nodules in male rats in the NTP study (1985). (An increased occurrence of neoplastic liver nodules or malignant liver tumors did not occur in female rats, male mice, or female mice.) The general USEPA guidance for rat liver lesions (USEPA, 1986) states that if the incidence of neoplastic liver nodules, but not the incidence of liver carcinomas, is increased significantly, the chemical should be classified as Group C.

Examination of the specific data on liver lesions in male rats from the NTP chlorobenzene study suggests a lack of biological significance of the observed increase in the incidence of neoplastic nodules, for several reasons. The incidence of neoplastic nodules was increased above the control group at the $p<0.05$ level only in the high dose group. Liver carcinomas occurred only in the control group; none occurred in either treated group. Finally, the combined incidence of neoplastic nodules and carcinomas was not statistically significant. This information was considered by the USEPA Science Advisory Board Halogenated Organics Subcommittee in making a recommendation that chlorobenzene be classified as Group D (USEPA, 1986). The Lists and Levels Subcommittee concluded that the data on liver lesions in male rats did not warrant classification in Group C, and recommended that the contaminant be reclassified as Group D. This involves removing the uncertainty factor of 10 used to account for possible carcinogenicity in the current Health-based MCL.

Recommendations

The Lists and Levels Subcommittee recommends that the current Health-based MCL for chlorobenzene of 4.5 ug/L be increased by a factor of 10. Application of the policy for rounding to one significant figure results in a Health-based MCL of 50 ug/L.

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ADDENDUM TO DICHLOROBENZENE SUPPORT DOCUMENT
March 1, 1988

Since the release of the New Jersey Drinking Water Quality Institute Support Document for Dichlorobenzenes in January, 1987, several new developments have occurred which influence the carcinogenic classification of p-dichlorobenzene (p-DCB). The original carcinogenic classification of p-DCB was B2, probable human carcinogen, based on the significant incidence of rat kidney tumors and mouse liver tumors. It is nesessary in order to be classified as a probable human carcinogen, that at least two significant instances of increased tumor rate occur in different species, strains and experiments (U.S.EPA, 1987). A significant factor for the weight of evidence criteria has been the dose related increase in male rat kidney tumors. Research performed by Swenberg and coworkers (Short et al. 1986, Short et al. 1987, Swenberg 1987) and Alden et al. (1987) has made a significant contribution in establishing the mechanism of p-DCB induced kidney tumors. The histopathology of p-DCB induced kidney tumors has a characteristic profile which has been observed with several other compounds notably decalin, linolene and 3-methyl pentane. These compounds appear to induce the accumulation in the kidney of a protein known as alpha-2-microglobulin, produced under the influence of androgens in several mammalian species including human. Unlike other species, the male rat has difficulty in excreting this protein, which is exacerbated further in the presence of these tumorigenic compounds. The globulin produces degeneration of the epithelial cells in the proximal convoluted tubules, dilation and regeneration of the tubules. Increased tubular proliferation is associated with the further development of kidney adenomas and carcinomas, which are observed under prolonged administration of these nephrotoxicants.

Since the development of these kidney tumors appear only in male rats, with a mechanism which favors tumorigenesis in male rats, the significance to possible human carcinogenesis is questionable. Therefore, the incidence of male rat kidney tumors associated with p-DCB exposure cannot contribute to the weight of evidence of p-DCB carcinogenicity. The increased liver tumors seen in male and female mice is controversial and it has been looked upon as only limited evidence of carcinogenicity (U.S.EPA, 1987). There is no evidence that p-DCB is genotoxic. Therefore, U.S.EPA (1987) has elected to classify p-DCB as a group C, limited evidence for carcinogenicity.

If p-DCB is considered to be a possible carcinogen, the risk assessment should be approached by either defining a no-observed-adverse-effect-level (NOAEL) or if this is not possible, selecting the lowest-observed-adverse-effect-level (LOAEL) from a chronic study. A LOAEL can be noted from the NTP(1987) study which shows an increase in hepatocellular degeneration, necrosis and cell size alteration in male and female B63F1 mice exposed to

300mg/kg p-DCB for two years. The computation would be:

$$ADI = \frac{300mg/kg \times 5/7 \text{ days/week}}{100x \times 10 \times 10} =$$

$$ADI = 0.021429 \text{ mg/kg}$$

$$MCL = \frac{0.021429mg/kg * 70kg * 0.2}{2L}$$

$$MCL = 0.15 \text{ mg/L} = 150 \text{ ug/L}$$

where:

300mg/kg	=	LOAEL
5/7	=	days of exposure per week
100	=	uncertainty factor appropriate for NOAEL from a chronic animal study
10	=	factor for conversion of a LOAEL level to a NOAEL
10	=	factor to protect against possible carcinogenicity
0.2	=	source contribution factor
70kg	=	assumed weight of an adult human
2L	=	assumed volume of water consumed by an adult human per day

In conclusion, there is justification to reclassify p-DCB as a category II compound on the basis of evidence for possible carcinogenicity. As a result, the MCL is 150 ug/L based on liver toxicity in mice.

The U.S.EPA has promulgated an MCL of 75ug/L for p-DCB. The MCL is based on a NOAEL of 150 mg/kg dose derived from the subchronic rat study conducted by the National Toxicology Program (NTP,1987), and was the basis of the Longer-term and Lifetime Health Advisory (U.S. EPA, 1985, Anderson, 1988). In the Health Advisory it was stated that, the NOAEL of 150 mg/kg/day was selected because renal lesions were observed in male rats at higher doses. These renal lesions consisted of kidney cortical tubular degeneration which is known to result from accumulation of alpha-2-microglobulin.

The risk assessment presented here differs from the one presented in the U.S. EPA Health Advisory because, as discussed above, it was felt that renal toxicity resulting from alpha-2-microglobulin is not a relevant endpoint for human risk assessment.

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ADDENDUM TO CIS-1,2-DICHLOROETHYLENE HEALTH-BASED MAXIMUM CONTAMINANT LEVEL

The current New Jersey Health-based MCL for this chemical is 10 ug/L, based on information on the trans- isomer, since no relevant information on the cis- isomer was available. USEPA (Federal Register, 1/13/91) has finalized its MCLG and MCL for cis-1,2-dichloroethylene at 70 ug/L, based on a subchronic oral study in rats by McCauley et. al. (unpublished). The endpoint of concern is decreased hematocrit and hemoglobin. The NOAEL in this study was 32 mg/kg/day, and an uncertainty factor of 3000 was applied to arrive at an RfD of 0.01 mg/kg/day. The MCLG derived from this RfD, using a 20% Source Contribution Factor, is 70 ug/L (Charles Abernathy, USEPA Office of Water, personal communication). The Lists and Levels Subcommittee has reviewed this study and the risk assessment used to derive the MCLG. The Subcommittee feels that this risk assessment is protective of public health, and recommends adoption of the Health-based MCL of 70 ug/L.

CIS- and TRANS-1,2-DICHLOROETHYLENE
Review of proposed U.S. EPA MCLG

Prepared by Lubow Jowa and Gloria Post
September 21, 1990

Updated by Gloria Post
August 12, 1992

Proposed U.S. EPA MCL

The final USEPA MCLG (and MCL) for trans-1,2-dichloroethylene is 100 ug/L (Federal Register, January 30, 1991).

The basis for this MCLG is a study conducted by Barnes et al. (1985) in which CD-1 mice were given trans-1,2-dichloroethylene for 90 days in their drinking water at levels of 17, 175, or 387 for males and 23, 224, 452 mg/kg/day for females.

In male mice significant increases in serum alkaline phosphatase were observed at the two highest doses, while in female mice the thymus weight, calculated as % body weight, was decreased at the two highest doses. No changes in fluid consumption or body weight gain were observed. A NOAEL of 17 mg/kg/day in male mice was identified based on normal serum chemistry, and used to derive the MCLG of 100 ug/L.

The final USEPA MCLG (and MCL) for cis-1,2-dichloroethylene is 70 ug/L. This MCLG is based on a 3-month study on cis-1,2-dichloroethylene by McCauley et. al. which is unpublished. A recommendation will be made on the Health-based MCL for cis-1,2-dichlroethylene after this study is obtained and reviewed. The MCLG which was previously proposed by USEPA (May 22, 1989) for this contaminant was also 70 ug/L, but it was based on information on the isomer 1,1-dichloroethylene, since relevant toxicity information on the cis- isomer was not available.

N.J. MCL

The N.J. MCL and Health-based MCL is currently 10 ug/L for both cis- and trans-1,2,-dichloroethylene.

New Jersey's MCL is based on the toxicity of the isomer 1,1-dichloroethylene, since inadequate toxicity information existed regarding trans-1,2-dichloroethylene and cis-1,2-dichloroethylene during the preparation of the Health-based MCL document. The Barnes et al. (1985) study was not available to the preparer at that time.

Discussion

Since the time of the preparation of the N.J. Health-based MCL, two studies on the effects of trans-1,2-dichloroethylene administered through drinking water to rodents were published. Besides the Barnes (1985) study cited above, Hayes et al. (1987) administered trans-1,2-dichloroethylene to the drinking water of Charles River rats. The doses of 402, 1314 or 3114 mg/kg/day were given to males and 353, 1257 or 2809 mg/kg/day to females. The authors reported no compound-related effects on water consumption, terminal body weights, hematology, serum chemistry, urinalysis or histopathology. However, significant dose-dependent increases in kidney weights and kidney weight ratios at the 1257 and 2809 mg/kg/day doses were observed in the female rats.

From the two published studies described above, it appears that the effects of trans-1,2-dichloroethylene administered by drinking water are less severe than those seen with 1,1-dichloroethylene. Also, with the existence of these two apparently well conducted studies, there is no longer the need to develop a risk assessment for trans-1,2-dichloroethylene on the basis of the toxicity of an isomer.

Recommendation

It appears that the U.S. EPA risk assessment approach to develop the proposed MCL for trans-1,2-dichloroethylene was reasonable and appropriate. It is recommended that New Jersey revise its Health-based MCL and MCL to 100 ug/L to reflect the current knowledge on this chemical's toxicity.

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Basis for Proposed Revision of Formaldehyde Health-based MCL

Gloria Post, May 12, 1993

At the time that the Health-based Support Document for formaldehyde was developed, no chronic oral studies on formaldehyde had been conducted. Therefore, the risk assessment was based on an inhalation study. Formaldehyde was classified in Group B2, probable human carcinogen, and a potency factor based on nasal tumors was derived. It is always desirable to avoid extrapolating between different exposure routes, in the case of formaldehyde this is especially important because the only tumors attributable to formaldehyde in the inhalation study were nasal. Since this is the point of contact for inhalation, the justification for extrapolation to oral exposure is not strong.

Chronic oral studies on formaldehyde have since been conducted. Both USEPA and New Jersey DEPE have developed Reference Doses based on the NOAEL in the chronic rat bioassay reported by Til et. al. (1988). New Jersey has proposed classification of formaldehyde by the oral route in Group C, based on carcinogenicity by inhalation, reported tumor promoting effects by oral exposure (Takahashi et al., 1986), and results of a chronic study by Maltoni et al. (1989). A Reference Dose of 0.015 mg/kg/day by has been developed, and the resulting Health-based MCL is 105 ug/L. The basis for this proposed Health-based MCL is discussed in more detail in the attached Addendum. USEPA classified formaldehyde as Group D, and their Reference Dose is therefore 10 times higher, 0.15 mg/kg/day, with the Health Advisory of 1000 ug/L.

Because the Addendum was written in 1988, the basis for the revision to the MCLG given in the Addendum was reviewed as part of the Triennial Review process. No information was located which indicates that the MCLG derived in the Addendum should be revised.

ADDENDUM TO FORMALDEHYDE HEALTH-BASED MAXIMUM CONTAMINANT LEVEL SUPPORT DOCUMENT
Prepared by Gloria Post
August 8, 1988

Introduction

Since the Health-based Maximum Contaminant Level Support Document for formaldehyde was finalized in March, 1987, new data regarding the oral toxicity of formaldehyde has become available. This new information has significantly improved our ability to conduct a risk assessment for exposure to formaldehyde via drinking water. This document summarizes the newly available data and proposes a modification of the health-based maximum contaminant level for formaldehyde.

At the time that the Support Document was written, no chronic oral bioassays of formaldehyde had been reported, and the risk assessment was based on results of inhalation bioassays. It is always desirable avoid extrapolating between routes of exposure; in the case of formaldehyde, this is especially important because the only tumors attributed to formaldehyde exposure during the inhalation study were nasal. Since these tumors occurred at the point of contact, the justification for basing a drinking water risk assessment on them is not strong.

Summary of Recent Oral Studies

Takahashi et al.(1986) conducted a two stage stomach carcinogenesis assay in rats utilizing N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) as the initiator and testing formaldehyde (formalin) and three other compounds as promoters. Male Wistar rats were given MNNG alone (30 per group), formalin alone (10 per group), neither (10 per group), or both (17 per group). MNNG was given at 100 mg/l in the drinking water, in conjunction with a 10% NaCl diet, for the first 8 weeks of the study. Formaldehyde was given as 0.5% formalin in the drinking water during weeks 8 through 40. Surviving animals were sacrifice and autopsied at the end of week 40, and the stomachs of the rats were examined grossly and microscopically. The actual doses of formaldehyde received by the animals is not known, since drinking water consumption was not determined.

No stomach pathology was observed in the untreated group. Forestomach papillomas occurred in 8/10 (80%) animals rats given formaldehyde alone. In rats given MNNG alone, adenocarcinoma of the pylorus occurred in 1/30 (3%), preneoplastic hyperplasia of the pylorus occurred in 7/30 (23%), and adenocarcinoma of the duodenum occurred in 3/30 (10%). In the group given both MNNG and formaldehyde, forestomach papillomas occurred in 15/17 (88%), adenocarcinoma of the pylorus in 4/17 (23%), preneoplastic hyperplasia of the pylorus in 7/17 (41%), and adenocarcinoma of the duodenum in 1/17 (5.9%). MNNG did not significantly increase the incidence of forestomach papilloma caused by formaldehyde.

The increase in the incidence of pyloric adenocarcinoma in the formaldehyde plus MNNG group was significantly higher than in the MNNG only group ($p < 0.05$).

Til et al. (1988) conducted a two year chronic oral bioassay of formaldehyde in rats. Wistar rats (70 per sex per group) were exposed to formaldehyde in their drinking water at intended doses of 0, 5, 25, and 125 mg/kg/day for up to two years. The dose levels were selected on the basis of results of a 13-week oral study in rats (Johannsen et al., 1986). The actual dose levels, calculated from drinking water consumption data, were 0, 1.2, 15, and 82 mg/kg/day in males, and 0, 1.8, 21, and 109 mg/kg/day in females. Animals (10 per group) were sacrificed at 53 and 79 weeks, and the remaining rats were sacrificed at 105 weeks. Parameters evaluated were general appearance, body weight gain, food consumption and water consumption, ophthalmological observations, hematology, clinical chemistry, and complete gross and microscopic pathology. The study has been submitted for publication in Food and Chemical Toxicology (J.J. Clary, personal communication).

No adverse effects were observed in the low dose and mid dose groups. In the high dose group, decreased body weights were observed in males and females and kidney weight was significantly increased in females. Pathological changes of the stomach occurred in the high dose group. These included an increased in incidence of a raised and thickened limiting ridge of the forestomach, surface lesions of the forestomach and/or glandular stomach, papillary epithelial hyperplasia, hyperkeratosis, and focal ulceration of the forestomach, and chronic atrophic gastritis, ulceration, and glandular hyperplasia of the glandular stomach. Additionally, the incidence and degree of renal papillary necrosis was increased in the high dose animals. No treatment related tumors were observed.

Appropriateness of Recent Oral Studies for Risk Assessment

As discussed above, it is not desirable to base the risk assessment for formaldehyde in drinking water on chronic inhalation data. Two oral studies have recently been reported which provide information not available at the time the Formaldehyde Support Document was written, and these studies were evaluated to determine their appropriateness for serving as the basis for the health-based drinking water standard.

The study of Takahashi et al. contains several deficiencies which limit its suitability for using it as the basis for risk assessment. The formalin used as the treatment material contained 15% methanol in addition to 37% formaldehyde (Clary, 1987). The dose of formaldehyde to the rats, as discussed above, is not known. The number of animals per treatment group is very small and only one sex was used. The rats were treated with formaldehyde for only 32 weeks. Only the organs of the peritoneal cavity were included in the pathological examination.

It was decided to categorize formaldehyde in Group C, possible human carcinogen (see NJDWQI, 1987). Risk assessments for Group C compounds are based on a non-carcinogenic endpoint and additional uncertainty factor of 10 is used to account for possible carcinogenicity. Although neither of the studies suggests that oral exposure to formaldehyde causes cancer, the additional uncertainty factor is recommended for the following reasons: inhalation of formaldehyde causes nasal malignancies in rats and mice; formaldehyde significantly increased the incidence of malignancies when given as a promoter in conjunction with the initiator, MNNG; evidence exists suggesting that formaldehyde exposure may cause benign tumors of a type which do not have the potential to progress to malignancy.

Calculation of health-based MCL:

NOAEL from Til et al.: 15 mg/kg in males, 21 mg/kg in females. Select 15 mg/kg for conservatism.

$$\text{Acceptable Daily Intake (ADI)} = \frac{15 \text{ mg/kg/day}}{100 \times 10} = 0.015 \text{ mg/kg/day}$$

where:

15 mg/kg/day = NOAEL

100 = uncertainty factor appropriate for use with a NOAEL from a chronic animal study

10 = additional uncertainty factor used for possible human carcinogens

$$\text{MCL} = \frac{(0.015 \text{ mg/kg/day})\ (0.2)\ (70 \text{ kg})}{2 \text{ L/day}} = 0.105 \text{ mg/L} = 105 \text{ ug/L}$$

where:

0.015 mg/kg/day = ADI

70 kg = assumed weight of human adult

0.2 = contribution from drinking water alone

2 L/day = assumed daily drinking water consumption

Conclusion

Based on the results of recent oral studies of formaldehyde toxicity in rats, a revision of the health-based MCL is recommended. A health-based MCL of 110 ug/L is proposed (using 2 significant figures, as consistent with the other health-based MCLs).

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ADDENDUM TO XYLENE HEALTH-BASED MCL SUPPORT DOCUMENT

SUMMARY

The Xylene Health-based MCL Support Document originally adopted by the Drinking Water Quality Institute recommends a health-based MCL of 44 ug/L. This is based on an inhalation NOAEL of 0.73 mg/kg/day in a study of developmental effects in rats, primarily cleft palate, with an uncertainty of 100 for intraspecies and interspecies variation.

In this addendum it is recommended that the original MCL be replaced with an MCL based on increased minimal chronic nephropathy in adult rats (Condie et al., 1988). This effect is evident with the 150 mg/kg/day oral gavage dose of the mixed xylene isomers in female rats. Since this is probably a LOAEL, the proposed MCL is 1.0 mg/L. The rationale is given below.

BACKGROUND

Since the adoption of the original Support Document, other studies (Ungvary and Tatrai, 1985; Hass and Jakobsen, 1987) have been completed, which either found no developmental effects or found effects after exposure to much higher concentrations than reported by Mirkova et al. (1983). In addition, two other studies (Nawrot and Staples, 1980; Marks et al., 1982) that were thought to have observed developmental effects at oral doses in the same range of total exposure as Mirkova et al. were found to contain errors in the Results section, reporting effects at doses of milligrams instead of grams per kilogram animal weight (T. Marks, pers. comm.).

The Mirkova et al. study tested a sufficient number of rats, monitored xylene air concentration daily and tested neonatal biochemical parameters. Rates and statistics were presented for analyses of pre- and postimplantation losses, fetal weight and percent with hemorrhages. There was a moderate, statistically significant degree of fetotoxicity at the highest (500 mg/cu. m.) dose, in contrast to other studies. However, it is not clear what isomers and other contaminants constituted their "industrial" (but phonetically read as "technical") xylene mixture. It reported the relative rates of cleft palate incidence (up to 2.4 times more in the 500 mg/cu. m. group), but not the percentage of animals with cleft palate in each exposure group or a statistical analysis. There was no data on the elevated rates of hydrocephalus, microphthalmia, and reduced or absent ossification of the bones of the skull. While the mean levels of fetal (? -- see below) lung enzyme activities were presented in a figure and statistics were given, there was no information on the standard deviation of the results. No data were presented for liver, brain and heart enzyme activity, even though elevated activities were mentioned. The Methods section said that organ enzyme activities were tested on the 21st day of gestation, 1 month and 3 months postnatally, but went unreported except for lung "21 days after birth" (or after conception?). Similarly, the organ enzyme activities, cited from an earlier publication in Bulgarian, as evidence of the maternal toxicity of xylenes, were not analyzed statistically (Mirkova et al., 1982).

It must be noted that the Mirkova et al. study was the only one that began exposures from the day of conception to the day prior to birth (vs the middle of the three gestational weeks), as well as dosing during 5 out of the 7 days

of the week. Thus, the study may not be strictly comparable. Nevertheless, since the Mirkova et al. study was deficient in the description of certain experimental parameters and findings, lack of corroborative evidence of effects at lower concentrations served to undermine confidence in the study originally used to set the standard. Of the other studies, the oral gavage study by Marks et al. (1982) observed a NOAEL of 1000 mg/kg/d in mice, while the inhalation study by Ungvary et al. (1985) observed a NOAEL of 500 mg/kg/d in rats (assuming a pulmonary absorption factor of 0.64 (USEPA, 1985)). With an uncertainty factor of 100 (when using a teratogenicity study), these results yield a health-based maximum contaminant levels of 64 mg/L and 32 mg/L, respectively.

It is recommended that minimal chronic nephropathy in female rats be the basis of the oral LOAEL of 150 mg/kg/day (Condie et al., 1988). The histopathology was characterized by scattered areas of tubular dilatation and atrophy with occasional signs of regeneration. Though no statistics were presented, there was a clear dose-response relationship: 1/10 among the controls, and 3/10, 6/10, and 7/10 in the low, medium, and high dose groups, respectively. In addition, there were statistically significant changes in liver weight in the lowest dose group of males exposed to mixed xylenes (150 mg/kg/day) and the lowest dose group of females exposed to para-xylene (250 mg/kg/day). Both sexes displayed statistically significant gains in liver weight in the all of the intermediate dose groups exposed to pure isomers (1000 mg/kg/day) or mixed xylenes (750 mg/kg/day).

While the NTP (1986) study of chronic exposure to mixed xylenes, which was the basis for the USEPA MCL, did not find evidence of increased minimal chronic nephropathy, it is possible that the small number examined after 13 weeks and the advanced age of the rats and mice examined after 2 years obscured the presence of an effect that may be more obvious when conducting a complete study with younger, healthier animals. Since the results of a subchronic study are being used in parallel with the results of a well conducted chronic study, only safety factors for the use of a LOAEL (10), interspecies variation (10), and intraspecies variation (10) need be used.

Thus, the evidence indicates that 150 mg/kg/day is a reasonable LOAEL and that 0.15 mg/kg/day is a reasonable RfD. The proposed MCL is 1.0 mg/L.

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1,1-DICHLOROETHANE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Division of Science and Research

New Jersey Department of Environmental Protection

Prepared by Gloria B. Post
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Approved by Lists and Levels Subcommittee, May 15, 1989.

EXECUTIVE SUMMARY

1,1-Dichloroethane is a chlorinated aliphatic hydrocarbon which has been detected in drinking water supplies. This compound is one of the less toxic of the chlorinated aliphatics. Exposure of cats to 1,1-dichloroethane by inhalation was found to produce kidney damage. A Maximum Contaminant Level (MCL) of 46 ug/L was derived to protect against renal damage.

BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties

Chemical Name:	1,1-Dichloroethane
Synonyms:	1,1-dichlorethane, chlorinated hydrochloric ether, ethylidene chloride, ethylidene dichloride
CAS Number:	75-34-3
Chemical Formula:	$C_2H_4Cl_2$
Chemical Structure:	HCl_2C-CH_3
Molecular Weight:	98.96
Physical State:	Colorless liquid
Melting Point:	-96.98 °C
Boiling Point:	57.3 °C
Vapor Pressure:	182 mm Hg at 20 °C
Specific Gravity:	1.175 at 20 °C
Water Solubility:	5500 mg/L at 20 °C
Log Octanol/Water Partition Coefficient:	1.79
Odor Threshold (air):	120 ppm (Verscheuren, 1983) 200 ppm (Verscheuren, 1983)
Odor Threshold (water):	Information not located
Conversion Factor:	1 ppm = 4.05 mg/m^3

Production and Use

1,1-Dichloroethane has been used as a chemical intermediate and as a solvent for extraction and degreasing (NCI, 1978). In contrast to 1,2-dichloroethane, which is one of the most widely produced hydrocarbons, 1,1-dichloroethane is used in relatively small quantities. In 1979, there was no known U.S. production of this compound (Infante and Tsongas, 1982). The number of workers exposed to 1,1-dichloroethane, in a study conducted by NIOSH in 1972-74, was 4,600, while for 1,2-dichloroethane, 2,900,000 workers were estimated to be exposed (Parker et al., 1979).

Guidelines, Regulations, and Standards

The Time Weighted Average concentration recommended by the Occupational Safety and Health Administration is 100 ppm. The Time Weighted Average and the Short Term Exposure Limit concentrations recommended by the American Conference of Government and Industrial Hygienists are 200 ppm and 250 ppm, respectively (Toxnet, 1988). The Office of Drinking Water, USEPA, has not yet released its Health Advisory for 1,1-dichloroethane.

ENVIRONMENTAL EXPOSURE

Fate and Transport

Evaporation is expected to be the predominant loss mechanism from the soil surface and from water. Biodegradation is not expected in subsurface soil; therefore, 1,1-dichloroethane is expected to persist in subsurface soil and to enter groundwater by leaching (USEPA, 1984).

Ambient Levels

1,1-Dichloroethane was detected in raw and finished water samples from 4 of 25 of the largest New Jersey water purveyors by the NJDEP Bureau of Safe Drinking Water in 1978 through 1984. The compound was detected a total of 29 times in this sampling, which was conducted primarily in purveyors using surface water sources in response to consumer complaints of suspected contamination. The mean value detected was 4.8 ug/L. In a study of potable water in New Jersey, 1,1-dichloroethane was detected in 5 of 495 samples (Kreitzman, 1986). In the U.S. EPA Groundwater Supply Survey, it was detected in 3.9% of random samples; the maximum value was 3.2 ug/L (Westrick et al., 1984).

METABOLISM AND PHARMACOKINETICS

Absorption

Available information indicates that 1,1-dichloroethane is well absorbed after oral administration. In a metabolic disposition study conducted by Mitoma et al. (1985), an oral dose of ^{14}C labelled 1,1-dichloroethane in corn oil was given to B6C3F1 mice and Osborne-Mendel rats following dosing 5 days per week for 4 weeks with non-labelled 1,1-dichloroethane. The doses given were 700 mg/kg to rats and 1800 mg/kg to mice. Within 48 hours, the percentages of the labelled dose excreted in expired air were 86% in rats and 70% in mice. Most of the remainder was accounted for as CO_2 and in the carcass, with only 1%, in both mice and rats, excreted in urine and feces. The amount, if any, of unmetabolized 1,1-dichloroethane in the feces was not reported. Total recovery was 93% in rats and above 99% in mice.

Distribution

Little information is available on the distribution of 1,1-dichloroethane.

Metabolism

In the study of Mitoma et al. (1985), after 48 hours, the percentages of the dose converted to CO_2 were 5% in rats and 25% in mice. The percentages excreted in urine and feces, and assumed to be metabolized, were 0.9% in rats and 1.6% in mice. The percentages remaining in the carcass, and assumed to be metabolized, were 1.4% in rats and 2.4% in mice. The total percentages of the dose assumed to be metabolized were 7.4% in rats and 29% in mice.

In *in vitro* studies, 1,1-dichloroethane is a substrate for hepatic microsomal cytochrome P-450, and its metabolism is induced by phenobarbital but not beta-naphthoflavone (VanDyke and Wineman, 1971; Salmon et al., 1981; McCall et al., 1983). Both oxidation and dechlorination reactions take place, and metabolites are acetic acid, 2,2-dichloroethanol, and probably mono- and dichloracetic acid (McCall et al., 1983). The rate of microsomal dechlorination of 1,1-dichloroethane was found to be 10 to 25 time greater than the rate for the more toxic isomer, 1,2-dichloroethane (VanDyke and Wineman, 1971; McCall et al., 1983).

Excretion

As discussed above, most of an orally administered dose of 1,1-dichloroethane is excreted in exhaled breath, with much smaller amounts excreted as exhaled CO_2 and as metabolites in urine and feces. In the study conducted by Mitoma et al. (1985) described above, the percentages remaining in the carcass after 48 hours were 1.4% in rats and 2.4% in mice.

Human Exposure and Body Burden

Little information is available on human exposure to 1,1-dichloroethane. Potential exposure routes are ingestion of contaminated water, inhalation of contaminated ambient air, and occupational exposure in an industrial setting.

HEALTH EFFECTS

Overview

1,1-Dichloroethane is among the least toxic of the chlorinated aliphatic hydrocarbons, and is much less toxic than its isomer,

1,2-dichloroethane. Subchronic exposure to 1,1-dichloroethane caused kidney damage in cats, but not in rats, rabbits, guinea pigs or dogs. Available chronic bioassay data provides no conclusive evidence for carcinogenicity of 1,1-dichloroethane.

Human

No reports of toxicity occurring occupationally were located. 1,1-Dichloroethane was previously used as an anaesthetic, but was found to cause cardiac arrhythmias at high concentrations. It is likely that exposure to high concentrations would also cause CNS depression and respiratory tract and skin irritation, as do other chlorinated aliphatics (USEPA, 1984). No information on chronic human toxicity was located.

Animal

Acute

The oral LD_{50} value in rats reported in the literature is 725 mg/kg (Clayton and Clayton, 1982). However, the validity of this value is in doubt, since the dose used in the 78 week chronic bioassay in rats was higher than this (National Cancer Institute, 1978).

Chronic/Subchronic

Only limited information is available regarding subchronic effects of orally administered 1,1-dichloroethane. The National Cancer Institute (1978) conducted a subchronic study in order to establish the maximum tolerated dose for the chronic bioassay. 1,1-Dichloroethane in corn oil was given to groups of 5 male and 5 female Osborne-Mendel rats and B6C3F1 mice 5 days per week for 6 weeks, followed by a two week observation period. The doses given to rats were 562, 1000, 1780, 3160, and 5620 mg/kg/day, and the doses given to mice were 100, 1780, 3160, 5620, and 10,000 mg/kg/day. The mean body weight depression in male rates at 562 and 1000 mg/kg/day was 16% and 29% respectively. In female rats, 20% body weight depression occurred at 1780 and 3160 mg/kg/day, and 2 of 5 rats in the 3160 mg/kg/day group died. Information on effects in rats at the higher dose levels was not given. In mice, body weight depression did not occur; two male and three female mice died at the 5620 mg/kg/day dose level. No further evaluations of toxicity, such as gross or microscopic pathology or clinical chemistry, were conducted.

Hofman et al. (1971) conducted a subchronic inhalation study. Rats (10), cats (4), rabbits (4), and guinea pigs (10) were exposed to 500 ppm 1,1-dichloroethane 6 hours per day, 5 days per week for 13 weeks, and no effects were observed in blood creatine, blood urea nitrogen, SGOT, SGPT, or body weight gain. The same animals were then exposed to 1000 ppm 6 hours per day, 5 days per week for an additional 13 weeks. No effects were observed in rats, rabbits,

or guinea pigs. In cats, blood urea nitrogen and creatinine were elevated. Histopathological examination revealed renal tubular dilatation and degeneration.

An unpublished study conducted by the Dow Chemical Company is cited in Clayton and Clayton (1982). It is reported that rats, guinea pigs, rabbits, and dogs exposed to 500 or 1000 ppm 7 hours per day, 5 days per week, for six months, showed no evidence of toxicity as measured by gross and microscopic pathology and hematology.

In a study of embryo- and fetotoxicity of 1,1-dichloroethane (Schwetz et al., 1974), hepatotoxicity was also evaluated in both pregnant and non-pregnant female Sprague-Dawley rats. The experimental groups consisted of pregnant rats exposed to 0 (43), 3800 ppm (16), and 6000 ppm (19) 1,1-dichloroethane 7 hours per day on days 6 through 15 of gestation, and liver weight and SGPT were determined 6 days after the last exposure. Non-pregnant females were concurrently exposed and were evaluated immediately following the last exposure (4 per group) and six days following the last exposure (6 per group). SGPT activity, gross liver appearance, alterations in demeanor, or signs of toxicity were not observed in the treated rats. The ratio of liver weight to body weight was increased only in non-pregnant rats exposed to 6000 ppm evaluated 6 days after the last exposure; no effect was seen on absolute liver weight in non-pregnant rats exposed to 6000 ppm, on absolute or relative liver weight in pregnant rats, or on liver weight in non-pregnant animals evaluated immediately after the last exposure.

Behavioral and Central Nervous System

1,1-Dichloroethane was formerly used as an anaesthetic in humans (USEPA, 1984). Although no reports of central nervous system effects were located, the compound would be expected to cause non-specific CNS depression as do other volatile organic solvents.

Reproductive, Embryotoxic, and Teratogenic

No studies of the reproductive or teratogenic effects of orally administered 1,1-dichloroethane have been conducted. Schwetz et al. (1974) conducted an evaluation of the embryotoxicity and fetotoxicity of inhaled 1,1-dichloroethane in Sprague-Dawley rats. Experimental groups consisted of controls (43), 3800 ppm (16), and 6000 ppm (19) exposed 7 hours per day on days 6 through 15 of gestation. Exposure to 1,1-dichloroethane had no effect on the incidence of fetal resorptions, on fetal body measurements, or on the incidence of gross or soft tissue anomalies. The incidence of delayed ossification of sternebrae was significantly increased by exposure to 6000 ppm. The incidence of vertebrae with bipartite centra was significantly decreased, compared to controls, in the group exposed to 3800 ppm. Maternal food consumption and weight gain was slightly, but significantly, decreased by 1,1-dichloroethane exposure.

Additional

1,1-Dichloroethane was by far the least cytotoxic of a series of six halogenated alkanes tested in cultured hepatocytes from normal livers and from livers containing preneoplastic lesions. The concentration needed to decrease viability to 50% was 10 fold higher than for the next most toxic compound, chloroform (Chang et al., 1985).

Genetic

Overall, the results of genotoxicity testing of 1,1-dichloroethane are variable.

1,1-Dichloroethane was negative in the Ames assay with microsomal activation in five Salmonella strains (Simmon et al. (1977). In contrast, positive results for mutagenicity in Salmonella with metabolic activation were reported when incubation took place in sealed dessicators; the strain in which positive results occurred and the concentration of 1,1-dichloroethane tested were not given (Riccio et al., 1983). Positive results were reported in an enhanced viral transformation assay in Syrian hamster embryo cells, but details of the protocol were not given (Nesnow, 1982).

1,1-Dichloroethane was found to covalently bind to rat and mouse DNA, RNA, and protein after intraperitoneal injection. In in vivo studies, the binding was found to be mediated by hepatic microsomal cytochrome P-450, and weakly by lung microsomes. Binding was inhibited by the addition of glutathione and/or cytosol (Colacci et al., 1985).

1,1-Dichloroethane was negative for transformation of BALB/c-3T3 cells when tested in sealed glass chambers without metabolic activation. 1,1,1-Trichloroethane and trichloroethylene were positive when tested in the same protocol (Tu et al., 1985).

Carcinogenicity

An oral carcinogenicity bioassay for 1,1-dichloroethane was conducted by the National Cancer Institute (1978) in Osborne-Mendel rats and B6C3F1 mice. The compound was given in corn oil 5 days per week for 78 weeks, followed by an observation period of 33 weeks for rats and 13 weeks for mice. Each dosage group consisted of 50 animals of each sex, per species, and 20 vehicle controls and untreated controls per sex and species were used. The dosages were adjusted during the course of the study, and the time-weighted average dosages were calculated to be 764 and 382 mg/kg/day in male rats, 950 and 475 mg/kg/day in female rats, 2885 and 1442 mg/kg/day in male mice, and 3331 and 1665 mg/kg/day for female mice.

Survival was poor in both treated and untreated groups, particularly in rats. Pneumonia occurred in 80% of rats. For example, in male rats, which were the group with highest mortality, survival at the end of the study was 30% in untreated controls, 5% in vehicle controls, 4% in the low dose group, and 8% in the high dose group. A dose-related marginal increase in mammary adenocarcinoma and hemangiosarcoma was observed in female rats. In female mice dosed with 1,1-dichloroethane, there was a statistically significant increase in the incidence of benign endometrial uterine polyps. It was concluded that this bioassay provided no conclusive evidence for the carcinogenicity of 1,1-dichloroethane.

Several other studies relating to the carcinogenicity of 1,1-dichloroethane have been reported. Klaunig et al. (1986) conducted an initiation/promotion study in which 1,1-dichloroethane was administered to male B6C3F1 mice in their drinking water. The mice (35 per group) were either initiated by treatment for 4 weeks with diethylnitrosamine in the drinking water, or non-initiated, followed by treatment for 24 weeks (10 mice per group) or 52 weeks (25 mice per group) with 0 mg/L, 835 mg/L, or 2500 mg/L 1,1-dichloroethane in the drinking water. At sacrifice, complete gross necropsy and histological examination of lung, liver, and kidney, was conducted. In addition to 1,1-dichloroethane, chloroform and 1,2-dichloroethane were tested concurrently in a similar manner. None of the three compounds tested increased the number or incidence of lung or liver tumors by themselves, nor increased the tumor formation in initiated mice.

In a study conducted by Herren-Freund and Pereira (1986), 1,1-dichloroethane was tested for initiation in the rat liver foci bioassay, along with a number of other compounds. To test for initiation, rats were treated with 1,1-dichloroethane (7.33 mmol/kg) 12 or 18 hours after partial hepatectomy, and then treated with the promoter phenobarbital (500 ppm in drinking water) starting 7 days after initiation for 10 weeks. Livers were then analyzed for the incidence of altered foci with biochemical markers associated with preneoplastic lesions. 1,1-Dichloroethane did not increase the incidence of lesions.

Story et al. (1986) tested the initiating and promoting potentials of nine chlorinated aliphatics including 1,1-dichloroethane in male Osborne-Mendel rats. For initiation, the test compound was injected intraperitoneally 24 hours following partial hepatectomy, followed by dosing with 0.05% phenobarbital in the diet for 7 weeks. For promotion, the rats were initiated with diethylnitrosamine following partial hepatectomy, and then dosed with the test compounds by gavage 5 days per week for 7 weeks. Initiating and promoting ability was assessed by the formation of foci with markers indicating a preneoplastic state, as above. 1,1-dichloroethane did not show initiating activity, but did significantly increase the number of positive foci when tested as

a promoter.

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

The NCI bioassay and other studies discussed above do not provide sufficient evidence to consider 1,1-dichloroethane as a carcinogen. Therefore, 1,1-dichloroethane was classified as New Jersey Category III (NJDWQI, 1987) and the risk assessment is based on a non-carcinogenic endpoint.

Because no study involving oral administration of 1,1-dichloroethane is considered suitable for risk assessment, studies utilizing inhalation exposure were evaluated. The study of Schwetz et al. (1974), in which effects on liver weight were observed in rats exposed to 6000 ppm, was not considered most appropriate for risk assessment because the doses received by the rats were higher than the doses received by the animals in the study of Hofman et al. (1971).

Hofman et al. (1971) observed kidney toxicity in cats exposed to 1000 ppm 1,1-dichloroethane for 13 weeks following exposure to 500 ppm for 13 weeks. No effects were observed during the exposure to 500 ppm, as determined by clinical chemistry determinations. No effects were observed in rats, rabbits, or guinea pigs subjected to the same exposure regiment as the cats.

Calculation of the Health-based Maximum Contaminant Level

The NOAEL in cats observed by Hofman et al. (1971) of 500 ppm was selected as the basis for derivation of the Acceptable Daily Intake (ADI). The ADI was derived as follows:

$$ADI = \frac{(2025\ mg/m^3)\ (1.8\ m^3/day)\ (5\ days/week)\ (6\ hours/day)\ (0.25)}{10 \times 10 \times 10 \times 5\ (\ 5\ kg)\ (7\ days/week)\ (24\ hours/day)}$$

ADI = 0.0065 mg/kg/day = 6.5 ug/kg/day

where: 2025 mg/m^3 = NOAEL (500 ppm x 4.05 mg/m^3/ppm)

1.8 m^3/day = respiratory rate of cat weighing 5 kg (derived from Fiserova-Bergerova and Hughes, 1983)

5 kg = assumed weight of cat

0.25 = assumed pulmonary absorption factor (no data for 1,1-dichloroethane; based on assumed similarity to 1,1,1-trichloroethane [NJDWQI, 1987]).

5/7 days/week = days/week exposed

6/24 hours/day = hours/day exposed

10 x 10 x 10 = uncertainty factors appropriate for use with a NOAEL from a subchronic animal study

5 = additional uncertainty factor because of small number of animals used in the study.

$$MCL = \frac{(6.5\ ug/kg/day)\ (0.2)\ (70\ kg)}{2\ L/day} = 46\ ug/L$$

where: 6.5 ug/kg/day = ADI
0.2 = contribution from drinking water alone
70 kg = assumed weight of human adult
2 L/day = assumed daily drinking water consumption

Assumptions and Uncertainties

The small number of cats, the most sensitive species in the study used to derive the health-based MCL, necessitated the incorporation of an additional uncertainty factor of 5. An additional uncertainty is the derivation of a drinking water maximum contaminant level from a study employing inhalation, rather than oral, exposure.

It was assumed that a 70 kg adult consumes 2 liters of drinking water per day, and that 20% of total exposure to 1,1-dichloroethane is through drinking water.

Conclusions

A health-based maximum contaminant level for 1,1-dichloroethane in drinking water of 46 ug/L has been derived, based on renal toxicity in cats exposed by inhalation.

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METHYL TERTIARY BUTYL ETHER
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Division of Science and Research

New Jersey Department of Environmental Protection

Prepared by Gloria Post

July 1994

BACKGROUND INFORMATION AND PROPERTIES

General Information and Physical Constants

Synonyms	2-methoxy-2-methylpropane methyl tert-butyl ether MTBE
CAS#	1634-04-4
Chemical formula	$C_5H_{12}O$
Chemical structure	$CH_3-O-C(CH_3)_3$
Molecular weight	88.13
Physical state	colorless liquid
Melting point	-109°C
Boiling point	55.2°C
Vapor pressure	245 mm Hg at 25°C
Specific gravity, density	0.7405 at 25°C
Water-odor threshold	680 ug/L
Air-odor threshold	none available
Solubility	4.8g/100 g of water
Octanol/water partition coefficient	1.05

All data was obtained from United States Environmental Protection Agency (USEPA), 1989.

Production and Use

Methyl tert-butyl ether (MTBE) is prepared synthetically by reacting methanol with isobutylene, or from t-butyl alcohol and diazomethane. In 1979, $3,45 \times 10^{11}$ grams of MTBE was produced in the United States (HSDB, 1988). MTBE production increased the fastest of any chemical in the 1980s, and it is anticipated that this growth will continue through the 1990s. The 1991 US supply was 100 million barrels per day, and it was anticipated that both supply and demand will more than double by 1997.

MTBE is used to increase the octane rating of gasoline, and more recently has been added to gasoline to meet the requirements of the Clean Air Act, which require increased oxygen content of gasoline in both CO and ozone non-attainment areas (Ainsworth, 1991). Typical concentrations of MTBE in gasoline are 2 to 8 percent by volume for increased octane rating (USEPA, 1989), and 15% for the oxygenated fuel program (USEPA, 1993). MTBE is also used medically to dissolve gallstones (Allen et al., 1985).

Guidelines, Regulations, and Standards

The USEPA Drinking Water Health Advisory levels for MTBE are as follows: for a 10 kg child - One-day and Ten-day Health Advisories are 3000 ug/L and Longer-term Health Advisory is 500 ug/L. For a 70 kg adult, Longer Term Health Advisory is 2000 ug/L and Lifetime Health Advisory is 40 ug/L (USEPA, 1989). USEPA's Reference Concentration (RfC) for chronic inhalation of MTBE is 3 mg/m^3, based on effects observed in rats in the 24 month inhalation study of Chun et al., 1992 (USEPA, 1994a).

ENVIRONMENTAL EXPOSURE

Fate and Transport

MTBE is not expected to significantly hydrolyze in the environment, nor to be degraded in the presence of activated sludge. Based on physical properties, MTBE is expected to volatilize readily from water (USEPA, 1989).

MTBE is relatively mobile in soils. It migrates rapidly to groundwater and acts as a cosolvent for less polar constituents of gasoline (USEPA, 1989).

MTBE is not expected to bioaccumulate in the food chain, nor to be found extensively in food. In air, MTBE reacts with hydroxyl radicals, forming tertiary-butyl formate and acetone (USEPA, 1989).

Environmental Levels

MTBE has been identified in the potable water in New Jersey at concentrations ranging from 1 to 81 ppb in a survey conducted from 1985-1986 (A-280 Sampling, 1986). It has been found in concentrations up to 10,000 ppb in private wells in New Jersey by the Bureau of Water Supply, New Jersey Department of Environmental Protection (NJDEP). The databases maintained by the Bureau of Safe Drinking Water, NJDEP, were analyzed in regard to the occurrence of MTBE in water supplies. MTBE was reported in the nonpublic database in about 10% of wells sampled and 10% of those wells had concentrations greater than 70 ppm. About 60 of 630 public community supplies reported MTBE (Schorr, 1994).

MTBE concentrations in air arising from consumer use of gasoline containing the additive have recently been measured (Anderson,

1993). A study carried out by International Technology Corp. measured air levels at 10 service stations in the New York metropolitan area, including full- and self-service stations with and without advanced vapor recovery systems. The highest concentrations were found at the location where the gasoline is pumped into the cars; mean MTBE concentrations during a four hour period at this location were below 1 ppm, with a maximum concentration below 2.6 ppm. An additional study carried out by EOHSI measured commuter exposures during refueling and commuting. Exposures during refueling ranged from 13 to 4100 ppb, and during commuting from 1.2 to 160 ppb.

METABOLISM AND PHARMACOKINETICS

Absorption, Distribution, and Excretion

MTBE is well absorbed after oral and dermal administration (Bio-Research 1990a, 1990b) and via inhalation (Savolainen, 1985; Bio-Research 1990c). MTBE is widely distributed after absorption (Savolainen, 1985; Bio/dynamics, 1984). The half life for MTBE in plasma was less than two hours after oral administration, and was similar after other routes of administration. Elimination is virtually complete within 48 hours of dosing (Bio-Research 1990b). Elimination of MTBE is primarily via exhalation, with a significant percentage excreted in the urine. The percentage excreted in the urine decreases with higher dose, suggesting saturation of metabolism. Less than 1% of the dose was excreted in the feces (Bio-Research 1990b).

Metabolism

MTBE is metabolized via demethylation to tertiary-butanol and formaldehyde by cytochrome P-450 *in vitro* (Brady et al., 1990) and *in vivo* (Savolainen et al., 1985). After oral, dermal, and intravenous administration of ^{14}C-MTBE, metabolites detected in urine included 2-methyl-1,2-propanediol and alpha-hydroxyisobutyric acid (Bio-Research 1990b).

Human Exposure and Body Burden

MTBE has been used clinically to dissolve gallstones. It is perfused through a catheter into the gallbladder.

Human exposure to MTBE occurs occupationally and to consumers through the handling of gasoline containing it. Human exposure also can occur through inhalation and ingestion of MTBE in contaminated potable water supplies.

HEALTH EFFECTS

Overview

Like other ethers, MTBE has an anaesthetic effect. Results of studies of reproductive and teratological effects and genetic toxicity do not warrant classification of MTBE as a reproductive toxicant, a teratogen, or a mutagen. Subchronic oral studies of MTBE showed effects including increased kidney weight (Robinson, 1990). Carcinogenicity bioassays of MTBE in mice and rats were recently completed (Burleigh-Flayer et al., 1992; Chun et al., 1992).

Human

In the treatment of gallstones with MTBE, overfilling of the gallbladder, resulting in overflow into the abdominal cavity, has resulted in mild transient sedation. In one case in which 15 ml of MTBE could not be recovered from the gallbladder and slow extravasation was suspected, the patient went into a coma and hemolysis and renal failure occurred (Ponchon et al., 1988).

Recently, controlled exposure studies as well as epidemiology studies have been conducted to evaluate effects of MTBE inhalation in humans. Studies conducted by USEPA (Gerrity, 1993) involved controlled exposures of health young adults to 5 mg/m^3 (1.4 ppm) for one hour. MTBE did not cause symptoms such as headaches, eye irritation, or nasal irritation. A mild odor was detected by females, but not males. In additional studies conducted at Yale University (Cain, 1993), the effects of one hour exposure to 1.7 ppm MTBE on physiological and behavioral parameters were examined. MTBE was detected by slight odor at this level, and caused a very slight, statistically significant, increase in headaches reported.

Field epidemiology studies conducted in Fairbanks and Anchorage by the Centers for Disease Control and the Alaska Department of Health were prompted by complaints by the public of symptoms after exposure to gasoline containing MTBE. The symptoms suspected to be associated with MTBE included headaches, cough, nose or throat irritation, nausea, and dizziness. A higher incidence of symptoms was reported in those groups expected to have greater exposure to gasoline. Because of limitations of the studies, they did not provide definite evidence that MTBE caused the symptoms. The symptoms observed were acute, mild, and short in duration (USEPA, 1993).

Studies conducted in New Jersey were described by Anderson (1993). No difference in symptoms such as headaches, nausea, coughing, lightheadedness, and eye irritation was seen in state garage workers exposed to gasoline containing MTBE and similar workers exposed to non-MTBE gasoline.

Animal

Acute and Subacute

The oral LD_{50} for MTBE in rats was 3.9 g/kg (Arco, 1980). The inhalation LC_{50} for 4 hour exposure was approximately 40,000 ppm (Arco, 1980).

Rats were exposed to MTBE 6 hours per day for 9 days at concentrations of 100, 300, 1000, and 3000 ppm. An increase in phosphorous levels in blood occurred in females exposed to 1000 and 3000 ppm, relative liver weights were increased in both sexes exposed to 3000 ppm. Histologically detectable inflammation of the nasal mucosa and trachea were observed in the rats exposed to 1000 and 3000 ppm (Bio/Dynamics Inc., 1981).

A 28 day inhalation study in rats and mice was reported by Chun and Kintigh (1993). Groups of animals (10/sex/species/dose level) were exposed to 0, 400, 3000, or 8000 ppm MTBE 6 hours/day, 5 days per week.

In rats, ataxia was seen in the two highest dose groups. Body weight decreased in the highest dose group, and increased kidney, liver, and adrenal weights occurred in the two highest dose groups. Increased protein accumulation was seen in the kidneys of male rats in the two highest dose groups, but no change in alpha-2u-globulin activity was observed. Increased cell proliferation, as indicated by bromodeoxyuridine (BrdU) uptake, was seen in kidneys of male rats in the two highest dosing groups, but not in kidneys of female rats.

In mice, liver weight was increased in the two highest dose groups. Centrilobular hepatocellular hypertrophy was seen in mice in the highest dose group. Increased cell proliferation in the liver, as indicated by increased BrdU uptake in the nuclei, was seen in the livers of female mice from the two highest dose groups and male mice from the highest dose group.

Longer Term

In an unpublished study conducted by Inveresk Research International (1980), rats (10 per sex per group) were exposed to the MTBE by inhalation at concentrations of 250, 500, and 1000 ppm for 6 hours/day, five days/week for 13 weeks. A control group was subjected to air only for the same period. Food consumption, body weight and water consumption were monitored. Measurements of clinical chemistry parameters, hematology, urinalysis were taken at the end of exposure showed no dose-related increases or were within normal values. There were neither any gross nor histopathological findings attributable to the MTBE exposure. The only report effect was the observation of an increasing depth of anesthesia with increasing concentrations of MTBE.

In a study sponsored by the MTBE Task Force (Dodd and Kintigh), groups of rats (25 per sex per group) were exposed to concentrations of 0, 800, 4000, or 8000 ppm MTBE 6 hours per day, 5 days per week for 13 weeks. Parameters included body weight, food consumption, hematology, clinical chemistry, adrenal hormone analysis, organ weights, and gross and microscopic pathology. In addition, the study focused on potential neurotoxicity and included functional observational battery, motor activity, and histological examination of the nervous system of 6 animals per group (see Behavioral and Central Nervous System, below). Body weight gain was decreased in the high dose groups. Statistically significant dose related changes occurred in the weights of the liver, kidney, and adrenal gland, but no pathological changes were observed in these organs. The incidence of lymphoid hyperplasia and hemosiderosis in the spleen was increased in male rats exposed to 8000 ppm.

A subchronic oral (gavage) study of MTBE in rats has recently been reported by Robinson et al. (1990). This study was conducted by the USEPA Health Effects Research Laboratory for the purpose of providing information relevant to the development of health advisories to the USEPA Office of Drinking Water. In this study, male and female rats were dosed with 100, 300, 900, or 1200 mg/kg of MTBE in corn oil daily for 90 days.

The results of this study confirmed that MTBE is not highly toxic, and no specific target organ for MTBE was identified. As in the earlier inhalation studies, anaesthesia was observed in the animals given the highest dose, 1200 mg/kg. Some differences in organ weight and in clinical chemistry attributable to MTBE treatment were observed. These findings included: increased kidney weight, increased relative liver weight, decreased blood urea nitrogen, decreased serum calcium and glucose (in females only), increased serum cholesterol (in females only), and decreased lactic dehydrogenase. The only histological finding attributable to treatment was in the renal tubules of the high dose male rats.

Chronic bioassay data for MTBE is discussed under Carcinogenicity, below.

Behavioral and Central Nervous System

Like other ethers, MTBE causes an anaesthetic effect. This has been observed in humans in whom the gallbladder has been perfused with MTBE for treatment of gallstones, in cases in which overfilling of the gallbladder occurred (Ponchon et al., 1988). In the animal studies described above (eg. Inveresk, 1980; Robinson et al., 1990), anaesthesia occurred upon exposure to MTBE.

The subchronic study of Dodd and Kintigh (1989) discussed above specifically included parameters of neurotoxicity, including the functional observational battery, measure of motor activity, and histopathological evaluation of the nervous system of some animals from each group. Changes in motor activity were minor and

inconsistent between dose groups and sexes. Minor elevations in body temperature were observed in the two higher dose groups. No pathological changes were observed in the nervous system tissues. It was concluded that MTBE was not neurotoxic at the doses administered in the study.

Reproductive, Embryonic and Teratogenic

Available data do not indicate that MTBE causes reproductive toxicity or teratogenic effects.

A teratology evaluation in rats and mice was conducted by Conaway et al. (1985). Pregnant rats (25 per group) and mice (30 per group) were exposed via inhalation during the period of organogenesis to 0, 250, 1000, or 2500 ppm MTBE. Parameters examined included maternal body weight, food and water consumption, and liver weight, number of resorptions, fetal size and sex distribution, and fetal abnormalities. Food consumption decreased in the treated animals, but maternal or fetal body weight was not affected. The incidence of soft tissue malformations and major skeletal abnormalities was not significantly increased by MTBE treatment. A low incidence of fused sternebrae, considered a minor skeletal abnormality, was observed in the treated mice, while none occurred in the control mice.

In a one generation reproductive study, male rats exposed to target concentrations of MTBE at 300, 1300, and 3400 ppm for 6 hours/day, 5 days/week for 12 weeks were mated to female rats exposed to the same concentrations for 3 weeks. Exposures continued through the mating period and the females had continued exposures during gestation and from days 5-21 lactation of the litters (Fla) (no exposures days 0-4 lactation). A second litter was produced under the same mating and post mating exposure regimen. No adverse effects resulting from treatment were reported. The only finding was an increased incidence of dilated renal pelvis in the low-and high-dose females and in all pups sacrificed on day 21 of lactation (Biles et al., 1987).

Tyl (1989) conducted a developmental toxicity study of MTBE in rabbits exposed by inhalation. Pregnant rabbits (15 per group) were exposed to 0, 1000, 4000, or 8000 ppm MTBE on days 6 through 18 of pregnancy. MTBE caused reduced food consumption and body weight gain in the two higher exposure groups, and increased maternal liver weight in the 8000 ppm group. MTBE did not affect parameters of developmental toxicity, fetotoxicity, or malformation or variation at any exposure level.

Neeper-Bradley (1991) conducted a two-generation reproduction study in CD (Sprague-Dawley) rats, with exposure levels of approximately 400, 3000, and 8000 ppm. No effects were seen on mating, fertility, or gestational parameters. Maternal exposures to 400 ppm caused no effects. The two higher dosing groups had reduced body weight and body weight gains during postnatal development in both generations.

Genetic

A battery of genetic toxicology studies was conducted on MTBE by Arco (1980). MTBE was negative in mutagenicity tests in Salmonella and Saccharomyces, with and without metabolic activation, in the sister chromatid exchange assay in Chinese hamster ovary cells with and without metabolic activation, and in the in vivo clastogenicity assay in rats. In the mouse lymphoma forward mutation assay, MTBE was negative without metabolic activation, but was reproducibly positive in the presence of the S-9 fraction. It was suggested that this could be due to the production of formaldehyde, which is positive in this assay, from MTBE.

A rat in vivo cytogenetics study was conducted, with exposures up to 8000 ppm (BRRC, 1989), and a Drosophila sex-linked recessive lethal test with MTBE concentrations up to 0.3% in aqueous sucrose (Hazelton, 1989). Both of these studies gave negative results.

Exposure of CD-1 mice to concentrations of MTBE up to 8000 ppm, 6 hours per day for 2 days, did not induce bone marrow micronuclei (Vergnes and Kintigh, 1993).

Carcinogenicity

Carcinogenicity bioassays for MTBE in mice and rats were recently completed.

Fischer 344 rats (50/sex/dose group) were exposed to 0, 400, 3000, or 8000 ppm MTBE 6 hours per day, 5 days per week, for 24 months (except for the male rats from the 3000 and 8000 ppm groups which were sacrificed at weeks 97 and 82 respectively, due to excessive mortality) (Chun et. al, 1992). The main cause of death in the males from the higher exposure groups was chronic progressive nephropathy. Ataxia, as well as decreased body weight and body weight gain, was seen in high dose males and females. Females in the two higher dosing groups had increased liver and kidney weights. Swollen periocular tissue, salivation, and prostration were also related to exposure. Gross pathology and histopathologic examination revealed nephropathy in all groups of males and the two highest dose groups in females.

The incidence of adenomas and carcinomas of the kidney was increased in males in the two highest dose groups, and one renal adenomas was seen in a female rat in the 3000 ppm group. Kidney tumors seen in male rats for some chemicals are not considered relevant to potential human carcinogenicity because they occur through the accumulation of a protein, alpha-2u-globulin, in the kidney of male rats, and this protein is not produced by humans (USEPA, 1991).

Recent studies submitted under Toxic Substances Control Act (TSCA) to USEPA by producers of MTBE indicate that the kidney tumors caused by MTBE do not arise through the alpha-2u-globulin mechanism (Fowler and Chun, 1993). Alpha-2u-globulin reactivity in the

kidneys of the rats from the 13 week study of Dodd and Kintigh (see above) was evaluated using an immunohistochemical procedure. No alpha-2u-globulin reactivity was seen in the kidneys from the female rats, and activity in the kidneys of male rats exposed to MTBE was not increased compared to the controls.

Additionally, the number of testicular interstitial cell adenomas was increased in the treated groups. This increase was not statistically significant and there was a high incidence of these tumors in the controls.

Burleigh-Flayer et al. (1992) reported results of a chronic inhalation bioassay in CD-1 mice. Groups of 50 mice/sex/dose group were exposed to 0, 400, 3000, or 8000 ppm MTBE 6 hours/day, 5 days/week, for 18 months. Ataxia was seen in both sexes exposed to 8000 ppm, and body weight gain and absolute body weight were also reduced in the high dose groups. A dose-dependent increase in liver weight was observed. Kidney weights were increased in all groups of exposed male mice and in females exposed to 8000 ppm.

A statistically significant increase in the incidence of liver adenomas was seen in the female mice in the 8000 ppm group. Additionally, an increase in the incidence of hepatocellular carcinomas from 2/50 in the control group to 8/50 in the 8000 ppm group occurred in males; this increase was reported to be not statistically significant at the $p < 0.05$ level by the authors. However, further review of the data by the USEPA Office of Health and Environmental Assessment shows that this tumor incidence is significant if the analysis is based on animals at risk instead of total animals in the study (*USEPA, 1994b*).

A chronic oral study in rats was recently completed by the Bologna Oncology Institute in Italy. No published report of the results of this study is available, but the results were reported at the 1993 annual meeting of the Collegium Ramazzini in Carpi, Italy. A letter which reports on the presentation of this study at the meeting was submitted to USEPA by Arco Chemical Company (Capaldi, 1993). Sprague-Dawley rats (60/sex/treatment group) were given 0, 250 mg/kg, or 1000 mg/kg MTBE in olive oil, once per day, 4 times per week for 104 weeks by gavage, beginning at 8 weeks of age. It was reported that the total number of malignant tumors was reduced in the high dose animals compared to controls. No increase in kidney tubule tumors was observed. There was a dose-related and statistically significant increase in combined lymphomas and leukemias (4% in controls, 10% in low dose, 20% in high dose, in females), but specific tumor types combined were not discussed. A significant increase in hemolymphoreticular tumors when combined among anatomical sites was reported. A marginal increase in malignant uterine sarcomas in low dose animals was reported. A dose related increase in testicular Leydig cell tumors was reported.

QUANTITATIVE RISK ASSESSMENT

Carcinogenicity Classification:

MTBE is classified in as a Possible Human Carcinogen (Category II, see NJDWQI (1987); equivalent to USEPA Group C). This classification is based on the results of the chronic inhalation studies in rats (Chun et. al, 1992) and mice (Burleigh-Flayer et. al, 1992) discussed above. Possible Human Carcinogens are contaminants for which limited evidence of carcinogenicity exists from animal studies, in the absence of human data. Examples of such limited evidence includes a malignant tumor response in a single well-conducted experiment that does not meet the conditions for sufficient evidence; the presence of benign, but not malignant, tumors with an agent showing no response in a variety of short-term tests for mutagenicity; and responses of marginal statistical significance in a tissue known to have a high or variable background rate (USEPA, 1986).

USEPA is currently evaluating MTBE in regard to cancer classification (USEPA. 1994c). Currently, USEPA's evaluation "suggests a tentative classification as Group C". USEPA is delaying final classification until it can review data from recent oral studies in rodents conducted at the Bologna Oncology Institute. These data are not yet available to USEPA or to New Jersey, but based on preliminary discussions, USEPA feels that this data "may sustain the Group C classification or support a higher (e.g. Group B2) classification" (USEPA, 1994c). The State of New York has recently regulated MTBE based on cancer risk, and has calculated the 1 x 10-6 lifetime cancer risk level in drinking water based on the liver carcinomas seen in male mice by Burleigh-Flayer, 1992 (USEPA, 1994b).

In the development of NJ Health-based MCLs, the risk assessment for a Possible Human Carcinogen is based on a non-carcinogenic endpoint, with the incorporation of an additional uncertainty factor of 10 to account for possible carcinogenic effects (NJDWQI, 1987). This approach is also followed by the USEPA Office of Water in development of Maximum Contaminant Level Goals for drinking water, which are analogous to New Jersey Health-based MCLs.

Studies Relevant for Risk Assessment

The study of Robinson et al. (1990) is currently the only available oral study which is suitable for development of a health-based level for drinking water, and therefore was chosen as the basis for the Health-based MCL.

In developing a health-based guidance for MTBE, increased relative kidney weight was selected as the endpoint. Increased relative kidney weight occurred in both males and females, in a dose dependent manner. The increased relative kidney weight was statistically significant ($p < 0.05$) in females dosed with 300, 900, and 1200 mg/kg and above, and in males dosed with 900 and 1200

mg/kg. At lower doses, the relative kidney weight was elevated compared to controls, but the increase was not statistically significant.

The dose of 100 mg/kg/day was the NOAEL (No Observed Adverse Effect Level), based on absence of significant increased relative kidney weight in female rats at this dose.

Calculation of Health-Based Maximum Contaminant Level

The Health-based Maximum Contaminant Level was derived as follows:

$$\frac{(100\ mg/kg/day)\ (70\ kg)\ (0.2)}{(1000)(10)(2\ L/day)} = 0.07\ mg/L \text{ or } 70\ ug/L$$

Where:

100 mg/kg/day = NOAEL

70 kg = assumed body weight of adult

0.2 = relative source contribution factor, to account for routes of exposure other than drinking water

1000 = uncertainty factor applied for a NOAEL from a subchronic study

10 = additional uncertainty factor applied to Possible Human Carcinogens

2 L/day = assumed daily water consumption of an adult

Assumptions and Uncertainties

Since no chronic oral study of MTBE is available for review, the risk assessment was based on subchronic oral toxicity data.

It is assumed that a 70 kg adult consumes 2 liters of drinking water per day, and 20% of the exposure to MTBE is through drinking water.

Summary

A Health-based MCL value for methyl tertiary-butyl ether has been derived, based on increased relative kidney weight seen in a subchronic gavage study (Robinson et al., 1990). An additional uncertainty factor of 10 was incorporated based classification as a Possible Human Carcinogen. The value derived to protect from health effects from lifetime exposure is 70 ug/L.

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APPENDIX

Guidance Levels for MTBE Based on Organoleptic Effects

The potential for organoleptic effects from water contaminated with MTBE was evaluated by the Connecticut Department of Health Services. Both taste and odor from MTBE in water are detectable at approximately 700 ug/L. A calculation of the level at which MTBE would be detected during showering was also conducted, based on assumptions on the size of the shower and the amount of water used during the shower. This evaluation was reviewed by Dr. Paul Sanders of the Division of Science and Research, who found it to be technically sound. It was estimated that the odor of MTBE could potentially be detected during showering at levels exceeding 100 ug/L.

SUMMARY: MTBE is not expected to be detected by taste and odor in water at levels below approximately 700 ug/L. MTBE is not expected to be detected by odor during showering at levels below 100 ug/L. Therefore, organoleptic effects are not anticipated at concentrations at or below the Health-based MCL of 70 ug/L.

REFERENCE: Action Level for Methyl Tertiary Butyl Ether (MTBE) in Drinking Water. Hari V. Rao, Carolyn Jean Dupuy, and David R. Brown. Connecticut Department of Health Services. (Undated).

ADDENDUM TO NAPHTHALENE HEALTH-BASED MCL SUPPORT DOCUMENT

SUMMARY

The Naphthalene Health-based MCL Support Document dated April 3, 1989, written by Lubow Jowa, recommends a Health-based MCL of 2870 ug/L. This is based on a NOAEL of 41 mg/kg/day in a chronic oral study in rats (Schmahl, 1955), with an uncertainty factor of 100 for intraspecies and interspecies variation.

In this addendum, it is recommended that an additional uncertainty factor of 10 be applied to this Health-based MCL, to result in an MCL of 287 ug/L, which may be expressed with one significant figure as 300 ug/L. The reasons for this recommendation are given below:

BACKGROUND

Since the completion of this Support Document, a chronic inhalation bioassay of naphthalene in mice has been completed by NTP (1992). Groups of male and female B6C3F1 mice were exposed to 0 ppm (75 per sex per group), 10 ppm (75 per sex per group), or 30 ppm (150 per sex per group). In females, the incidence of alveolar/bronchiolar adenomas and the combined incidence of alveolar/bronchiolar adenomas and carcinomas was significantly greater in the high dose group than in the controls. Additionally, naphthalene exposure caused increased incidence and severity of chronic inflammation and metaplasia of the olfactory epithelium, hyperplasia of the respiratory tract, and also caused chronic lung inflammation. The authors of the study concluded that there was some evidence of carcinogenic activity for naphthalene in female mice, and no evidence of carcinogenic activity in male mice.

It is recommended, based on the results of the NTP study, that naphthalene be classified as a Group C carcinogen. Although the organ in which tumors occurred was lung and the exposure was through inhalation, several factors indicate potential relevance to oral exposures. Naphthalene has been observed to selectively accumulate in lungs of animals after oral exposure (Eisele, 1985). Furthermore, the lung, particularly the non-ciliated cells of the bronchiolar epithelium (Clara cells) are a target for naphthalene toxicity after exposure by routes other than inhalation (intraperitoneal injection) (Mahvi et. al., 1977; Tong et. al., 1981). These effects occur in mice but not in the rat (O'Brien et. al., 1985) or hamster (Buckpitt and Bahnson, 1984). The pulmonary toxicity of naphthalene is believed to result from activation to reactive species by mixed function oxidases, which are present at high levels in the Clara cells (O'Brien et. al., 1985), and that the differences in species sensitivity result from preferential production of a particular stereoisomeric form of naphthalene epoxide in mice, as well as a greater overall rate of metabolism in lung tissue from mice as compared to rats and hamsters (Chang et. al., 1991). Data from fresh samples of human lung tissue from two

patients undergoing resection for tumor removal indicates that human pulmonary mixed function oxidases can metabolize naphthalene to naphthalene oxide (Buckpitt and Bahnson, 1986). Based on the above information, it is reasonable to classify naphthalene as a possible human carcinogen via oral exposure (Group C).

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NAPHTHALENE

HEALTH-BASED MAXIMUM CONTAMINANT LEVEL SUPPORT DOCUMENT

Division of Science and Research

New Jersey Department of Environmental Protection

Prepared by Lubow Jowa

April 3, 1989

EXECUTIVE SUMMARY

Naphthalene is a white crystalline solid recovered during the processing of petroleum or coal tar. It is released into the water by industrial processes. Individuals are exposed to naphthalene primarily by inhalation through the use of mothballs. Overexposure to naphthalene in humans has been associated with increase in cataract formation and the occurrence of hemolytic anemia. In experimental animals, the principle target tissues have been identified as the nonciliated bronchiolar epithelial (Clara) cell and eye tissues. Naphthalene does not appear to be mutagenic and there is no evidence of carcinogenic potential on the basis of limited studies. A risk assessment was performed based on one chronic study available on naphthalene, in which no detrimental effects were seen in experimental animals upon exposure. As a result, an MCL of 2.87 mg/L was obtained which should be protective of possible human health effects incurred from ingestion of naphthalene in drinking water.

BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties

Synonyms	tar camphor
CAS#	91-2-3
Chemical formula	$C_{10}H_8$
Chemical structure	
Molecular weight	128.16
Physical state	white flakes or powder
Melting point	80.2°C
Boiling point	217.9°C
Vapor pressure	1 mm at 53°C
Specific gravity, density	1.152
Air-odor threshold	5×10^{-1} mg/m^3
Conversion factor	1 mg/m^3 = 0.191 ppm
Solubility	31-34 mg/L at 22°C distilled water
Octanol/water partition coefficient	3.01/3.45

(all data obtained from Verschueren, 1981)

Production and Use

Naphthalene is produced by recovery from coal-tar feed stocks or from aromatic petroleum refinery streams (U.S.EPA, 1987). Total domestic consumption of naphthalene for 1985 has been estimated to be 540 million pounds. Major uses for naphthalene include: an intermediate in the production of phthalic anhydride (55% of consumption), the insecticide carbaryl (20%), beta-naphthol (8%), synthetic tanning agents (2%), surfactant (5%), miscellaneous organic intermediates (2%), and use as a moth repellant (2%) (U.S.EPA, 1987).

Guidelines, Regulations and Standards

The time weighted average (TWA) concentration recommended for naphthalene by the Occupational Safety and Health Administration is 10 ppm (OSHA, 1983). The American Conference of Governmental and Industrial Hygienists (ACGIH) also recommend an 8 hour TWA of 10 ppm with a 15-minute short term exposure limit of 15 ppm (ACGIH, 1988).

ENVIRONMENTAL EXPOSURE

Naphthalene is released into the environment from coal gasification emissions, wastewater from oil and gas fields, oil spills, combustion gases from coal-fired boilers, residential wood stoves, moth balls, chain saw engines, automobile exhaust, cigarettes, and landfill gas (U.S. EPA, 1987). Naphthalene has been detected in industrial effluent at concentrations of up to 32 mg/L, municipal wastewater treatment plant effluent at 22 ug/L, and drinking water at 1.4 ug/L, well water and ground water (U.S. EPA, 1987).

METABOLISM AND PHARMACOKINETICS

Absorption

Naphthalene appears to be absorbed well from all routes of exposure in both man and animals. The rate and extent of absorption by any route has not been studied extensively, however, judged by the toxicity observed from accidental as well as intentional exposure, the amount of naphthalene absorbed must be presumed to be significant.

Metabolism

The metabolism of naphthalene has been studied to a limited degree in man, and more extensively in animals. The key metabolites of naphthalene with toxicological significance are 1-naphthol, 2-naphthol, 1,2-dihydroxynaphthalene and 1,2-naphthoquinone. Most of the metabolites are excreted as conjugates of glucuronide or mercapturic acids (U.S. EPA, 1987).

Human Exposure and Body Burden

Very little information is available to estimate human exposure to naphthalene. It appears that naphthalene in drinking water contributes very little to the overall body burden, since it is rarely found as a drinking water contaminant. The most significant non-occupational source of naphthalene exposure appears to be inhalation of indoor air containing mothball vapors as well as cigarette smoke (U.S.EPA, 1980).

HEALTH EFFECTS

Overview

Naphthalene has been reported to cause acute hemolytic anemia and cataracts in humans upon accidental or occupational exposures. It has been reported to produce cataracts in rats, rabbits and mice and to produce pulmonary toxicity in rodents. There is no evidence that naphthalene is mutagenic. One chronic study on naphthalene has indicated that there is no evidence of carcinogenicity, while another chronic study by the National Toxicology Program is still in progress.

Human Health Effects

The most common health effects to humans upon exposure to acute, sublethal doses of naphthalene are cataracts, sometimes accompanied by retinopathy and hemolytic anemia, which can lead to jaundice and renal disease from precipitated hemoglobin. These effects have been reported both in infants and adults (U.S. EPA, 1980).

Hemolytic anemia caused by naphthalene exposure seems to be associated with a relative deficiency of enzymes responsible for maintaining reduced glutathione (GSH), lowering its availability. In the absence of GSH, the red cell hemoglobin undergoes oxidative degeneration, leading to fragility of the cell membrane. Levels of GSH are maintained by the enzyme glucose-6-phosphate dehydrogenase (G6PDH). Deficiency of this enzyme, occurring in certain ethnic groups as well as in neonates, explains a higher incidence of naphthalene associated hemolytic anemic reported for these population groups. Hemolytic anemia was reported in infants whose skin had been rubbed with baby oil, who absorbed naphthalene from blankets and clothing stored in moth balls (Dawson et al., 1958).

Several case studies of naphthalene-induced cataracts have been documented. In one instance, 8 out of 32 workers who were exposed to naphthalene in a manufacturing plant developed cataracts (U.S. EPA, 1980).

Wolf (1976) reported 6 cases of carcinomas among 15 workers exposed to vapors of naphthalene and coal tar for 7-32 years at a coal-tar naphthalene production facility. Four of the six cases were carcinomas of the larynx in workers who smoked; the other two were carcinomas of the pylorus and cecum. It should noted that coal tar components include well known carcinogens, i.e. benzo(a)pyrene, which may account for the incidence of carcinomas in this population.

Animal Studies

Acute toxicity

Oral LD_{50} values reported for orally administered naphthalene range from 1,780 mg/kg to 9,430 mg/kg in the rat. Ocular changes can occur from a single dose of 1000 mg/kg naphthalene in rabbits (U.S. EPA, 1987). In CD-1 mice dropping of the eye lid with clear red secretions was observed with doses of 400 mg/kg or higher (Shopp et al., 1984).

Orally administered naphthalene is believed to be initially metabolized in the liver; the metabolites travel through the blood stream to the eye where further metabolism takes place (van Heyningen, 1979). Evidence in rats and rabbits suggests that 1,2-dihydroxynaphthalene is enzymatically converted to 1,2-naphthoquinone which then reacts with eye proteins resulting in damage (van Heynigan, 1979). In addition, it has been suggested that lipid peroxides, produced by the metabolism of naphthalene, play a role in cataract formation by depleting the GSH content of the lens, as well as reacting with the lens itself to form cataracts (Yamauchi et al., 1986).

Rodents administered naphthalene intraperitoneally, suffered from selective pulmonary bronchiolar epithelial (Clara) cell necrosis, but not hepatic or renal necrosis. The extent and severity of this lesion appears to correlate with the degree of covalent binding of metabolites to the lung, however, it is not certain whether the source of the metabolites is the lung or the liver. This effect is highly variable with different species and strains not showing the same degree of sensitivity (U.S. EPA, 1987).

Subchronic studies

Shopp et al. (1984) conducted a 90-day study in 5 groups of 112 male and 112 female CD-1 mice administered naphthalene in doses of 0 (naive), 0 (vehicle) 5.3, 53, and 133 mg/kg/day in corn oil by gavage. No significant effects on body weight were noted for males or females. A significant decrease in the absolute weight of the brain, spleen, and liver was noted for females receiving 133 mg/kg. However, organ/body weight ratios were significantly different only for the spleen. Of the changes noted from the clinical chemistry data, the increase in blood protein content in males receiving 53 or 133 mg/kg, the decrease in blood urea nitrogen in all treated females, and the decrease in calcium ion concentrations in males receiving 53 or 133 mg/kg were considered to be treatment related. The authors concluded that these changes gave little evidence of toxicity at any dosage and were biologically irrelevant. No significant changes were noted in hematology, the mixed-function oxidase activity or immunoassay (humoral immune response, lymphocyte responsiveness, popliteal

lymph node response and bone marrow function) for either sex.

A subchronic oral toxicity study was performed for the National Toxicology Program (NTP) (1980a). Naphthalene in corn oil was administered by gavage to ten male and female F344 rats at dose levels of 0, 25, 50, 100, 200, or 400 mg/kg/day, 5 days/week for 13 weeks. Two males died at the 400 mg/kg dose during the first week of exposure. A significant decrease in body weight gain (>10%) was observed among males and females of the 200 and 400 mg/kg and in females at 100 mg/kg, without a decrease in food consumption. Comprehensive histological examinations showed a low, not dose-related incidence of renal and liver lesions. Minor hematological changes were observed in the males and females of the 400 mg/kg dose group.

In a similar study performed for the NTP (NTP,1980b) B6C3F1 mice were exposed to naphthalene by corn oil gavage at doses of 0, 12.5, 25, 50, 100, or 200 mg/kg/day (NTP, 1980b). Transient signs of toxicity (lethargy, rough hair coats and decreased food consumption) occurred at weeks 3 to 5 in the 200 mg/kg dose groups. Dose-related decreases in body weight gain were seen in females, but were not statistically significant. No compound-related changes were observed in any organs, including kidneys, thymus, eyes, and lungs. Furthermore, there were no hematological compound-related changes as well.

Chronic toxicity

Schmal (1955) reported that naphthalene administered by food or intraperitoneally was not carcinogenic in rats (in house breed). Naphthalene was dissolved in oil and given six times daily in food to rats which were approximately 100 days old. The daily dose was between 10 to 20 mg/day and continued until the 700th experimental day when treatment ceased (a total of 10 g was administered) and the animals were maintained until spontaneous death. A thorough gross examination was performed, and organs which looked unusual were examined histologically. No compound-related increase in tumors nor any signs of toxicity were noted.

Behavioral and Central Nervous System

No reports on the effects of naphthalene on behavior or on central nervous system were located in the literature.

Reproductive, Embryotoxic, and Teratogenic

Single oral doses of 300 mg/kg naphthalene were administered daily for 8 consecutive days to 50 pregnant mice beginning on day 7 of gestation (Plasterer et al., 1985). A significant increase in maternal lethality ($p<0.05$) and a decrease in mean maternal body weight was observed as well as a decrease of number of pups per litter ($p <0.05$). There was no decrease in pup survival or mean

body weights. No gross congenital abnormalities were detected.

Naismeth and Matthews (1986) reported a study in which 18 artificially inseminated New Zealand white rabbits per group were orally dosed with naphthalene at 0, 40, 200, or 400 mg/kg from days 6 to 8 (gestation). Mild signs of toxicity was observed in the dams: decreased activity, dyspnea, weight loss, cyanosis, salivation, and loose stools or diarrhea, occurred in an apparent dose-related fashion. However, no differences in reproductive parameters were noted. Several malformations were observed but did not appear to be dose-related.

Genetic

Naphthalene was tested in Salmonella strains TA98, A100, TA1535 and TA1537 with and without S9 activation and was found to be nonmutagenic (McCann et al. 1975, Godek, et al. 1985). Connor et al. (1985) reported that naphthalene was not mutagenic in two S. typhimurium strains, UTH8414 and UTH 8413 with full DNA repair capability or in TA100 and TA98, which cannot repair DNA.

Carcinogenicity

Groups of 30 male and female a/J strain mice were exposed via inhalation to naphthalene at concentrations of 0, 10, or 30 ppm, 6 hours a day, 5 days per week for 6 months (Adkins et al, 1986). At the end of the exposure period, the lungs were histologically examined. Exposure to naphthalene did not result in changes in total number of mice with tumors, but was associated with an increase of adenomas per tumor-bearing mouse. No apparent dose-response was observed.

Schmal (1955) reported that naphthalene administered by food or intraperitoneally was not carcinogenic in rats (in house breed). Naphthalene was dissolved in oil and given six times daily in food to 28 rats which were approximately 100 days old. The daily dose was maintained between 10 to 20 mg/day and continued until the 700th experimental day when treatment ceased (a total of 10 g was administered) and the animals were maintained until spontaneous death. A thorough gross examination was performed, and organs which looked unusual were examined histologically. No tumors were found in the animals.

A carcinogenicity study performed for the National Toxicology program on naphthalene has been completed. The results of this study are still being evaluated (NTP,1989).

RISK ASSESSMENT

Although the chronic data on naphthalene is sparse, there is little evidence to support the possibility of naphthalene being carcinogenic. The Schmal study (1955) indicates no occurence of

tumors, while the Adkins (1986) fails to show an increase in the number of tumor-bearing animals with dose. Therefore, it would be appropriate to place naphthalene into category III and derive a NOAEL based on a systemic toxicity endpoint.

The NTP (1980b) study as well as the Shopp (1984) study could be used as the basis of a risk assessment for naphthalene exposure through drinking water. In the NTP study (1980b), mice showed transient signs of toxicity (lethargy, rough hair coats and decreased food consumption) occurring at weeks 3 to 5. Therefore, a NOAEL derived from this study would be 100 mg/kg (5 days per week). Similarly, in the Shopp et al.(1984) study, absolute and relative spleen weights were reported to be reduced in the 133 mg/kg/day dose group of females. Therefore, a NOAEL of 53 mg/kg/day could be derived from this study.

The only lifetime study to examine naphthalene toxicity is the Schmahl (1955) study. Naphthalene was administered into the diet at a dose rate of 10-20 mg/kg and continued until 700 days at which time a total of 10 g had been administered. The animals were followed until spontaneous death occurred. No compound-related effects were noted. A NOAEL of 41 mg/kg/day can be determined on the basis of 10 g per rat, 0.35 kg average body weight, and 700 days of exposure.

There are compelling reasons why the Schmahl (1955) study should be used as the basis for deriving an MCL. It is the study of longest duration and thereby the study of choice for chronic risk assessment determination necessary to derive the MCL. Problems with the study include a limited sample size and lack of the type of rigorous study protocol design required of an NTP study. It also fails to show compound-related toxic effects necessary to be confident of the NOAEL. However, its NOAEL is in the range of the NOAEL levels reported in the subchronic studies. The subchronic studies are less suitable for risk assessment because of their shorter duration, and like the Schmahl (1955) study, they also lack definitive signs of toxicity.

Calculation of Health-Based Maximum Contaminant Level (MCL)

Derivation of ADI

Schmahl (1955) NOAEL = 41 mg/kg/day

$$\frac{41\ \text{mg/kg/day}}{100} = 0.41\ \text{mg/kg/day}$$

ADI = 0.41 mg/kg/day

$$\frac{0.41\ \text{mg/kg/day} \times 0.2 \times 70\text{kg}}{2\text{L}} = 2.87\ \text{mg/L}$$

MCL = 2.87 mg/L =2870 ug/L

where:
100 = factor for intra- and interspecies variation
0.2 = source contribution factor
70kg = weight of adult male
2L = water consumption per day

Assumptions and Uncertainties

Several uncertainties exist with regard to selection of the appropriate study and definition of NOAEL used to calculate the MCL. First, few of the chronic or subchronic naphthalene studies show any clear signs of toxicity, and none demonstrates a dose-response relationship. Second, the only chronic ingestion study (Schmahl, 1955) lacks detail regarding study design and description of observed effects. Unfortunately, the results of the chronic study conducted by the National Toxicology Program are not yet available, and could not be considered in this assessment.

It is assumed that a 70 kg adult consumes 2 liters of drinking water per day and that 20% of the exposure to naphthalene is through drinking water.

CONCLUSIONS

The Schmahl (1955) study is the only chronic study available on the toxic effects of naphthalene, and thereby the most suitable study to use for deriving a health-based MCL. Based on no observed toxic effects to rats exposed to naphthalene in this study, a MCL of 2.87 mg/L (2870 ug/L) for naphthalene is recommended.

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1,1,2,2-TETRACHLOROETHANE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Division of Science and Research
New Jersey Department of Environmental Protection

Prepared by
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March 7, 1989

EXECUTIVE SUMMARY

1,1,2,2-Tetrachloroethane was once used extensively as an industrial solvent and intermediate but it presently has limited use since less toxic substitutes are available. The compound has been detected in NJ surface water and groundwater supplies. The odor threshold is 0.5 mg/L in water. Tetrachloroethane is a known toxicant to the liver, kidney and central nervous system in both humans and laboratory animals. It is classified by EPA as a possible human carcinogen (Group C) since there is limited animal and no human evidence for carcinogenicity. A health-based maximum contaminant level (MCL) of 1 ug/L was derived for 1,1,2,2-tetrachloroethane to protect from liver damage and possible carcinogenicity.

BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties

Chemical name: 1,1,2,2-tetrachloroethane

Synonyms: tetrachloroethane, acetylene tetrachloride, sym-tetrachloroethane, 1,1-dichloro-2,2-dichloroethane

CAS number: 79-34-5

Chemical formula: $C_2H_2Cl_4$

Chemical structure: $Cl_2CH-CHCl_2$

Molecular weight: 167.86

Physical state: colorless, heavy, mobile liquid

Melting point: -36°C

Boiling point: 146.3°C

Vapor pressure: 5 mm Hg at 21°C

Specific gravity/density: 1.58658 at 25°C/4°C

odor threshold (air): <3ppm (ACGIH, 1980)
sweetish, suffocating, chloroform-like odor (Windholz, 1983)

odor threshold (water): detection limit: 0.5 mg/L (IARC, 1979)
Solubility: very sparingly soluble in water
2,900 mg/l at 25°C

Conversion factor: 1ppm in air is equivalent to 6.87 mg/m^3

Production and Use

1,1,2,2-Tetrachloroethane is principally used as an intermediate for trichloroethylene and other two carbon atom chlorinated hydrocarbons. As a nonflammable solvent, tetrachloroethane can also be used for fats, oils, wax resins, rubber and the cleaning and degreasing of metals. The compound has been an ingredient in soil sterilization, weed killer and insecticide formulations and in the manufacturing of paint, varnish and rust removers (Windholz, 1983; Hawley, 1981). Present uses of tetrachloroethane are highly limited since there are less toxic substitutes now available.

In 1967, an estimated 222 million kgs. of this compound was

produced for the closed-cycle synthesis of trichloroethylene but today, no US firms manufacture tetrachloroethane (IARC, 1979; Stanford Research Institute (SRI)). In 1982, it was reported that 65,500 kg. of tetrachloroethane were imported into the United States (SRI).

Guidelines, Regulations and Standards

The Occupational Safety and Health Administration (OSHA) has established a 8-hr. time-weighted average for air concentrations of tetrachloroethane at 5 ppm for the work place environment. In comparison, the National Institute for Occupational Safety Health recommends that occupational air exposure be limited to approximately 1 ppm (concentration by volume of air no greater than 6.87 mg/m^3) for a ten hour work day and for a 40 hour work week (NIOSH, 1976). The American Conference of Governmental Industrial Hygienists also suggests a TWA of 1 ppm for tetrachloroethane (ACGIH, 1984).

Under the Clean Water Act, ambient water quality criteria were determined for the protection of human health from the potential effects due to 1,1,2,2-tetrachloroethane exposure via the consumption of aquatic organisms and water. The recommended criteria, which are based on a 10^{-6} incremental increase of cancer risk over a lifetime, are 0.17 ug/L for water and fish consumption and 10.7 ug/L for fish consumption only (Federal Register, 1980).

ENVIRONMENTAL EXPOSURE

Fate and Transportation

Due to its moderately volatile nature, tetrachloroethane primarily volatilizes when released onto land surfaces. Tetrachloroethane in the atmosphere is extremely stable but photodegrades rapidly upon diffusion into the stratosphere. When the compound is released into surface water bodies, the majority volatilizes within a matter of days to weeks (Syracuse Research Corporation (SRC)).

Since tetrachloroethane is poorly adsorbed to soil, it is possible for the compound to leach into groundwater systems (SRC). There is evidence that tetrachloroethane slowly biodegrades under these anaerobic conditions into a final product, 1,1,2-trichloroethane (SRC).

Ambient Levels

1,1,2,2-tetrachloroethane can be released into the air during the manufacturing process of trichloroethylene from its use as a solvent, removing agent, degreaser and other applications (Verschueren, 1983). In addition, tetrachloroethane has been reported to be emitted from various hazardous waste sites (Harkov,

1985).

An on-site field collection program for select organic chemical concentrations in ambient air reported that the average urban concentrations of 1,1,2,2-tetrachloroethane was 0.01 ppb or less (Singh et al., 1982). Of the seven cities included in these short-term studies, the highest concentration never exceeded 0.1 ppb (Singh et al., 1982). In another study measuring selected airborne volatile organics in three New Jersey locations, 9 out of 38 samples taken in Newark, NJ had detectable levels of tetrachloroethane (Harkov, 1983). The geometric mean of tetrachloroethane concentration in Newark was 0.01 ppb whereas the mean was zero for the two other NJ sites.

Tetrachloroethane has also been detected in groundwater and surface water supplies. Investigations conducted in New Jersey reported 67 out of 608 surface water samples had detectable levels of tetrachloroethane, the highest level reaching 3.0 ppb (Page, 1981). Groundwater analysis found that 64/1072 NJ wells had quantifiable levels of tetrachloroethane with the maximum concentration reported at 2.7 ppb (Page, 1981). The researchers ensured that both the groundwater and surface water samples were taken from every NJ county, that samples represented urban, suburban and rural areas, and that areas of different common land uses (such as farming, industrial, residential etc.) were included. In addition, the study drew upon an equal number of sites from rural areas as from more developed areas (including industrial areas or locations near landfills) (Page, 1981).

A 1976 U.S. EPA report noted that tetrachloroethane was found in three drinking water samples, effluent released from three different chemical plants, and a sewage treatment facility (Shackelford and Keith, 1976). Levels of tetrachloroethane in tap water have been detected at 0.11 ug/L and in effluent emissions at a level of 2.2 mg/l (IARC, 1979).

METABOLISM AND PHARMACOKINETICS

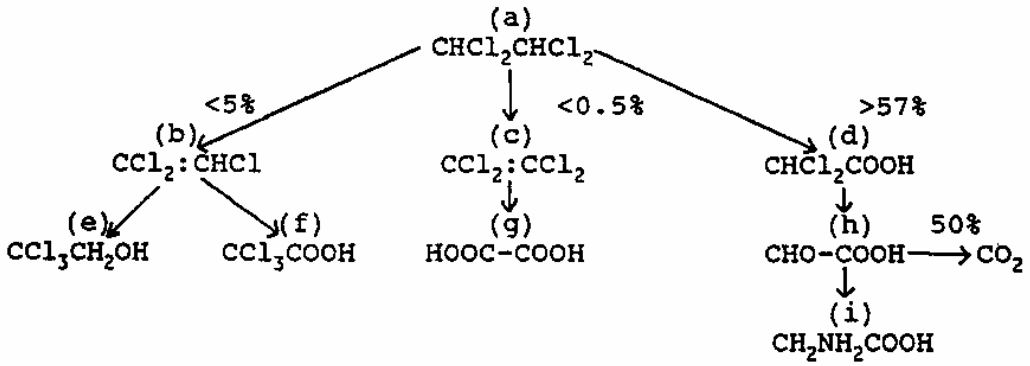
Absorption

1,1,2,2-tetrachloroethane is readily absorbed through the skin, lungs and the gastrointestinal tract (Gosselin, 1984; Clayton, 1982). In a study with human subjects, it was observed that 97% of the inhaled tetrachloroethane was retained in the lungs one hour after exposure (Morgan, 1970).

Metabolism

Tetrachloroethane is apparently metabolized by hepatic cytochrome P-450 via various step-like processes of hydrolytic cleavages and oxidations (Casciola, 1984; Yllner, 1971). The proposed primary metabolic pathway involves the hydrolytic fission

of C-Cl bonds producing glyoxylic acid and eventually carbon dioxide (Yllner, 1971). Tetrachloroethane can also be dehydrochlorinated via a nonenzymic pathway that leads to the formation of tetrachloroethylene (Yllner, 1971). In addition, <u>in vitro</u> experimentation has shown that trichloroethylene can be generated from the dehydrochlorination of tetrachloroethane which may subsequently act as the precursor to the more excretable metabolites, trichloroacetic acid (TCA) and trichloroethanol (TCE) (Yllner, 1971). Based on these findings, the following metabolic pathway for 1,1,2,2-tetrachloroethane has been suggested (Yllner, 1971):



KEY: (a) tetrachloroethane
(b) trichloroethylene
(c) tetrachloroethylene
(d) dichloroacetic acid
(e) trichloroethanol
(f) trichloroacetic acid
(g) oxalic acid
(h) glyoxylic acid
(i) glycine

<u>Excretion</u>

In a mouse study involving intraperitoneal administration of ^{14}C-labeled tetrachloroethane, it was noted that half of the compound was expired as CO_2 within a three day period (Yllner, 1971). Approximately 4% of the original compound, along with minute amounts of tetrachloroethylene and trichloroethylene, was also expired. About 30% of the injected compound was detected in the urine which contained dichloroacetic acid, trichloroacetic acid, trichloroethanol, oxalic acid, glyoxylic acid and urea. Sixteen percent of the tetrachloroethane remained in the body.

<u>Human Exposure and Body Burden</u>

Human exposure to 1,1,2,2-tetrachloroethane can potentially occur through many routes including ambient air and contaminated water supplies even though this is not a naturally-produced substance. It has been reported that the major source of human exposure to tetrachloroethane is from ambient air near industrial sources (SRC). In addition, the compound has been identified in certain food products, specifically in the volatile flavor components of broiled beef (MacLeod and Coppock, 1976). See

Environmental Exposure section for further discussion of environmental media contamination.

Occupational exposure to this solvent can also occur in toiletry preparations, industrial controls and electrical services industries (NIOSH, 1977). NIOSH estimated in 1977 that approximately 5,000 workers in the U.S. are potentially exposed to tetrachloride (NIOSH, 1977).

HEALTH EFFECTS

Overview

1,1,2,2-tetrachloroethane is a known toxicant to the liver, kidney and central nervous system in both humans and animals. In experimentation with various laboratory species chronically exposed to tetrachloroethane, alterations to the hemopoietic system, testicles, thyroid glands and adrenal glands have been observed. The compound has also been associated with reproductive abnormalities and limited genotoxic activity. In a NCI carcinogenicity bioassay, a significant increase in hepatocellular neoplasms was reported in B6C3F1 mice receiving chronic administrations of tetrachloroethane via gavage although no such association was detected in a test group of Osbourne-Mendel rats.

Human

The acute and chronic toxic effects associated with 1,1,2,2-tetrachloroethane exposure are observed primarily in the liver, gastrointestinal system and the central nervous system, and can occur as a result of ingestion, inhalation or cutaneous absorption. The gastrointestinal and hepatic effects are symptomatically exhibited as nausea, vomiting, gastric pain, jaundice and enlargement of the liver (ILO, 1983). CNS disorders associated with tetrachloroethane exposure include such effects as tremors, vertigo, loss of feeling in extremities and parathesis (NIOSH, 1976). In several cases of occupational overexposure to tetrachloroethane that have resulted in death, post-mortem examinations have revealed pathologic damage in the liver as well as alterations in the kidneys and heart (Willcox, 1915). Liver damage ranged from cell necrosis and fatty degeneration to extreme liver destruction (Willcox, 1915; Lynch, 1967). Tetrachloroethane has also been associated with changes in leukocyte and lymphocyte populations (Fairhall, 1949).

An occupational study of 380 workers exposed to tetrachloroethane during bracelet manufacturing operations in Bombay, India, investigated the health effects associated with dermal and inhalation exposures (Lobo-Mendonca, 1963). The author estimated that the average breathing zone concentration of tetrachloroethane ranged between 9-98 ppm (60-670 mg/m^3) with the majority of samples between 20 and 65 ppm (140-450 mg/m^3). The

epidemiological study reported gastrointestinal and neurological complaints including anorexia, abdominal pain, an increased incidence of nervous complaints and a finding that 35% of the exposed worker population experienced fine tremors of the fingers. The study was limited by incomplete environmental data, a highly transitory population and reported symptoms that are related to many common ailments.

In another epidemiology study investigating the effects of tetrachloroethane on workers in a penicillin factory, investigators reported gastrointestinal-related disorders in 31% of the exposed population (Jeney, 1957). Shortly after the plant opened in 1952, liver disorders began appearing in workers resulting in various administrative and engineering controls to be enacted over a three year period while the health study was conducted. Air samples within the facility ranged from 1.5 to 247 ppm depending upon the location and ventilation system available. No neurological disorders were reported but adverse symptoms noted included loss of appetite, epigastric pain and headaches. Thymol coagulation tests for liver dysfunction showed a correlation between positive results and duration of employment at the penicillin factory. The authors believed that even the lowest concentrations of tetrachloroethane caused liver damage (Jeney, 1957).

ANIMAL

Acute

The oral LD_{50} with rats for 1,1,2,2-tetrachloroethane is 250 mg/kg (Gohlke, et al. 1977). A dermal LD_{50} with rabbits was reported at 6.38 g/kg (Smyth et al., 1969). Acute exposure to tetrachloroethane in test animals causes central nervous system depression and liver damage (NIOSH, 1976; IARC, 1979).

Chronic

Schmidt investigated the low-level chronic toxic effects associated with inhalation of tetrachloroethane in a 9-month study with 210 male rats. 105 Of the rats were exposed, on the average, to 13.3 mg/m^3 (1.94 ppm) for 4 hours per day while another 105 male rats received "air only" exposure as controls (Schmidt, 1972). Between the 90th and 170th day of the study, the exposed rats weighed significantly less than controls (415 ± 5.3g versus 435 ± 4.9g) but after 265 days, wide variations in body weight were reported and a significant difference was no longer observed. After the 265 day exposure period, histological examination revealed that the total fat count of the liver was increased approximately 34% in the exposed group as compared to the controls.

In another chronic inhalation toxicity study, Navrotskiy (1971) tested the hypothesis that continual exposure to low concentrations of tetrachloroethane would alter the blood chemistry

of exposed species. 350 Rats and rabbits were exposed at 2, 10 or 100 mg/m^3 (0.3, 1.46, or 14.6 ppm) for 3-4 hours /day for 7-11 months. While the authors provided limited evidence on the experimental design as well as the test results, several important observations were reported. At the 100 mg/m^3 dose level, a wide range of changes were reported in rabbits including, increased total serum proteins, decreased hemoglobin levels, and reduced erythrocyte counts. An apparent dose-response relationship was seen in the suppression of hemagglutinin levels and the phasic fluctuations in acetylcholine content and cholinesterase activity. No effects were reported in rabbits exposed to 0.3 ppm tetrachloroethane. At autopsy, rabbits exposed to 14.6 ppm showed signs of developing liver and kidney degeneration (Navrotskiy, 1971).

Gohlke et al. (1976) investigated the chronic effects associated with tetrachloroethane via stomach intubation in male albino rats. For a 25 week period, groups of 10 test animals each were exposed to doses of 3.2 or 8 mg/kg body weight of tetrachloroethane in 5 ml/kg peanut oil/gavage. Another group was treated with peanut oil only while an additional control group did not receive any treatment. In a two week follow-up period, all rodents were examined by histological and enzyme histochemistry techniques. Even at the dosing level of 3.2 mg/kg body weight, damage was seen in the kidneys, testicles, liver, thyroid glands and adrenal glands. Inflammation of the liver and kidney in addition to irreparable testicular and thyroid gland changes continued throughout the observation period (Gohlke, 1976). While the authors considered the 3.2 mg/kg dose as a chronic threshold dose, it would be more appropriately considered as the lowest observed effect level.

Reproductive, Embryotoxic and Teratogenic

An investigation involving pregnant AB-Jena and DBA strain mice treated with high levels of 1,1,2,2-tetrachloroethane revealed that the compound is associated with reproductive abnormalities. Specifically, embryotoxicity and a low incidence of malformations (exencephaly, cleft palate, anophthalmia, and fused ribs and vertebrae) were reported at dosings of 300-400 mg/kg bw/day of 1,1,2,2-tetrachloroethane during organogenesis (Schmidt, 1976). An earlier 9-month chronic inhalation study by Schmidt found neither an effect on the male reproductive capacity nor any macroscopic malformations in the offspring of 7 male rats exposed to 1.94 ppm tetrachloroethane for 4 hours daily, as compared to controls (Schmidt, 1972).

Behavioral and Central Nervous System

Studies indicate that mice exposed to highly acute levels of tetrachloroethane vapors (beginning at doses of approximately 1,020 ppm) can lead to central nervous system disturbances, ranging from

prostration to loss of reflexes (Lazarew, 1929; Pantelitsch, 1933). Both a 9 month inhalation study and a chronic subcutaneous injection experiment on separate individual adult male cynomolgus monkeys involving high levels of tetrachloroethane (vapor: ranged 1,000-4,000 ppm; injection: 1-5 ml) produced CNS depression in the test animals (Horiuchi, 1962).

Genetic

The limited activity of 1,1,2,2-tetrachloroethane in short-term genotoxic tests is summarized in Table 1. One study reported the compound as mutagenic in Salmonella typhimurium strains TA 1530 and TA 1535 but not in TA 1538 which indicates that tetrachloroethane induces base-substitution mutations only (Brem et al., 1974). Other gene mutation studies have found negative results in Drosophila melanogaster sex-linked recessive lethal mutation and the reciprocal translocation tests (Woodruff et al., 1985). Tetrachloroethane did not induce chromosome aberrations in Chinese hamster ovary cells with or without a rat liver metabolic activation system but did cause sister chromatid exchanges in both test conditions. It is of interest to note that tetrachloroethane did not induce DNA-modifying activity with either rat or mouse hepatocytes (Williams, 1983).

Table 1: Summary of the In Vitro Testing of 1,1,2,2-tetrachloroethane's Genotoxic Activity

End Point	Test System	Results (activation) with	Results (activation) without	References
Gene Mutation	Yeast	nt	+	Callen, 1980
	S. typhimurium	-	-	Mitoma, 1984
		-	-	Nestman, 1980
		nt	+	Brem, 1974
	Drosophila	nt	-	Woodruff,1985 McGregor,1980
Chromosomal aberrations	Chinese hamster ovary cells	-	-	Galloway,1987
Sister Chromatid exchange	Chinese hamster ovary cells	+	+	Galloway,1987
Cell transformation	BALB/c 3T3 mouse cells	nt	-	Tu, 1985
Cell injury	ELD ascites	nt	-	Holmberg and

	tumor cells			Malmfors,1974
DNA growth,	E. coli	nt	+	Rosenkranz,1977 Brem, 1974
	rat hepatocytes	nt	-	Williams, 1983
	mouse hepatocytes	nt	-	Williams, 1983
	human embryonic intestinal cells	-	nt	McGregor, 1980

KEY: nt = not tested

Carcinogenicity

In 1978, the National Cancer Institute (NCI) conducted a bioassay for possible carcinogenicity of technical grade 1,1,2,2-tetrachloroethane using Osborne-Mendel rats and B6C3F1 mice. Over a 78 week period, tetrachloroethane was administered by gavage at two different dose levels to two groups of 50 male and 50 female for each rodent species. The high and low time-weighted average dosages were, respectively, 108 and 62 mg/kg/day for the male rats, 76 and 43 mg/kg/day for female rats and 282 and 142 mg/kg/day for both sexes of mice. Two groups of twenty animals from each species and sex were used as untreated and vehicle (corn oil intubation) controls (NCI, 1978).

The NCI study found no statistically significant incidence of neoplasms in either the male or female rats. However, it was noted that two hepatocellular carcinomas and one neoplastic nodule, which are rare tumors for male Osborne-Mendel rats, were observed in the high dose males. In comparison, a highly significant dose-related incidence of liver carcinomas were reported for both the male and female mice. As a result, 1,1,2,2-tetrachloroethane is considered an liver carcinogen in B6C3F1 mice of both sexes whereas there is inconclusive evidence concerning the compound's carcinogenicity in Osborne-Mendel rats (NCI, 1978).

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

The only study available which provides information on the carcinogenicity of tetrachloroethane is the National Cancer Institute's rodent bioassay which reported that the compound is a liver carcinogen in both sexes of B6C3F1 mice but that there was no evidence of carcinogenicity in the Osborne-Mendel rat strain. It should be noted that there is considerable debate over the validity of liver tumors in B6C3F1 mice (U.S. EPA, 1987). Given that there is limited animal evidence and no human data available, tetrachloroethane is catagorized as a possible human carcinogen (Group C; U.S. EPA, 1987)(Group II; NJDWQI, 1987). Based on this classification, a systemic toxic endpoint and a carcinogenic safety

factor are used for conducting the risk assessment.

There are two studies which may be useful for assessing the health affects of 1,1,2,2-tetrachloroethane. Since the Gohlke gavage study most closely reflects the human oral route of exposure, it is the preferred study for establishing a health-based MCL. Because it is uncertain whether the lowest dose used in the Gohlke study is a NOAEL or a LOAEL, the inhalation study by Schmidt may also be considered. For each of these investigations, a maximum contaminant level for drinking water in ug/L was derived.

The chronic study by Gohlke et al. (1976) involved stomach intubation of tetrachloroethane into groups of ten male albino rats for a 25 week period. Histological changes in the liver, kidney, testicles, thyroid glands and adrenal glands was observed in both dosage levels of 8 and 3.2 mg/kg, with 3.2 representing the lowest observed adverse effect level (LOAEL).

The Schmidt chronic inhalation study (Schmidt, 1972) with rats reported a significant increase in the fatty content of the liver in the exposed group over the controls. The rats received an average concentration of tetrachloroethane of 13.3 mg/m^3 for 4 hours per day, seven days per week.

Calculations of the Health-Based Maximum Contaminant Level Using the Gohlke (1976) Study

Using the findings of the Gohlke study the Acceptable Daily Intake (ADI) was determined by the following calculations:

$$ADI = \frac{(LOAEL)(d)}{(CF)(UF)(SF)} = \frac{(3.2\ mg/kg)(5/7)}{(10)(100)(10)} = 0.00023\ mg/kg/day$$

whereby; LOAEL = Lowest Observable Adverse Effect Level

d = Conversion of 5 day/week exposure to 7 day/week exposure: 5/7

CF = Conversion Factor from a LOAEL to a No Observable Adverse Effect Level (NOAEL)

UF = Uncertainty Factor appropriate for use with a NOAEL from a chronic study

SF = Safety Factor of 10 used in a systemic toxicity risk assessment for a Group C carcinogen (US EPA, 1985).

$$MCL = \frac{(ADI)(DW)(AAW)}{(DWC)} = \frac{(0.00023\ mg/kg/day)(0.2)(70\ kg)}{(2\ L/day)}$$

MCL = 0.00161 mg/L
= 1.6 ug/L

whereby: ADI = Acceptable Daily Intake

DW = Contribution from drinking water alone

AAW = Assumed weight of an adult human

DWC = Assumed daily drinking water consumption

Calculation of the Health-Based Maximum Contaminant Level Using the Schmidt (1972) Study

A LOAEL from the study by Schmidt et al. (1972) was also used to derive a potential MCL value. Since this study was based on inhalation of 1,1,2,2-tetrachloroethane, a route-to-route extrapolation is necessary to convert the inhalation dose received to an equivalent effective oral dose in the test species. The U.S. EPA (1984) has outlined a method to convert inhalation dose to an absorbed dose in the rat. This procedure is presented below, illustrating the equations used to estimate the rat respiratory and absorbed rates in the Schmidt study which is then extrapolated to an absorbed dose (ADI) in the human. This value is subsequently used to determine a potential MCL.

Estimation of Rodent Absorbed Dose

In order to determine the absorbed dose, the breathing rate for this laboratory test animals must be estimated. The formula for estimating the rat respiratory rate represents a surface area proportionality whereby;

Respiratory rate = RR = $(0.105)(BW/0.113)^{2/3}$ m^3/d (Anderson et al., 1977)

For the estimation of the absorbed dose in the Schmidt (1972) study;

RR = $(0.105)(0.415/0.113)^{2/3}$ m^3/d = 0.250 m/d

Therefore;

$$AD = \frac{(LOAEL)(EP)(A)(RR)}{(BW)} = \frac{(13.3\ mg/m^3)(4\ hr/24\ hr)(1)(0.250\ m^3/d)}{0.415\ kg}$$

AD = 1.34 mg/kg/day

whereby;

BW = body weight of rats = 0.415 kg

in Schmidt study at 110 days into a 265 day study (no experimental information on BW at the conclusion of study)

AD = Absorbed Dose in the rat

EP = study exposure period in hours per day (7 days per week)

A = Pulmonary absorption factor, based on Morgan, 1970 where absorption was reported at 97% = 100%

RR = Respiratory rate for rats

Extrapolation to an ADI in humans

$$ADI = \frac{AD}{(OAF)(SF)(UF)(CF)} = \frac{1.34\ mg/kg/day}{(1)(10)(100)(10)}$$

= 0.000134 mg/kg/day

whereby;

ADI = Acceptable Daily Intake for humans

OAF = Oral absorption factor, assumed to be 100%

CF = Conversion Factor from a LOAEL to a No Observable Adverse Effect Level (NOAEL)

UF = Uncertainty Factor appropriate for with a NOAEL from a chronic study

SF = Safety Factor of 10 used in a systemic toxicity risk assessment for a Group C carcinogen (US EPA, 1985).

$$MCL = \frac{(ADI)(DW)(AAW)}{(DWC)} = \frac{(0.000134\ mg/kg/day)(0.2)(70\ kg)}{(2\ L/day)}$$

= 0.000938 mg/L
= 0.938 ug/L

whereby: ADI = Acceptable Daily Intake

DW = Contribution from drinking water alone

AAW = Assumed weight of an adult human

DWC = Assumed daily drinking water consumption

Assumptions and Uncertainty

Derivation of the health-based MCL is based on the assumption that 1,1,2,2-tetrachloroethane is a possible carcinogen (NJDWQI Group II; EPA Group C) and therefore the risk assessment uses a systemic toxic endpoint with an additional safety factor for possible carcinogenicity. For the purposes of this risk assessment, liver damage represented the primary toxic endpoint since both animal studies and human case studies have reported hepatic alterations as a result of tetrachloroethane exposure. In order to account for a carcinogenic potential, a safety factor of 10 is incorporated into the determination of the ADI.

Extrapolation from rodent studies to human values relies upon the following assumptions; that an adult human consumes 2 liters of water per day and that 20% of the drinking water contributes to the total human exposure of tetrachloroethane.

Both studies were used for the purposes of deriving a drinking water standard for tetrachloroethane because of their limitations and complementary nature. While the Schmidt study has the lower LOAEL, it is limited in its applicability because of the test's inhalation route of exposure and the minimal information on experimental protocols. For instance, the authors did not provide details on final body weights so that the estimation of the rat respiratory rate was based on the mid-study weight rather than a final weight. The Gohlke gavage study is more applicable as an oral exposure study, but is limited by the fact that the investigation's lowest dose was not a NOAEL. In the final analysis, the risk assessments conducted with each study provided values within the same order of magnitude and thereby confirmed that a MCL of 1 ppb is an appropriate health-based maximum contaminant level.

Conclusion

A health-based MCL of 1 ug/L for 1,1,2,2-tetrachloroethane was derived to protect against possible liver toxicity and carcinogenicity.

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1,1,2-TRICHLOROETHANE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL

Division of Science and Research
New Jersey Department of Environmental Protection

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EXECUTIVE SUMMARY

1,1,2-trichloroethane (1,1,2-TCE) is primarily used as a feedstock intermediate in the production of 1,1-dichloroethylene. Human exposures to 1,1,2-TCE occur from ambient air and drinking water. Acute exposure to 1,1,2-TCE in human results in central nervous system (CNS) depression and irritation of eyes and skin, while possible damage to kidney, lung, and gastrointestinal (GI) tract may result from long term exposure. A health-based maximum contaminant level (MCL) of 2.7 ug/L is proposed for 1,1,2-TCE to protect from liver damage and depressed immune status.

BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties

Chemical name	1,1,2-Trichloroethane
Synonyms	Ethane Trichloride NCI-C04579 RCRA Waste Number U227 RCRA Waste Number U359 beta-T beta-Trichloroethane 1,1,2-Trichlorethane 1,2,2-Trichloroethane Trojchloroetan (1,1,2) (Polish) Vinyl trichloride
Trade Names	beta-T
CASRN	79-00-5
Chemical formula	C_2-H_3-Cl_3
Chemical structure	
Molecular weight	133.42
Dissociation constant	Not available
Physical state	Colorless liquid
Melting point	-36.5° C
Boiling point	113.8°C at 760 MM Hg
Specific gravity, density	1.4416 at 20° C/ 4° C
Taste threshold in water	Not available

Water-odor threshold	Not available
Air-odor threshold	Not available
Odor threshold (air)	Not available
Conversion factor	1 mg/l is equivalent to 183 ppm and 1 ppm is equivalent to 5.46 mg/m^3 at 25° C, 760 Torr
Water solubility	0.44g/100g water at 20° C
Octanol/water partition	2.17

Production and Use

Production

1,1,2-Trichloroethane (1,1,2-TCE) is produced in the U.S. directly or indirectly from ethylene and as a co-product in the manufacture of other chlorinated hydrocarbons. Dow Chemical is the sole producer of 1,1,2-TCE (U.S. International Trade Commission, 1979). The quantity produced is proprietary information.

Use

1,1,2-TCE is primarily used as a feedstock intermediate in the production of 1,1-dichloroethylene (vinylidene chloride) (Archer, 1979). It is also used in adhesives and lacquer, production of teflon tubing, and coating formulations. Other uses are as a solvent for chlorinated rubbers and polyesters, fats, waxes and natural resins (Hawley, 1981).

Guidelines, Regulations, and Standards

The American Conference of Governmental Industrial Hygienists (ACGIH, 1988) recommended a threshold limit value (TLV) of 10 ppm (45 mg/m^3) and a short-term exposure limit (STEL) of 20 ppm (111 mg/m^3) for 1,1,2-TCE. The Occupational Safety and Health Administration (OSHA) recommended a standard of 10 ppm (45 mg/m^3) for 1,1,2-TCE (CFR, 1985).

The EPA's water quality criteria for protection of human health is 6 ug/l (10^{-5} risk level) (U.S. EPA, 1980).

ENVIRONMENTAL EXPOSURE

Fate and Transport

1,1,2-TCE may enter the atmosphere from its use in the

manufacture of 1,1-dichloroethylene and its use as a solvent. It may also be discharged in wastewater associated with these uses. Releases to water is primarily lost through evaporation (half-life of days to weeks) (Zoeteman et al, 1989). Once in the atmosphere, 1,1,2-TCE photodegrades by reaction with hydroxyl radicals (half-life of 24 days in unpolluted atmospheres to a few days in polluted atmospheres). 1,1,2-TCE has a low soil partition coefficient and will therefore not partition into sediment, but likely pass through soil into the groundwater where biodegradation is unlikely to occur. 1,1,2-TCE does not bioconcentrate well (Wilson et al, 1981; Wilson et al, 1983).

Ambient Levels

In New Jersey drinking water samples 1,1,2-TCE was detected at levels ranging from 1 to 34 ppb. Twenty-three of 29 samples containing 1,1,2-TCE were found in samples from the Hawthorne Water Department (A-280 sampling, 1986).

1,1,2-TCE was also detected in 53 to 603 samples in representative New Jersey surface water, with a maximum level of 18.7 ppb (Page, 1981). In groundwater 1,1,2-TCE was detected in 72 of 1069 samples in New Jersey (maximum level of 31.1 ppb), with some of the high levels being detected under urban land use areas (Page, 1981; Greenberg et al, 1982).

1,1,2-TCE has been detected in the atmosphere in New Jersey cities (0.01 to 0.037 ppb) but is not very prevalent (9 of 263 samples were positive in one study) (Harkov et al, 1981; Harkov et al, 1983; Lioy et al, 1983).

METABOLISM AND PHARMACOKINETICS

Absorption

Available pharmacokinetic data indicate that 1,1,2-TCE is readily absorbed from injection sites, skin, gastrointestinal (GI) tract and the lungs of man and animals (ACGIH, 1979).

Distribution

Little information was found in the available literature regarding the distribution of 1,1,2-TCE to individual tissues. In a study conducted by Mitoma et al. (1985) rats and mice were given 1,1,2-TCE by gavage for 4 weeks, followed by a single dose of [^{14}]C-1,1,2-TCE. Two days after treatment, carcass levels of radioactivity were found ranging from 2.3 to 3.9% of the administered dose.

Metabolism

1,1,2-TCE has been demonstrated to be metabolized by the

hepatic cytochrome p-450 system. The urinary metabolic products of 1,1,2-TCE *in vivo* have been identified as thiodiacetic acid, mono-, di-, and tri- chloroacetic acid, as well as mono-, di-, and tri- chloroethanol (Yllner, 1971; Ivanetich and Van Den Honert, 1981).

Excretion

In laboratory animals rapid excretion of 73-87% of an absorbed dose occurs via the urine, 6-8% is expired unchanged while the rest is expired as carbon dioxide (IARC, 1979).

Human Exposure and Body Burden

Occupational exposures to 1,1,2-TCE occur in the blast furnace and steel mill, telephone communication, engineering and scientific instrument manufacturing industries (IARC, 1979). The general population may be exposed to 1,1,2-TCE from ambient air in the vicinity of industrial sources, and from contaminated drinking water. Major exposure routes are inhalation, dermal absorption and ingestion (US EPA, 1980).

HEALTH EFFECTS

Overview

Acute exposure to 1,1,2-TCE in humans appears to be characterized by a narcotic effect on the central nervous system (CNS) and eye, skin and GI tract irritation, while possible kidney, lung, and GI damage may result from long term exposure. In animals 1,1,2-TCE has been shown to cause CNS depression and damage to the liver and kidney following single intraperitoneal injections. Studies investigating the chronic toxicity, carcinogenicity, mutagenicity or teratogenicity of 1,1,2-TCE are very limited. However, chronic exposure of experimental animals to 1,1,2-TCE has been reported to result in immunotoxicity, carcinogenicity, and hepatotoxicity characterized by altered hepatic enzyme activities. 1,1,2-TCE has been classified by U.S. EPA as a possible human carcinogen (Group C).

Human

Acute exposure of humans to 1,1,2-TCE results in increased blood flow to the skin, irritation of the respiratory tract and eyes, visual and GI disturbances and CNS depression (Hardie, 1964; Wahlberg, 1984a; Wahlberg, 1984b).

Long-term exposure to 1,1,2-TCE vapors resulted in chronic gastritis, fat deposition in the kidneys and damage to the lungs (Hardie, 1964).

Animal

Acute

Animals exposed to high concentrations show local irritation of eyes and mucous membranes, loss of tendon reflexes and death due to respiratory arrest (Gosselin et al, 1984). Hepatotoxicity as indicated by increased serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) activities (Tyson et al., 1983), and serum lactate dehydrogenase (White et al., 1985) was reported. Fatty degeneration with central necrosis of the liver and inflammation of the GI tract as a result of acute 1,1,2-TCE exposure were also reported (Wright and Schaffer, 1932).

The oral LD_{50} in rats range from 100 to 835 mg/kg body weight (Verschueren, 1983; White et al., 1985; Lundberg et al., 1986; Smyth et al., 1969).

Subchronic/Chronic

In a 90-day study, White et al.(1985) administered 1,1,2-TCE (95% purity) in drinking water to CD-1 mice of both sexes (16/sex) at levels of 20, 200 and 2,000 mg/l for 90 days. Control groups consisted of 24 mice/sex. Based on fluid consumption and body weight data, average intakes were determined to be 0, 4.4, 46 and 305 mg/kg/day for males and 0, 3.9, 44 and 384 mg/kg/day for females. Fluid consumption, organ weights, hematology, serum chemistry and hepatic microsomal activity were monitored. Fluid consumption in high-dose males was depressed 30%. High-dose females had reduced hemoglobin and hematocrit values and both sexes had altered serum chemistries indicating liver injury. In high-dose females, these changes included significant increases in levels of liver glutathione, SGOT, SGPT, serum alkaline phosphatase (SAP), fibrinogen levels and liver weight, both absolute and as % body weight. The SGOT, SAP and fibrinogen levels were significantly increased at all dose levels but the increase was not dose-dependent. In mid- and high-dose males, a significant decrease was found in liver glutathione level and absolute weights of liver and kidney, while a significant increase in SAP was found in high-dose animals. While hepatic microsomal activities were not affected at any dose in male mice, mid- and high-dose females had a significant increase in cytochrome P-450 content and aniline hydroxylase activity.

In the second phase of the study conducted by White et al. (1985), Sanders et al. assessed immunological effects of 1,1,2-TCE (Sanders et al, 1985). Humoral immune status was elevated by enumeration of IgM antibody forming cells (AFC) against sheep erythrocytes (sRBC), measurement of hemagglutinuation titers, and evaluation of spleen lymphocyte responsiveness to lipopolysaccharides (LPS). Cell-mediated immune status was

evaluated by the delayed-type hypersensitivity (DTH) and popliteal lymph node proliferation responses to sRBC. Cell-mediated immunity was unaltered in both sexes by 1,1,2-TCE exposure at any levels. Hemagglutination depression, on the other hand, was observed in both sexes in the mid- and high-dose groups. Macrophage function was depressed only in the high-dose males. Spleen lymphocyte responsiveness to the B cell mitogen, LPS, was unaltered in males, but was significantly decreased in high-dose females. Females also exhibited a greater degree of hemagglutination depression than males following exposure to 1,1,2-TCE.

NCI (1978) administered 1,1,2-TCE in corn oil to Osborne-Mendel rats and B6C3F1 mice of both sexes (50/sex) by gavage for 5 days/week for 78 weeks, followed by a 13-week (in mice) to 35-week (in rats) observation period. Rats and mice were exposed to time-weighted average doses of 0, 46 or 92 mg/kg/day and 0, 195 or 390 mg/kg/day, respectively. No non-neoplastic, dose-related changes were reported for either sex of either species. However, treated rats had hunched appearance, rough fur, urine stains on abdomen, dyspnea, and squinted eyes with reddish exudate in the latter part of the study. These signs were also noted in control rats. Treated mice did not show any abnormal clinical signs other than abdominal distention which was later determined to be due to liver tumors (see carcinogenicity Section).

Reproductive, Embryonic and Teratogenic

Available information in the literature does not indicate reproductive, embryonic or teratogenic effects produced by 1,1,2-TCE exposure.

Seidenberg et al. (1986) screened 1,1,2-TCE for developmental toxicity using Chernoff/Kavlock development toxicity screen. 1,1,2-TCE at 350 mg/kg/day (in corn oil) was administered by gavage to pregnant ICT/SIM mice on gestation days 8 to 12. Maternal mortality occurred in 3 of 30 cases. No significant effects on litter size, pup survival, or pup weights were observed.

The embryotoxic effects of 1,1,2-TCE on chick embryos was studied by Elovaara et al., (1979). A solution of 0.6 to 13.3 ug of 1,1,2-TCE/egg were injected into air space of fertilized chicken eggs at 2, 3, or 6 days of incubation. A dose-dependent survival of the embryos at day 14 was noted regardless of the day of treatment. Macroscopic malformations of various kinds were produced at all doses. However, the lack of anatomic and physiologic maternal-fetal relationships renders it unsuitable for assessing potential teratogenic risks to humans.

Behavioral and Central Nervous System

No studies concerning behavioral effects of 1,1,2-TCE were found in the literature. 1,1,2-TCE has a narcotic action at low concentrations.

Genetic

Available information on genetic effects of 1,1,2-TCE did not strongly indicate mutagenicity of this chemical.

Barber et al. (1981), Simmon et al. (1971) and Rannug et al., (1978) reported that 1,1,2-TCE was not mutagenic in the Salmonella typhimurium tests. Tu et al. (1985) reported weakly positive results for 1,1,2-TCE in the BALB/C-3T3 cell transformation assay. DiRenzo et al. (1982) and Mazzullo et al. (1986) reported covalent binding of 1,1,2-TCE to DNA of animal tissues in vitro and in vivo, respectively.

Carcinogenicity

NCI (1978) conducted a cancer bioassay for 1,1,2-TCE in rats and mice. Technical grade (purity 91-99%) 1,1,2-TCE in corn oil was administered by gavage to Osborne-Mendel rats (50/sex) and B6C3F1 mice (50/sex) 5 days/week for 78 weeks. The rats and mice were observed for an additional 35 and 13 weeks, respectively. The low and high time-weighted average doses were 46 and 92 mg/kg/day for rats and 195 and 390 mg/kg/day for mice. Two groups of control animals consisted of untreated and vehicle-treated (by gavage) rats and mice (20/sex).

No statistically significant increased incidence in tumors at any site was observed in rats. However, the investigators indicated the possibility that the rats may not have received the dosage approximating the maximum tolerated dosage (NCI, 1978).

A statistically significant ($p<0.001$), dose-related increase in hepatocellular carcinomas in mice was observed. Both male and female developed a significant increase in the incidence of hepatocellular carcinoma ($p<0.001$). Hepatocellular carcinomas were observed in 2 of 20 (10%) vehicle control males, 18 of 49 (37%) low-dose males, and 37 of 49 (76%) high-dose males. In females, hepatocellular carcinomas were seen in 0 of 20 vehicle control mice, 16 of 48 (33%) low-dose mice, and 40 of 45 (89%) high-dose mice. Time to first observed hepatocellular carcinomas was also markedly decreased in high-dose mice when compared to vehicle controls (NCI, 1978).

A positive dose-related association between 1,1,2-TCE administration and the incidence of adrenal gland pheochromocytomas in mice of both sexes was indicated by the Cochran-Armitage test. Fisher exact tests confirmed these results for high-dose female mice but not for other groups. It was concluded that under the conditions of the bioassay, 1,1,2-

TCE was carcinogenic in B6C3F1 mice, causing hepatocellular carcinoma and adrenal pheochromocytomas (NCI, 1978).

Norpoth et al. (1988) treated two groups of male and female Sprague-Dawley rats (50/group/sex) with either 15.37 or 46.77 umole of 1,1,2-TCE in DMSO/rat by subcutaneous injection, once a week for 2 years. Two control groups received either DMSO or no treatment at all. High-dose animals developed significantly higher incidence of sarcomas when compared with the untreated controls. However, such a tumor incidence was not statistically significant when compared with the DMSO-treated controls. The investigators questioned their own findings based on the fact that they did not find spontaneous incidence of sarcomas among the untreated controls unlike what has been reported for the historical controls in the literature.

1,1,2-TCE has been classified as a possible human carcinogen (U.S. EPA Group C). Hepatocellular carcinomas and pheochromocytomas in one strain of mice (of both sexes) forms the basis for this classification (U.S. EPA, 1984).

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

Since 1,1,2-TCE is a possible human carcinogen (New Jersey Category 3), only non-carcinogenetic risk assessment will be performed to derive an acceptable level in the drinking water.

In the study conducted by NCI (1978) 1,1,2-TCE was administered to rats and mice by gavage for 78 weeks and the animals were observed for additional 13 weeks (in mice) to 35 weeks (in rats). Although as the study approached termination increasing numbers of treated rats showed clinical signs such as hunched appearance, rough fur, and dyspnea, these signs were also found in control rats. Thus it is difficult to determine whether these signs were induced by 1,1,2-TCE. This study was therefore judged inappropriate for deriving drinking water guidelines.

The 90-day mouse study conducted by White et al. (1985) reported altered hepatic enzyme activities in mice as a result of 1,1,2-TCE exposure in drinking water. In this study, the lowest-observed-adverse-effect level (LOAEL) seen in females was 44 mg/kg/day, which resulted in a reduction of cytochrome P-450 levels and aniline hydroxylase activity and an increase in SGOT, SAP and fibrinogen. In males, the LOAEL was 46 mg/kg/day, based on a reduction of liver glutathione levels. A no-observed-adverse-effect-level (NOAEL) of 4.4 and 3.9 mg/kg/day was identified in males and females, respectively. In the second phase of this study, alterations in immunologic response were also reported (Sanders et al., 1985). A NOAEL of 4.4 mg/kg/day for males and 3.9 mg/kg/day for females was identified. This

study was judged appropriate for the development of drinking water guidelines and was used to determine the health-based maximum contaminant level (MCL). A NOAEL of 3.9 mg/kg/day was identified for female mice based on altered activities of hepatic enzymes and depressed immunologic response.

Calculation of the Health-Based Maximum Contaminant Level

The 90-day mouse studies by White et al. (1985) and Sanders et al. (1985) were used for the determination of the MCL. A NOAEL of 3.9 mg/kg/day was identified for female mice. An additional uncertainty factor was used to account for a less-than-lifetime exposure.

$$\text{Acceptable Daily Intake (ADI)} = \frac{(3.9\ \text{mg/kg/day})}{(100)\ (10)}$$

$$= 0.0039\ \text{mg/kg/day}$$

where

3.9 mg/kg/day = NOAEL

100 = uncertainty factor appropriate for use with a NOAEL from a chronic animal study

10 = uncertainty factor to compensate for less-than-lifetime exposure

$$\text{MCL} = \frac{(0.0039\ \text{mg/kg/day})\ (0.2)\ (70\ \text{kg})}{(2\ \text{L/day})\ (10)}$$

$$= 0.0027\ \text{mg/L} = 2.7\ \text{ug/L}$$

where

0.2 = relative source contribution from *drinking* water

70 kg = assumed weight of an adult human

2 L/day = assumed water consumption by an adult

10 = additional safety factor to account for possible carcinogenicity of Group C carcinogens

Assumptions and Uncertainty

It is assumed that the mouse is a suitable model of 1,1,2-TCE effects in man. It is also assumed that a 70 kg adult consumes 2 liters of drinking water per day and 20% of the exposure to 1,1,2-TCE is through drinking water.

Conclusions

A health-based MCL for 1,1,2-TCE in drinking water of 2.7 ug/L has been derived, based on hepatotoxicitiy and immunotoxicity in chronically exposed mice.

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2,4,6-TRICHLOROPHENOL
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Division of Science and Research

New Jersey Department of Environmental Protection

May 4, 1989

Prepared by
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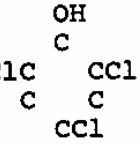
EXECUTIVE SUMMARY

2,4,6-Trichlorophenol (TCP) is prepared by the direct chlorination of phenol and was used as an intermediate for dyestuffs and pesticides. It is often contaminated with other toxic chlorinated phenol products including dibenzo-dioxins and dibenzo-furans. Water contamination by TCP results from chlorination of phenol in natural waters or in primary or secondary effluents of waste treatment plants, direct addition of chemicals to waterways, degradation products of chemicals in the water, wet and dry atmospheric fallout, or as metabolic byproducts of pesticides such as Lindane. Workers have been exposed to TCP in hospitals, the leather tanning and finishing industry, and treated lumber industries. Trichlorophenols produce redness and edema on skin contact and on prolonged contact mild to moderate chemical burns. In the eye they can produce conjunctival irritation and injury to the cornea and iritis. TCP is classified as a probable human carcinogen (U.S.EPA Group B2) and has been shown to induce lymphomas or leukemias in male F344 rats and hepatocellular carcinomas and adenomas in both sexes of B6C3F1 mice. A Health-Based Maximum Contaminant Level of 1 ug/L in drinking water was determined to result in an excess lifetime cancer risk of no more than one in a million.

TABLE OF CONTENTS

BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties (U.S.EPA, 1979; IARC, 1979; or HSDB, 1988 unless otherwise stated)

Synonyms	2,4,6-T Phenol, 2,4,6-Trichloro- Caswell No. 880C Trichlorfenol
Trade Names	Dowicide 2S, Omal, Phenachlor
CASRN	88-06-2
Chemical formula	$Cl_3C_6H_2OH$
Chemical structure	
Molecular weight	197.45 (Handbook of Chemistry and Physics, 1986)
Physical state	light pinkish-orange solid (NCI, 1979)
Melting point	69°C (Windholz, 1976)
Boiling point	246°C at 760 mm Hg
Vapor pressure	0.012 mm Hg (estimated) at 25°C (Mabey et al., 1981) 1 mm at 76.5°C (Sax, 1984)
Specific gravity, density	1.4901 at 20°C/ 4°C
Taste threshold in water	2.0 ug/L (U.S.EPA, 1980)
Water solubility	9×10^5 ug/L at 25°C (Roberts et al., 1977)
Log octanol/water partition coefficient	3.87 (U.S. EPA, 1980)
Odor	Strong phenolic odor (The Merck Index, 1983.)

Water-odor threshold	100 - 1,000 ug/L (U.S.EPA, 1980)
Odor threshold (air)	100 ug/L at 30°C; 1,222 ug/L at 25°C. Purity not specified (U.S.EPA 1980)
Bioconcentration factor	389 (estimated) (U.S.EPA, 1980)
Conversion factors	1ppm = 8.06 mg/m^3 1 mg/L = 124 ppm

Production and Use

2,4,6-Trichlorophenol (TCP) is prepared by the direct chlorination of phenol, was used as an intermediate for dyestuffs and pesticides, and is not known to occur naturally (IARC, 1979). TCP production was first reported in the U. S. in 1950 (U. S. Tariff Commission, 1951). At present there is no domestic manufacturer of TCP. In 1979, the U. S. production by two domestic companies was listed at 25,000 kg of the compound (National Toxicology Program, 1984). In 1980, the U. S. imported 250 kg of TCP (U. S. International Trade Commission, 1981). Frequently (TCP) is contaminated with unknown amounts of dibenzo-dioxins and dibenzofurans which could be carcinogenic or cause other adverse effects (IRIS, 1988; IARC, 1986).

TCP can also be produced when water containing phenol or other aromatic acids is treated with hypochlorite, suggesting possible human exposure in treated industrial waste water (Larson and Rockwell, 1977; Eisenhauer, 1964; Smith et al., 1975). TCP is also an end product of Lindane metabolism in mammals (Tanaka et al., 1977; Engst et al., 1976a).

This chemical has been used as a fungicide, bactericide, antiseptic, and preservative for a variety of materials including cloth, paper, glue, and wood products. In 1974, workers exposed to TCP were primarily in hospitals where it was used as a bactericide or in the leather tanning and finishing industry (NIOSH, 1977). Approximately 851 people involved in these two occupations were most at risk from exposure to TCP (NIOSH, 1980; Yoshida et al., 1987; Stanford Research Institute, 1976).

In 1984, the U. S. EPA prepared to cancel most non-wood uses of pentachlorophenol. Since TCP is used primarily as an unisolated intermediate in the production of 2,3,4,6-tetrachlorophenol and pentachlorophenol, this directly impacted the production and use of TCP. In 1978, the U. S. EPA began to prohibit the use of pesticides containing pentachlorophenol (IARC, 1986).

Guidelines, Regulations, and Standards

The U.S.EPA, using criteria proposed by the Carcinogen Assessment Group, classified TCP in Group B2 -Probable Human Carcinogen (Federal Register, 1984).

The International Agency for Research on Cancer (IARC) in 1979 found the available data did not permit an evaluation of the carcinogenicity of 2,4,5- and 2,4,6-trichlorophenol (IARC, 1979). IARC later determined there was limited evidence for carcinogenicity in humans from exposure to chlorophenols (IARC, 1982, 1986).

No occupational exposure standards were located for TCP. However, a related congener compound, pentachlorophenol, has a TWA (time-weighted-average) exposure limit for skin of 0.5 mg/m^3 (ACGIH, 1987).

The Clean Water Act (CWA), Ambient Water Quality Criteria, (based on human health) for water and fish consumption is 1.2 ug/L TCP, and for fish consumption only is 3.6 ug/L TCP (IRIS, 1988).

ENVIRONMENTAL EXPOSURE

Distribution

Industrial waste discharge is the principal point source of TCP water pollution. During the manufacture of chlorophenols and related herbicide compounds, a considerable amount of chemical waste is generated by the incomplete reaction of starting reactants, by-product formation, and incomplete recovery of desired products. Waste from the manufacture of TCP ranged from 2.8 to 19.5 percent. Other possible point sources include chemical spills and washing of drums in which these chemicals are stored. Contamination of water by TCP may be caused by chlorination of phenol present in natural water or in primary or secondary effluents of waste treatment plants, direct addition of chemicals to waterways, degradation products, chemicals in the water, and wet and dry atmospheric fallout (U.S.EPA, 1979).

Fate and Transport

The octanol/water partition coefficient value indicates that TCP may be adsorbed significantly to soils high in organic carbon content. In sandy soils TCP may have significant mobility. However, the significant biodegradability of TCP may prevent substantial accumulation in soil and groundwater due to leaching (U.S. EPA, 1984).

The half-life for TCP is estimated to be less than one day in air, one to 19 days in water, and to be completely biodegraded in soil in five days (Verschueren, 1983). In the presence of activated

sludge, complete ring cleavage of TCP occurred in three days (Ingols, et al., 1966). Degradation of TCP in aerated lagoon effluent was apparently complete within four days (Sidwill, 1971).

Blades-Fillmore (1980) demonstrated that TCP biodegradation was not significant in solvent water columns at concentrations found in Delaware River water (one microgram/liter) but did occur significantly by microorganisms attached to the surface. Presence of other carbon sources decreased TCP degradation by 25 to 40 percent and a 10 degree temperature decrease slowed degradation by factors of 1.4 and 2.3, respectively, for the solvent water interface and water alone. Biodegradation kinetics were related to the initial concentration but not directly proportional and were determined to be neither first nor zero order kinetics.

Many organochlorine compounds are metabolized in mammals to yield higher chlorophenols. Among these compounds that yield TCP by metabolic alterations are the following: alpha-hexachlorocyclohexane (rat)(Koransky et al., 1975; Freal and Chadwick, 1973); beta-hexachlorocyclohexane (rat) (Freal and Chadwick, 1973), (mouse) (Kurihara and Nakajima, 1974); Lindane (gamma-hexachlorocyclohexane) (rat) (Chadwick and Freal, 1972), (mouse) Kurihara and Nakajima, 1974); delta-hexachlorocyclohexane (rat) (Freal and Chadwick, 1973); gamma-2,3,4,5,6-pentachlorocyclohex-1-ene (rat) (Engst et al., 1976); pentachlorobenzene (rat) (Engst et al., 1976); 1,3,5-trichlorobenzene (rabbit) (Kohli et al., 1976). The exact metabolic pathways for these alterations remains unknown.

Ambient Levels

Analysis of 241 New Jersey water samples in the late 70's and early 80's demonstrated TCP in 7.5% of the samples. TCP occurred in 9.2% of the raw water samples, in 9.6% of the finished water samples, and 4.3% of the delivered water samples. Most of the sample concentrations were between 0 and 1 part per billion (ppb) with the highest being 7.3 ppb (NJDEP, unpublished, 1985).

METABOLISM AND PHARMACOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Toxicity data from experimental animals indicate that TCP is readily absorbed from the gastroenteric tract and from parenteral sites of injection. TCP does not penetrate intact rabbit or guinea pig skin (Dow Chemical Company, 1969; Gosselin et al., 1976).

TCP-^{14}C administered to rats by gavage at a level corresponding to 1 ppm in the diet for 15 days reached a plateau in urine and feces after three days. Twenty-eight percent of activity was located on water layer conjugates and 63 percent in chloroform layer of extractables from urine consisted of four trichlorophenol

isomers. These consisted of 2,4,6-TCP, 2,3,6- and 2,4,5- isomers. About 6.5 percent of administered activity was recovered from the feces. Approximately 99 percent of administered dose was recovered by this method. This research demonstrated that TCP is not stored in rats and it is not significantly degraded by rats, rather it is conjugated and to a certain extent isomerized (Bahig, et al., 1981).

Roberts et al. (1977) determined TCP permeates human skin epidermal membranes in vitro. The permeability coefficient of 9.9 cm/min x 10^4 for TCP produced no damage to the skin at any concentration up to the saturation point.

TCP is also an end product of lindane metabolism in mammals (Tanaka et al., 1977). Results of animal studies indicate that TCP is probably eliminated in the urine as conjugates of glucuronide and/ or sulfate. TCP has not been identified in fecal material.

Pekari et al. (1985) reported the half-life for the urinary excretion of TCP in humans averaged 18 hours. TCP occurred in the urine mainly as conjugates. TCP has been shown to bind reversibly to human serum albumin in a manner that is related to lipophilicity (Judis, 1982).

Human Exposure and Body Burden

Humans are primarily exposed to TCP through occupational routes of exposures and secondarily through metabolic breakdown products of certain chlorinated pesticides that result in the formation of TCP.

HEALTH EFFECTS

Overview

No data on the health effects of oral exposure to TCP in humans were found in the literature. Accidental exposure of humans to 4-chlorophenol by inhalation and dermal absorption produced clinical signs of headache, dizziness, respiratory disorder, vomiting, loss of coordination and tremor (Gurova, 1964). Limited evidence suggests that the kidney and liver are target organs for TCP toxicity (U.S. EPA, 1979). The National Cancer Institute reported that TCP in chronic oral studies produced significantly increased dose-related incidence of lymphomas or leukemias in male F344 rats and hepatocellular adenomas or carcinomas in male and female B6C3F1 mice (NCI, 1979).

IARC, (1986) after reviewing all the available human data, concluded that there is limited evidence for the carcinogenicity of occupational exposure to chlorophenols in humans. Based on the weight of the evidence, the U.S.EPA has classified TCP in the B2 Category - a probable human carcinogen (IRIS, 1988).

Human

Acute. No specific information was located on acute human exposure to TCP, however, trichlorophenols produce redness and edema on skin contact and on prolonged exposure mild to moderate chemical burns on skin. In the eye they induce conjunctival irritation and sometimes corneal injury and iritis. Dusts are irritating to the nose and pharynx (Gosselin et al., 1984).

Chronic. Continuous daily contact with trichlorophenols (isomer unspecified) and tetrachlorophenols has reportedly caused acneform dermatitis in humans (U.S.EPA, 1979). Kleu and Goltz (1971) reported on case histories of ten patients suffering from chloracne due to a 15 year exposure to a trichlorophenol formulation.

Smith et al. (1984) conducted a case-control study of the association between soft-tissue sarcoma and exposure to 2,4-D, 2,4,5-T phenoxy herbicides and TCP. Results concerning TCP involved workers in meat works and tanneries. Men developing soft-tissue sarcomas were 2.8 times more likely to have worked in meat works than controls. It is difficult to attribute this association to exposure to TCP alone since other phenoxy herbicides were involved.

Animal

Acute. Representative rat oral TCP LD_{50} values range from 820 to 2800 mg/kg of body weight, while the intraperitoneal value is 276 mg/kg (Gosselin et al., 1976; Christensen and Luginbyhl, 1975; Farquharson et al., 1958).

Typical clinical signs following injection of TCP into experimental animals are hyperpyrexia together with extremely rapid (3 to 5 minutes) onset of rigor mortis following death. Clinical signs of chlorophenol isomers studied in the rat fall into two classes, convulsive agents and nonconvulsive agents. TCP belongs to the convulsive group of isomers. TCP injected animals develop tremors after 40 to 120 seconds which become generalized almost immediately, followed by loss of righting reflex, coma, and death, if the dose is sufficient (Farquharson et al., 1958).

TCP inhibits mitochondrial oxidative phosphorylation in experimental animals at relatively low concentrations in tissues such as rat brain and diaphragm. Effective concentrations were very close to those of pentachlorophenol, a well known uncoupler of oxidative phosphorylation (Arrhenius et al., 1977). TCP also inhibits lactate dehydrogenase and hexokinase in vitro systems, a general property of uncouplers of oxidative phosphorylation. Although the correspondence between poisoning by pentachlorophenol and poisonings from trichlorophenols is not exact, there is sufficient evidence that the primary toxic mechanism of these

compounds in experimental animals is the inhibition of oxidative phosphorylation, thereby short-circuiting metabolism (U.S.EPA, 1979).

Subacute. Immunologic effects of TCP were investigated in young female rats throughout maturation, pregnancy, and lactation. No statistically significant effects of TCP treatment were found. However, antibody level, delayed-type hypersensitivity response reactions, and macrophage numbers were consistently greater in TCP-exposed animals compared with controls and may be biologically meaningful. Spleen weights of rats exposed to 300 ppm TCP and liver weights of rats exposed to 30 and 300 ppm TCP were significantly greater than controls. The immune system appears to be a sensitive target to toxic insult induced by chronic exposure to TCP (Exon and Koller, 1985).

Chronic. The National Cancer Institute in 1979 studied TCP for possible carcinogenic effects in male and female F344 (Fischer) rats and B6C3F1 mice. Maximum tolerated dosages for the two year studies were determined after a 7 week subchronic study in each species. Male and female rats and male mice received levels of 0, 5,000, or 10,000 ppm TCP in their feed. Female mice received levels of 0, 10,000, or 20,000 ppm TCP in feed for the first 38 weeks of the study when the dosages were decreased, due to excessive weight loss, to 0, 2,500, or 5,000 ppm. Average body weights of dosed rats and mice of both sexes were lower than the corresponding control animals throughout the bioassay and were dose related. There was no significant dose-related trend in mortality in either sex or species. A variety of nonneoplastic lesions was observed in both control and treated animals. Lesions such as these are commonly seen in aged B6C3F1 mice and occurred with no appreciable difference in either control or treated animals. Other than weight loss, which occurred across all treated groups of both species, no clinical signs were attributable to administration of TCP.

The incidence of tumors from the NCI study are presented in the carcinogenicity section.

Behavioral and Central Nervous System

No relevant information was found in the literature on human behavioral and central nervous system effects of TCP.

Reproductive, Embryotoxic, and Teratogenic

Hood et al. (1979) administered 2,4,5-trichlorophenol by gavage in single dosages of 800-900 mg per kg or in multiple doses of 250-300 mg per kg to pregnant mice without producing significant fetal effects.

Male Long-Evans rats were treated by gavage at dosages of 0, 100, 500, or 1000 mg/kg TCP for 11 weeks prior to being mated with untreated females. Males from the high-dose and control groups were subsequently bred with untreated females. The fetuses from these matings were examined on Day 18 post mating for sex, weight, and viability. Female rats were treated at the same dosages of TCP by gavage 5 days per week for two weeks prior to mating, then 7 days per week through Day 21 of gestation. Dams were permitted to deliver and the sex ratio, litter size, and litter weights were recorded. Offspring body weights were taken by sex on Days 1, 4, 7, 14, 21, 28, 35, and 42 postpartum.

Eight deaths occurred in the male high dose group during the first four weeks of dosing and significant weight loss occurred during Week 3. Urogenital staining occurred in all TCP-treated groups. No treatment-related differences were noted in the copulatory behaviors, semen parameters, or organ weights.

Survival of females was good in all treatment groups except the high-dose group, where three of sixteen deaths were related to TCP toxicity, the other deaths being dosage-related intubation errors. Female body weights were depressed in a dose-related manner for all treated groups at the end of the first and second week of dosing as well as Days 1, 7, and 14 of pregnancy, while only the high dose group weights were significantly different from control values. The only body weight differences noted were at the upper two dosages on Day 1 and these affected both male and female pups alike.

Treatment-related mortality was 28 percent at the highest dosages utilized in this study, indicating that this dose was above the maximum dose tolerated for this strain and that no additional information would be gained if this study were conducted at higher dosages. These findings further suggest that TCP is not the metabolite responsible for the reproductive toxicity associated with Lindane treatment (Blackburn et al., 1986).

Genetic

TCP is weakly but significantly active in mutagenicity screens at 400mg/l using S. cerevisiae MP-1 strain and has demonstrated activity in a mouse mammalian spot test, but is ranked among the weakest mutagens tested in that assay (Fahrig et al., 1978). TCP was characterized as negative in the Ames Test (Kopfler et al., 1985; Rasanen et al., 1977).

Carcinogenicity

Innes et al. (1969) reported indefinite tumorigenicity results from the continuous oral administration of 2,4,6-trichlorophenol in mice. Boutwell and Bosch (1959) found no evidence of tumor-promoting activity for TCP in a system that utilized

dimethylbenzanthracene as an initiator.

In the NCI TCP bioassay described above three types of neoplasms occurred in appreciable numbers of F344 rats. They were pituitary chromophobe adenomas in both sexes, interstitial-cell tumors in testes of males, and neoplasms of the hematopoietic system. Both of the earlier neoplasms occurred with equal frequency in dosed and control groups of animals, and the type, distribution, and incidence of these neoplasms is similar to that found in aged F344 rats. While leukemias and hematopoietic disorders also occur in the F344 rat (Davey and Moloney, 1970), their incidence in the dosed groups, the occurrence of hyperplasia in the bone marrow and leukocytosis in both sexes, together with the absence of any of these lesions in control animals, indicates that the effects were compound related. In male rats lymphomas or leukemias occurred at incidences that were dose related ($P = 0.006$) and in direct comparisons were significantly higher in the low-dose ($P = 0.019$) and high-dose ($P = 0.004$) groups than in the corresponding control group. Bone marrow hyperplasia occurred only in the treated groups at an incidence of 26/50, 15/50, 16/50, and 2/50 for the male low and high dose groups, and the female low and high dose groups, respectively. Leukocytosis occurred only in the treated groups at an incidence of 13/50, 11/50, 6/50, and 3/50 for the male low and high dose groups, and the female low and high dose groups, respectively.

The incidences of neoplasms in rats are summarized as follows:

	MALES			FEMALES		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Dose level ppm	0	5000	10000	0	5000	10000
mg/kg/day*	0	250	500	0	250	500
Number of Animals Necropsied	20	50	50	20	50	50
Malignant Lymphoma	1/20 (5%)	2/50 (4%)	0/50 (0%)	0/20 (0%)	0/50 (0%)	2/50 (4%)
Leukemia	3/20 (15%)	23/50 (46%)	29/50 (58%)	3/20 (15%)	11/50 (22%)	11/50 (22%)

*The mg/kg/day values are estimates based on an assumed average body weight of 350 grams and 17.5 grams/day food consumption.

Mouse neoplasms frequently occurring included hepatocellular and pulmonary neoplasms, hemangiosarcomas of various organs, and

malignant lymphomas. Except for hepatocellular neoplasms most neoplasms occurred in equal numbers in control and dosed animals and the type, distribution, and incidence of these neoplasms was similar to those found in aged B6C3F1 mice. Although the incidence of hepatocellular neoplasms and hyperplasias was high in all dosed groups, it was especially high in the two dosed groups of male mice, where most of the livers were affected.

In both male and female mice hepatocellular carcinomas or adenomas occurred at incidences that were dose related ($P < 0.001$), and in direct comparisons were significantly higher in the low- and high-dose male groups and the high-dose female group ($P < \text{or} = 0.001$) than in the corresponding control groups. Hyperplasia occurred in both control and treated groups at an incidence of 2/20, 12/49, 6/47, 1/20, 1/20, and 6/48 for the male control, low, and high dose groups, and the female control, low, and high dose groups, respectively.

The incidences of these lesions in mice is summarized as follows:

	MALES			FEMALES		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Dose level						
ppm	0	5000	10000	0	5000	10000
				after 38 weeks adjusted to 0	2500	5000
mg/kg/day*	0	650	1300	0	650	1300
				after 38 weeks adjusted to 0	325	625
Number of Animals with Tissues Examined Micro-scopically	20	49	47	20	50	48
Hepatocellular Adenoma	3/20 (15%)	22/49 (45%)	32/47 (68%)	1/20 (5%)	12/50 (24%)	17/48 (35%)
Hepatocellular Carcinoma	1/20 (5%)	10/49 (20%)	7/47 (15%)	0/20 (0%)	0/50 (0%)	7/48 (15%)

* The mg/kg/day values are estimates based on an assumed average body weight of 30 grams and 3.9 grams/day food consumption.

A variety of nonneoplastic lesions was observed in both control and treated animals. Lesions such as these are commonly seen in aged B6C3F1 mice and occurred with no appreciable

difference in either control or treated animals.

It is concluded that under the conditions of this bioassay, based on histopathologic examination, TCP was carcinogenic for male F344 rats, inducing tumors of the hematopoietic system. Further, based on histopathologic examination, TCP was carcinogenic for male and female B6C3F1 mice, inducing hepatocellular carcinomas and adenomas (NCI, 1979).

Based on the weight of the evidence, the U.S.EPA has classified 2,4,6-trichlorophenol in the B2 Category - a probable human carcinogen (IRIS, 1988).

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

TCP is a New Jersey Category I chemical since the weight of the evidence indicates it is a probable human carcinogen. The National Cancer Institute TCP bioassay using F344 rats and B6C3F1 mice is the only study appropriate for use in this risk assessment (NCI, 1979). The justification for using this study includes the following: sufficient numbers of animals of two species were used, animals were treated and observed for their lifetimes, the dosages were carefully selected, the study was well executed, statistical procedures were used to evaluate endpoint responses, the study exhibited consistent dose-related responses in multiple parameters of significant toxicological and pathological importance, and the study report was peer-reviewed.

Groups of 50 rats of each sex were administered TCP at either 5,000 or 10,000 PPM, for 106 or 107 weeks. Matched controls consisted of 20 untreated rats of each sex.

Groups of 50 male mice were administered TCP at either 5,000 or 10,000 ppm for 105 weeks. Groups of 50 female mice were administered TCP initially at 10,000 or 20,000 ppm for 38 weeks. Due to excessively lowered body weights in the dosed groups of the females, the doses for the females were reduced to 2,500 and 5,000 ppm, respectively, and the administration of the lowered doses was continued for 67 weeks. The time-weighted average doses for the female mice were 5,214 and 10,428 ppm, respectively. Matched controls consisted of 20 untreated mice of each sex.

While leukemias and hematopoietic disorders also occur in the F344 rat (Davey and Moloney, 1970), their incidence in the dosed groups, the occurrence of hyperplasia in the bone marrow and leukocytosis in both sexes, together with the absence of any of these lesions in control animals, indicates that the effects were compound related. In male rats lymphomas or leukemias occurred at incidences that were dose related ($P = 0.006$) and in direct comparisons were significantly higher in the low-dose ($P = 0.019$)

and high-dose (P = 0.004) groups than in the corresponding control group.

The incidence of hepatocellular neoplasms and hyperplasia was high in all dosed groups of mice. Most of the livers in both dosed groups of male mice were affected. In both male and female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related ($P < 0.001$), and in direct comparisons were significantly higher in the low- and high-dose male groups and the high-dose female group ($P <$ or $= 0.001$) than in the corresponding control groups. The incidence of hepatocellular adenoma and hepatocellular carcinoma in the male mouse was chosen as the most appropriate endpoint since this incidence in treated animals compared to their respective controls is 1.3 to 1.4 times the incidence of malignant lymphoma and leukemia in male rats.

Additional information on this study is provided in the previous carcinogenicity section of this report.

Calculations of Health-Based Maximum Contaminant Level

The U.S.EPA (1988), using the NCI 1979 study, modelled mouse hepatocarcinoma incidence data using the linearized multistage non-threshold procedure extra risk and reported an oral slope factor of 2×10^{-2} /mg/kg/day. This converts to a one in a million extra risk level in drinking water of 2 ug/L.

The NCI 1979 combined male mouse hepatocellular adenoma and hepatocellular carcinoma incidence data was modelled for this report using the multistage model of Crump and Crockett (1984) in the TOX_RISK software package of Clement Associates (1988).

The multistage model is given by:

$$P(d) = 1 - \exp(-q_0 - q_1 d - \ldots - q_k d^k) \text{ for } q_i > 0,\ i = 0,\ldots,k, \text{ and}$$
$$k = \#\text{ of doses} - 1.$$

This model is used to make estimates of the probability, P(d), that a carcinogenic response will occur when the subject is exposed to an amount (d) of the chemical in question. An animal to human conversion method: mg/M^2 surface area/day was utilized.

The carcinogenicity potency factor (upper bound) derived from the model is used to calculate the dose at a specified level of added risk:

$$\frac{10^{-6}\ \text{Risk}}{2.59 \times 10^{-2}\ \text{/mg/kg/day}} = 3.86 \times 10^{-5}\ \text{mg/kg/day}$$

$$3.86 \times 10^{-5}\ \text{mg/kg/day} \times 70\text{kg} = 2.70 \times 10^{-3}\ \text{mg/day}$$

$\frac{2.70 \times 10^{-3} \text{ mg/day}}{\text{2L drinking water}} = 1.35 \times 10^{-3}$ mg/L or 1ug/L

Where:
The upper bound 95% confidence limit extra risk oral slope factor (q_1^*) was determined to be 2.59×10^{-2} /mg/kg/day.

The risk level is 10^{-6} or one in one million.

This converts to a one in a million extra risk level in drinking water of 1 ug/L.

Assumptions and Uncertainty

The extrapolation of liver cancer risk from bioassay data to human liver cancer risk was carried out assuming that animals and man are equally as sensitive relative to a particular measure of dose and that people consume 2 liters of water a day. The slope and unit risk factors have been adjusted for differences in weight and surface areas and represent the incremental upper-bound lifetime risk estimated to result from a lifetime of exposure. Upper-bound estimates are protective of the sensitive subgroups in the population and may overestimate the actual risk by one to two orders of magnitude.

Conclusions

TCP induced lymphomas or leukemias in male F344 rats and hepatocellular carcinomas or adenomas in both sexes of B6C3F1 mice. The quantitative estimation of liver cancer hazard was based on the incidence of hepatocarcinoma in male mice in the NCI (1979) bioassay. A drinking water level of 1 ug TCP per liter was associated with a lifetime excess cancer risk of one in a million.

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