TETRACHLOROETHYLENE

QUANTIFICATION OF TOXICOLOGICAL EFFECTS

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16. ABSTRACT

This document quantifies the drinking water health effects of tetrachloroethylene through the review of several studies. These studies include animal and humans. Physical and chemical properties are discussed. Carcinogenicity of the compound is reviewed and evaluated through various studies.

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FOREWORD

Section 1412(b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish Maximum Contaminant Level Goals and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The Maximum Contaminant Level Goal is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the Maximum Contaminant Level Goal include health effects data and sources of exposure in addition to drinking water.

This document provides the health effects basis to support establishing values for tetrachloroethylene. To set these values, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and mechanisms of toxicity were evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document were comprehensive, only the reports considered most pertinent in the derivation of the Maximum Contaminant Level Goal are cited in the document. The comprehensive literature search in support of this document includes information published in the Health Assessment Document, its appendix, and the document "Response to the Issues and Data Submissions on Tetrachloroethylene (Perchloroethylene)."

When adequate health effects data exist, Health Advisory values for less than lifetime exposures (One-day, Ten-day and Longer-term, approximately 10% of an individual's lifetime) are included in this document. These values are not used in setting the Maximum Contaminant Level, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

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I. INTRODUCTION

The source documents for background information used to develop this report on the quantification of toxicological effects for tetrachloroethylene are the U.S. EPA (1985) health assessment document for tetrachloroethylene, its appendix (1986), and a recent draft document, "Response to the Issues and Data Submissions on Tetrachloroethylene (Perchloroethylene)" (U.S. EPA, 1990).

The quantification of toxicological effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic effects occur, while carcinogens are assumed to act without a threshold.

II. QUANTIFICATION OF NONCARCINOGENIC EFFECTS

In the quantification of noncarcinogenic effects, a Reference Dose (RfD, formerly termed the Acceptable Daily Intake), is calculated. The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a No-Observed-Adverse-Effect Level (NOAEL), or Lowest-Observed-Adverse-Effect Level (LOAEL),

identified from a subchronic or chronic study and divided by an uncertainty factor(s). The RfD is calculated as follows:

$$RfD = \frac{\text{(NOAEL or LOAEL)}}{\text{Uncertainty factor(s)}} = \_\_\_\_ \text{ mg/kg body weight/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based on professional judgment while considering the entire database of toxicological effects for the chemical. In order to ensure that uncertainty factors are selected and applied in a consistent manner, the Office of Drinking Water (ODW) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

- An uncertainty factor of 10 is generally used when good chronic or subchronic human exposure data identifying a NOAEL are available and are supported by good chronic toxicity data in other species.

- An uncertainty factor of 100 is generally used when good chronic toxicity data identifying a NOAEL are available for one or more animal species (and human data are not available), or when good chronic or subchronic toxicity data identifying a LOAEL in humans are available.

- An uncertainty factor of 1,000 is generally used when limited or incomplete chronic or subchronic toxicity data

are available, or when good chronic or subchronic toxicity data identify a LOAEL, but not a NOAEL, for one or more animal species are available.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less-than-lifetime study for deriving an RfD, the significance of the adverse health effect, pharmacokinetic factors, and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium-specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$\text{DWEL} = \frac{\text{(RfD) x (Body weight in kg)}}{\text{Drinking water volume in L/day}} = \_\_\_\_ \text{ mg/L } (\_\_\_ \ \mu\text{g/L})$$

where:

Body weight = assumed to be 70 kg for an adult.

Drinking water volume = assumed to be 2 L per day for an adult.

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (One-day, Ten-day, and Longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using a similar equation to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$HA = \frac{\text{(NOAEL or LOAEL) x (Body weight)}}{\text{(Uncertainty factor(s)) x (\_\_\_\_L/day)}} = \frac{\text{\_\_\_\_ mg/L}}{\text{(\_\_\_\_ µg/L)}}$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. One-day HA for a 10-kg child ingesting 1 L water per day.
2. Ten-day HA for a 10-kg child ingesting 1 L water per day.
3. Longer-term HA for a 10-kg child ingesting 1 L water per day.
4. Longer-term HA for a 70-kg adult ingesting 2 L water per day.

The One-day HA calculated for a 10-kg child assumes a single acute exposure to the chemical and is generally derived from a study of less than 7 days duration. The Ten-day HA assumes a limited exposure period of 1 to 2 weeks and is generally derived from a study of less than 30 days of duration. The Longer-term HA is derived for both the 10-kg child and a 70-kg adult and assumes an exposure period of approximately 7 years (or 10% of an

individual's lifetime). The Longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of an animal's lifetime).

Quantification of Carcinogenic Effects

The EPA categorizes the carcinogenic potential of a chemical, based on the overall weight of evidence, according to the following scheme:

- Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support causal association between exposure to the chemical and human cancer.
- Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
- Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
- Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.
- Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animals tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable, or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these estimates usually come from lifetime exposure studies in animals. In order to predict the risk for humans for animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less-than-lifetime studies, and for differences in size. The factor that compensates for the size differences is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 liters of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure via ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit and provides a low-dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit, and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to

suggest that any one of these models is able to predict risk more accurately than any others. Because each model is based upon differing assumptions, the estimates that are derived for each model can differ by several orders of magnitude.

The scientific database used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exists, such as the incomplete knowledge concerning the health effects of contaminants in drinking water; the impact of the experimental animal's age, sex, and species; the nature of the target organ system(s) examined; and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure, not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

III. NONCARCINOGENIC EFFECTS

Acute or chronic exposure to tetrachloroethylene can cause liver, kidney and CNS toxicity in a variety of species including

man. Tetrachloroethylene vapors are irritating to mucous membranes, eyes and skin. The most serious effects of tetrachloroethylene exposure (severe CNS depression/death) occur when high tetrachloroethylene concentrations are inhales or large doses are administered via gavage. Such effects are unlikely to occur due to tetrachloroethylene exposure via drinking water.

Although tetrachloroethylene toxicity has been studied in organ systems of many species, only limited data are available on the most sensitive end point of toxicity for the chronic ingestion of tetrachloroethylene. Assessment of tetrachloroethylene toxicity must be gleaned from inhalation studies and studies of acute/subchronic ingestion. Man may be the most sensitive species with respect to the CNS effects of acute tetrachloroethylene inhalation (Stewart et al., 1970). Liver and kidney toxicity from tetrachloroethylene exposure, often observed in experimental animals has not been studied in detail for humans. Several studies indicate that mice are more sensitive to tetrachloroethylene liver and kidney toxicity than are rats (Schumann et al., 1980; NTP, 1985; NCI, 1977). Guinea pigs suffer hepatotoxic effects at concentrations for which no changes were observed in rats, rabbits and monkeys (Rowe et al., 1952). No direct comparison has been made between the sensitivity of guinea pigs and mice to tetrachloroethylene, but similar toxic effects increase in liver weight) were observed in chronic studies of mice exposed to 200 ppm (1,360 mg/m^3) for 7 hours/day for 236 day for 8 months (Kylin et al., 1965; approximately

equivalent to 160 mg/kg/day, see Appendix) and chronic studies of guinea pigs exposed to 100 ppm (678 mg/m^3) for 7 hours/day for 236 days (Rowe, 1952; approximately equivalent to 63 mg/kg/day, see Appendix).

Observations in Humans

Inhalation exposure to tetrachloroethylene has been studied in man under controlled laboratory conditions and as a result of occupational exposure. In a study by Stewart et al. (1970), five male subjects were exposed to 100 ppm (678 mg/m^3) tetrachloroethylene for 7 hours/day on 5 consecutive days (approximately equivalent to 20 mg/kg/day; see Appendix). Subjects were monitored with respect to blood chemistry, ability to perceive tetrachloroethylene odor, pulmonary function, performance levels on behavioral/neurological tests, and asked to report on a variety of subjective complaints. Odor perception decreased over time during the course of the week. Perception at the beginning of each day decreased faster as the week progressed. After 3 hours of exposure on the first day, 3 or 8 subjects were unable to respond normally to a modified Romberg test, but were able to overcome this inability with greater mental effort. Subjective complaints during the five days included mild eye, nose and throat irritation, lightheadedness, mild frontal headache, sleepiness, and some difficulty in speaking. These complaints decreased over the course of the study week. Normal readings were obtained for all other tests. In follow-up studies, the

authors concluded that prolonged exposure to 100 ppm (678 mg/m^3) had no consistent adverse effects on performance in these behavioral tests (Stewart et al., 1974, 1977).

Other studies of human experimental exposure indicate the ability of tetrachloroethylene to cause eye irritation and CNS effects such as dizziness at concentrations of 100 to 600 ppm (695 to 4,100 mg/m^3; Rowe et al., 1952). Accidental industrial exposure to higher concentrations (exact concentrations unknown) produce more serious CNS effects and hepatotoxicity (Stewart et al., 1961; Hake and Stewart, 1977).

Observations in Other Species

Neurotoxicity: Severe ataxia and anesthesia in mice and rats have been observed at lethal concentrations of tetrachloroethylene (NTP, 1985). Less severe effects have been studies in experimental animals with the use of behavioral tests, but available studies indicate that effects on the liver or kidney occur at lower exposure levels. Goldberg (1964) exposed rats to 1,500 ppm (10,200 mg/m^3) and 2,300 ppm (15,600 mg/m^3) tetrachloroethylene for 2 weeks, 4 hours/day, 5 days/week. At 2,300 ppm (15,600 mg/m^3), ataxia and diminished escape avoidance response was observed. No effects were seen at exposure levels of 1.500 ppm (10,200 mg/m^3). Savolainen et al., (1977) exposed rats to 200 ppm (1,360 mg/m^3), 6 hours/day for 4 days. Little if any impairment over controls was observed.

Hepatotoxicity: The hepatotoxicity of tetrachloroethylene in experimental animals has been studied in greater detail than its behavioral/CNS effects. Acute effects in mice have been observed at concentrations as low as 200 ppm (1,360 mg/m^3; Kylin et al., 1963) or oral doses as low as 100 mg/kg (Schumann et al., 1980). Hepatotoxicity from exposure to concentrations as low as 100 ppm(678 mg/m^3; NTP, 1985) has been observed after chronic exposure; data on chronic ingestion of tetrachloroethylene are limited.

Kylin et al. (1963) observed reversible hepatotoxic effects (fatty degeneration) in mice exposed to 200 ppm (1,360 mg/m^3) for 4 hours (approximately equivalent to 160 mg/kg/day, see Appendix). Other acute studies demonstrate hepatotoxic effects at higher concentrations (Rowe et al., 1952).

The subchronic and chronic effects of tetrachloroethylene inhalation have been described in several studies, including NTP (1985), Carpenter (1937), Rowe et al. (1952), and Mazza (1972).

Hepatotoxic effects were observed in the NTP (1985) 13-week range finding study. Rats and mice were exposed to concentrations of 100, 200, 400, 800 and 1,600 ppm (678, 1,360, 2,710, 5,420 and 10,800 mg/m^3) for 6 hours/day, 5 days/week for 13 weeks (approximately equivalent to 160 to 2,600 mg/kg/day (mice) and 66 to 1,600 mg/kg/day (rats); see Appendix). Liver lesions (infiltration, necrosis and bile stasis) were observed in

mice exposed to concentrations of 400 ppm (2,710 mg/m^3) dose groups. Effects on the kidneys were also observed within this dose range and are described below.

Carpenter (1937) exposed rats of both sexes to 70 ppm (475 mg/m^3), 230 ppm 1,560 mg/m^3) or 470 ppm (3,190 mg/m^3), 8 hours/day 5 days/week for 150 days; approximately equal to 62, 200 and 410 mg/kg/day, see Appendix). Animals in the highest dose group exhibited hepatic and renal congestion and swelling. At the middle dose, congestion was only observed in the kidney. No significant changes were seen at the lowest dose.

Chronic effects on the liver and kidney were also observed in the NTP (1985) inhalation bioassay. Rats were exposed to concentrations of 200 and 400 ppm (approximately equal to 130 and 260 mg/kg/day; see Appendix) for 6 hours/day, 5 days/week for 103 weeks. Effects on the kidney were observed in all treated groups and are described below. Hepatotoxicity was observed in all treated male mice and female mice in the high dose group. The effects observed include increased incidences of degeneration (Vacuolation, infiltration, pigmentation, and hyperplasia) necrosis and nuclear inclusions.

In contrast to these findings, Rowe et al. (1952) observed no toxic effects in rats, rabbits or monkeys exposed to 400 ppm (2,710 mg/m^3) tetrachloroethylene for 7 hours/day, 5 days/week for 179 days. Guinea pigs exposed to the same regiment at 100,

200, 300 and 400 ppm (678, 1,360, 2,030 and 2,710 mg/m^3) showed a dose dependent increase in liver weight and fatty infiltration of the liver when exposed over 236 days (Rowe et al., 1952). Similar hepatotoxic effects were observed in mice exposed to 200 ppm (1,360 mg/m^3), 4 hours/day, 5 days/week for 8 months (Kylin et al., 1965; approximately equal to 160 mg/kg/day; see Appendix). Effects have also been observed in rabbits, but at higher concentrations. Mazza (1972) exposed rabbits to 2,790 ppm (18,900 mg/m^3), approximately equal to 840 mg/kg (see Appendix), for 4 hours/day, 5 days/week for 45 days and observed changes in serum levels of glutamic-oxaloacetic transaminase (SGOT), glutamic-pyruvic transaminase (SGPT) and glutamide dehydrogenase (GDH).

Hepatotoxic effects have also been observed as a result of oral exposure. Studies of acute oral exposure to tetrachloroethylene indicate that doses of 4,000 mg/kg or greater are lethal to experimental animals (Wenzel and Gibson, 1951; Smyth et al., 1969). A variety of hepatotoxic effects have been demonstrated at lower doses. Fujii (1975) found elevated serum enzyme levels in rabbits exposed to 2,186 mg/kg. Vaino et al. (1976) studied microsomal enzymes <u>in vitro</u> after <u>in vivo</u> exposure of rats to tetrachloroethylene in olive oil via gavage (2.6 mmol/kg [429 mg/kg]). Recovery of some microsomal enzyme activities (benzpyrene hydroxylase and p-nitroanisole O-demethylase) per gram liver (wet weight) were significantly lower than controls.

Mice appear to be mores sensitive to the effects of tetrachloroethylene exposure than rats. Schumann et al. (1980) administered tetrachloroethylene in corn oil to both rats and mice via gavage for 11 consecutive days at doses of 100, 250, 500 and 1,000 mg/kg. Histopathological changes including centrilobular hepatocellular swelling and increased liver weight were observed in all treated mice; rats were more resistant, with toxicity being apparent only at the highest does.

Similar hepatotoxic effects were observed in mice after subchronic exposure. In a study by Buben and O'Flaherty (1985), male Swiss-Cox mice were exposed to tetrachloroethylene in corn oil via gavage at doses of 1, 20, 100, 200, 500, 1,000, 1.500 and 2,000 mg PCE/kg 5 days/week for 6 weeks. Liver toxicity was evaluated by several parameters including liver weight/body weight ratio, hepatic triglyceride concentration, serum GEP and SGPT activity, hepatic DNA content, histopathological evaluation and hepatic dry weight/wet weight ratios. All parameters indicated liver toxicity at high doses. Increased liver triglycerides were first observed in mice treated with 100 mg/kg. Liver weight/body weight ratios were significantly different from controls for the 100 mg/kg group, and slightly higher than controls in the 20 mg/kg group.

Lifetime oral exposure to tetrachloroethylene was shown to cause liver and kidney toxicity in two separate studies (NCI, 1977; NTP, 1983). In the NCI study, Osborne-Mendel rats and

B6C3F1 mice were exposed to PCE in corn oil via gavage for 5 days/week for 78 weeks at does of 471 to 949 mg/kg (rats) and 386 to 1,072 mg/kg (mice). In addition to hepatocarcinogenic effects, toxic nephropathy was observed in all treatment groups for both species. In the NTP study, female B6C3F1 mice were exposed to tetrachloroethylene in corn oil (25, 50, 100 or 200 mg/kg) 5 days/week for 103 weeks. This report had not been audited as of June, 1985.

Renal Toxicity: Renal toxicity from tetrachloroethylene exposure via inhalation has been demonstrated in rabbits, rats and mice. Brancaccio et al. (1971) exposed rabbits to 2,280 ppm (15,500 mg/m^3, approximately equivalent to 680 mg/kg) for 4 hours/day, 5 days/week for 45 days. Decreases in glomerular filtration, renal plasma flow and maximal tubular excretion were observed. In the NTP (1985) 13-week range finding study, rats and mice were exposed to concentrations of 0, 100, 200, 400, 800 and 1,600 ppm (0, 678, 1,360, 2,710, 5,420 and 10,800 mg/m^3). Renal toxicity was not observed in rats, but mice exposed to concentrations of 200 ppm (1,360 mg/m3; equivalent to about 320 mg/kg/day; see Appendix) or greater exhibited karyomegaly of the tubular epithelium.

Carpenter (1937) exposed rats of both sexes to concentrations of 70 ppm (475 mg/m^3), 230 ppm (1,560 mg/m^3), and 470 ppm (3,190 mg/m^3) for 8 hours/day, 5 days/week for 150 days; approximately equal to 62, 200 and 410 mg/kg/day. At the two

highest doses, the kidney showed increased secretion, cloudiness, swelling and desquamation; the spleen was congested and showed an increase in pigment content. Renal toxicity was also observed in the NTP tetrachloroethylene bioassay (1985) in which male and female rats and mice were exposed to tetrachloroethylene for 6 hours/day, 5 days/week for 103 weeks. An increased incidence of tubular cell karyomegaly was observed for all treatment groups (200 and 400 ppm for rats, approximately equivalent to 130 and 260 mg/kg/day; 100 and 200 ppm for mice, approximately equivalent to the 120 and 240 mg/kg/day; see Appendix).

Other Effects: Reproductive and developmental effects have been shown to result from exposure of rats and mice to tetrachloroethylene. Pregnant rats and mice exposed to 300 ppm (2,000 mg/m^3) for 7 hours/day on days 6 through 15 of gestations (approximately equivalent to doses of 230 mg/kg [rats] and 560 mg/kg [mice]; see Appendix). Rats had twice the number of resorptions per implantation compared with controls, while mouse pups exhibited significant subcutaneous edema, delayed skull ossification and split sternebrae (Schwetz et al., 1975).

Study Selection for Quantification of Noncarcinogenic Effects

The entire data base on tetrachloroethylene must be evaluated before appropriate studies can be selected as the basis for One-day, Ten-day, Longer-term or Lifetime HA values. The

CNS, hepatic and renal toxicity of tetrachloroethylene are of primary concern. Although some data are available on human exposures to tetrachloroethylene, these data were not used as the basis for HA values. From the available data, it is not possible to judge the most sensitive toxic endpoint in man. The qualitative CNS effects observed subsequent to controlled inhalation exposure (Stewart et al., 1970) were not used as the basis for quantitation due to the subjective nature of the effects and the difficulty in extrapolating between inhaled and ingested doses.

The renal toxicity observed after chronic ingestion of tetrachloroethylene by rats and mice (NCI, 1977; NTP, 1983) is of concern. However, the most sensitive endpoint of toxicity identified from acute and subacute ingestion of tetrachloroethylene by laboratory animals appears to be hepatotoxicity in the mouse (Schumann et al., 1980; Buben and O'Flaherty, 1985).

Derivation of Health Advisory Values

Health Advisories (HAs) are generally determined for exposures of One-day, Ten-days, Longer-term (approximately 7 year exposure) and Lifetime if adequate data are available which identify a sensitive noncarcinogenic endpoint of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL\ OR\ LOAEL) \times (BW)}{(UF) \times (\_\_\ L/day)} = \_\_\_\_\_\ mg/L\ (\_\_\_\_\_\ \mu g/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of protected individual (10 kg for a child and 70 kg for an adult).

UF(s) = uncertainty factor (10, 100 or up to 1,000), based on nature and quality of data.

One-day Health Advisory

The available studies were not considered sufficient for derivation of a One-day HA. The Ten-day HA of 2.0 mg/L is recommended as a conservative estimate of 1-day exposure.

Ten-day Health Advisory

Hepatotoxicity in mice exposed to tetrachloroethylene was selected as the basis for calculating the Ten-day HA value.

Schumann et al. (1980) administered tetrachloroethylene in corn oil to rats and mice via gavage for 11 consecutive days at doses of 0, 100, 500 and 1,000 mg/kg. For mice, histopathological changes including increased liver weights were observed in all treated animals. The lowest does, 100 mg/kg/day, represents the LOAEL for the study. This value is consistent with the estimated LOAEL of 220 mg/kg/day for mice exposed to 200

ppm for 4 hours (Kylin, 1963; see Appendix). Applying an uncertainty factor of 1,000 may be overly conservative.

Buben and O'Flaherty (1985) treated mice with doses ranging from 20 to 2,000 mg/kg, 5 days/week for 6 weeks and observed a slight increase in liver weight in mice treated with 20 mg/kg; at 100 mg/kg, increases were significantly different from controls. On this basis, a dose of 20 mg/kg was identified as a NOAEL and 100 mg/kg was identified as a LOAEL.

Basing the Ten-day HA on the NOAEL of 20 mg/kg with an uncertainty factor of 100 is consistent with the protection of humans from the CNS effects observed by Stewart et al. (1980) at 100 ppm for 7 hours (approximately 16 mg/kg; see Appendix). The value was calculated as follows:

$$\text{Ten-day HA} = \frac{(20 \text{ mg/kg/day}) \ (10 \text{ kg})}{(100) \ (1 \text{ L/day})} = 2.0 \text{ mg/L}$$

where:

20 mg/kg/day = NOAEL based on the absence of hepatotoxicity in mice.

10 kg = assumed body weight of a child.

100 kg = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The study by Buben and O'Flaherty was also selected as the basis for the Longer-term HA. Lifetime carcinogenicity assays were not selected because of the high doses used (NCI, 1977; NTP, 1985). The NOAEL of 20 mg/kg/day and LOAEL of 100 mg/kg/day identified in this study are consistent with the estimates of LOAELs from chronic inhalation studies. A LOAEL of 63 mg/kg/day was estimated from chronic exposure of guinea pigs to 100 ppm for 7 hours/day (Rowe et al., 1952; see Appendix), and a LOAEL of 160 mg/kg/day from mice exposed to 200 ppm for 4 hours (Kylin, 1965). The Longer-term HAs for the child and adult were calculated as follows:

For a child:

$$\text{Longer-term HA} = \frac{(20\ \text{mg/kg/day})\ (5/7)\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 1.4\ \text{mg/L}$$

where:

20 mg/kg/day = NOAEL based on the absence of hepatotoxic effects in mice.

5/7 = Factor to convert 5 day/week exposure to daily exposure.

10 kg = Assumed body weight of a child.

100 = Uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = Assumed daily water consumption of a child.

For an adult:

$$\text{Longer-term HA} = \frac{(20 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 5.0 \text{ mg/L}$$

where:

20 mg/kg/day = NOAEL based on the absence of hepatotoxic effects in mice.

5/7 = Factor to convert 5 day/week exposure to daily exposure.

70 kg = Assumed body weight of an adult.

100 = Uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = Assumed daily water consumption of an adult.

Derivation of Reference Dose and the Drinking Water Equivalent Level

No suitable chronic oral or lifetime oral studies were located in the literature to serve as the basis for the Lifetime HA. NOAELs were not identified in the NCI (1977) study in which LOAELs were identified at high doses (386 mg/kg/day, mice; 471 mg/kg/day, rats). The NTP (1983) study in which lower doses were tested has not been validated.

Approximate NOAELs and LOAELs calculated from chronic and lifetime inhalation studies give less conservative estimates of toxic doses than the six-week oral study of Buben and O'Flaherty

(1985). LOAEL estimates of 63 mg/kg/day for guinea pigs exposed to 100 ppm, 7 hours,day (Rowe et al., 1952), 200 mg/kg/day for rats exposed to 230 ppm for 7 hour/day (Carpenter, 1937) and 160 mg/kg/day for mice exposed to 100 ppm for 6 hour/day (NTP, 1985) are consistent with the NOAEL of 20 mg/kg/day and LOAEL of 100 mg/kg/day identified in the study by Buben and O'Flaherty. In this study, mice were treated with doses of 20 to 2,000 mg/kg/day, 5 days/week for 6 weeks. A slight increase in liver weight was observed at 20 mg/kg; at 100 mg/kg, liver weight and hepatic triglyceride levels were significantly increased over controls. Using the NOAEL of 20 mg/kg/day and an uncertainty factor of 1,000 consistent with the use of data from less than lifetime studies, the RfD and DWEL were calculated as follows:

$$\text{RfD} = \frac{(20 \text{ mg/kg/day}) \ (5/7)}{(1{,}000)} = 0.0143 \text{ mg/kg/day}$$

where:

20 mg/kg/day = NOAEL.

5/7 = Factor to convert 5 day/week exposure to daily exposure.

1,000 = Uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

The DWEL for tetrachloroethylene based on noncarcinogenic effects and assuming 100% exposure from drinking water is calculated as follows:

$$\text{DWEL} = \frac{(0.0143 \text{ mg/kg/day}) \ (70 \text{ kg})}{(2 \text{ L/day})} = 0.5 \text{ mg/L}$$

The estimated excess upper bound cancer risk associated with lifetime exposure to drinking water containing tetrachloroethylene at 0.5 mg/L is approximately 1×10^{-3}.

IV. EVALUATION OF CARCINOGENIC EFFECTS

Tetrachloroethylene was tested for carcinogenic potential in B6C3F1 mice and Fischer 344 rats in the NCI Bioassay Program (NCI, 1977). In those bioassays, the test compound, containing a small amount of stabilizer, was administered in oil by gavage 5 days/week for 78 weeks. Under the experimental conditions employed in the studies, it was shown that tetrachloroethylene caused a significant increase in the incidence of hepatocellular carcinomas in both sexes of mice at both dose levels when compared with the untreated and vehicle control groups. In the rats, there appeared to be no significant increased incidence of neoplastic lesions at any site. The implications of these results must be tempered by the fact that, among the rats, there were high incidences of respiratory disease in all groups, high incidences of toxic nephropathy in the tetrachloroethylene groups and a higher mortality rate among the treated groups than the control groups. For a variety of reasons, it was decided that the bioassay would be repeated.

On the basis of the data reported in the NCI bioassay published in 1977, IARC (1979) concluded that there is limited evidence to state that it is a carcinogen in the mouse. Chemicals which fall into this category or classification by this Agency are usually there for two reasons. Firstly, the experimental data may be restricted such that it is not possible to determine a causal relationship between exposure and development of a lesion. Secondly, certain neoplasms, such as lung adenomas and hepatomas in mice, are considered by some investigators to be of lesser significance than tumors of other types occurring at other sites. In addition, some chemicals for which there is limited evidence of carcinogenicity in animals also have been studied in humans, with, in general, inconclusive results. While there is some evidence for increased risk of urinary tract cancer in dry cleaner works, there is insufficient evidence to demonstrate or refute a carcinogenic hazard for tetrachloroethylene alone. EPA concludes that the human evidence for tetrachloroethylene is inadequate to develop a more definitive conclusion.

An additional inhalation bioassay was conducted by the NTP in which rats were exposed to 200 and 400 ppm (1,360 and 2,710 $\mu g/m^3$) and mice to 100 and 200 ppm (678 and 1,360 $\mu g/m^3$) tetrachloroethylene (NTP, 1985). Statistically significant increases in mononuclear cell leukemia were observed to have an increased incidence of hepatocellular carcinoma. In addition, a statistically significant increase in the incidence of renal

adenomas/carcinomas (combined) was observed for male mice in the high dose group. Based on this and previous studies, it can be concluded that there is sufficient evidence of carcinogenicity in animals on exposure to tetrachloroethylene.

Controversy exists over the classification of tetrachloroethylene because different interpretations can be given to either the bioassay data on tetrachloroethylene or to the cancer guidelines (51 FR 33992). EPA recommended that "sufficient" evidence of carcinogenicity existed based on positive findings of carcinogenicity in two species with multiple tumor sites, and via two routes of administration. Using the same data, the Halogenated Organic Solvent Subcommittee of EPA's Science Advisory Board concluded that the evidence was "inadequate," and suggested a classification of Group C: possible human carcinogen (U.S. EPA, 1987).

A major difference between the analysis of the data by the subcommittee and that of the Agency (U.S. EPA, 1986) was the interpretation of the data on the tumor incidence in rats in the 1985 NTP inhalation bioassay. Concerning the finding of increased renal tumors in rats, the subcommittee questioned the diagnosis of neoplasia, and objected to the statistical analysis in which a significant increase was observed only when adenomas and carcinomas were combined for statistical analysis. The subcommittee also questioned the finding of mononuclear cell leukemia in rats. EPA has included preleukemic stages for

statistical analysis of the results. The committee raised questions concerning the method of staging and also questioned the diagnosis of the tumor. The subcommittee agreed that tetrachloroethylene caused an increase in mouse liver tumors, but they questioned the relevance of this tumor type to man.

EPA has carefully considered these questions; many are similar to questions arising for other compounds. For example, the question of mouse liver tumors is discussed in the cancer guidelines (51 FR 33992). Although uncertainty exists, sufficient understanding of the pathology of renal neoplasia and mononuclear cell leukemia exists to make reasonable judgments on these issues, have confidence in the diagnosis of these tumor types, and make reasonable decisions on methods of statistical analysis. Combining adenomas/carcinomas is a valid method for analyzing renal tubular cell neoplasia and is consistent with the cancer guidelines and the work of McConnell et al. (1986). The guidelines do not specifically mention staging leukemia, but preleukemic stages do not need to be included in the analysis to obtain a significant tumor increase in rats. Therefore, it can be concluded that this bioassay gives positive evidence of carcinogenicity in a second species (U.S. EPA, 1986).

The role of tetrachloroethylene metabolites in the manifestation of toxicity including carcinogenicity cannot be ignored. The available information indicates that there is no

reason to believe that qualitative differences in the metabolism of tetrachloroethylene among various animal species exists.

Tetrachloroethylene is metabolized by two metabolic pathways: oxidative pathway dependent upon cytochrome P 450 and the conjugative pathway involving glutathione. The major metabolite of oxidative pathway is trichloroacetic acid which is excreted in urine. Some of the intermediates in the trichloroacetic acid pathway possess cytotoxic and genotoxic activity.

The conjugative pathway, a multistep glutathione dependent pathway -- the so-called cysteine conjugate ß-lyase pathway is toxicologically important even though it is minor route of disposition of tetrachloroethylene. In this pathway, haloalkene, i.e., tetrachloroethylene, forms hepatic glutathione S-conjugate and the resulting conjugate(s) (glutathione, cysteine or N-acety(cystein S-conjugate) is transferred to the kidney where it is bioactivated by ß-lyase. There is evidence that this pathway is responsible for the nephrotoxicity, mutagenicity and possible nephrocarcinogenicity of chloroalkenes including tetrachloroethylene (Monks et al., 1990).

Quantification of Carcinogenic Effects

Using methodology described in detail elsewhere (51 FR 33992), the EPA's Carcinogen Assessment Group (CAG) has

calculated estimated incremental excess upper bound cancer risk associated with exposure to tetrachloroethylene in ambient water, extrapolating from data obtained in the 1977 NCI bioassay in mice with this compound (NCI, 1977). CAG employed a linearized, non-threshold multistage model to estimate the upper bound of the excess cancer rate that would occur at a specific exposure level for a 70 kg adult ingesting two liters of water and 6.5 grams of fish and seafood (fish factor) every day over a 70-year lifespan.

The National Academy of Sciences (NAS, 1977, 1980) and EPA's Carcinogen Assessment Group (Anderson, 1983) have calculated estimated upper bound incremental excess cancer risks associated with the consumption of tetrachloroethylene via drinking water alone by mathematical extrapolation from the high-dose animal studies. Each group employed the linearized, non-threshold multistage model, extrapolating from data obtained in the 1977 NCI bioassay in mice.

In all three instances, a range of tetrachloroethylene concentrations was computed that would be estimated to increase the risk by one excess cancer per million (10^{-6}), per hundred thousand (10^{-5}) and per ten thousand (10^{-4}) population over a 70-year lifetime assuming daily consumption of 2 liters of water by a 70-kg adult at the stated exposure level. The ranges of concentrations are summarized in Table 1.

The NCI bioassay also was the basis for the upper bound unit risk derivation, i.e., the risk associated with 1 μg/L drinking water or 1 $\mu g/m^3$ air (U.S. EPA, 1985). The upper bound risk associated with exposure to 1 μg/L water was estimated to be 1.5×10^{-6}; concentrations corresponding to risks of 10^{-4}, 10^{-5} and 10^{-6} were derived by extrapolation (Table 1).

V. OTHER CRITERIA AND STANDARDS

The World Health Organization has recommended a tentative guideline value of 10 μg/L for tetrachloroethylene in drinking water, based on carcinogenic properties (WHO, 1984).

The National Academy of Sciences (NAS, 1980) calculated 24-hour and 7-day SNARLs. The 24-hour SNARL was 172 mg/L, based on a 490 mg/kg LOAEL following i.p. administration, a 100-fold uncertainty factor, and a 70-kg adult drinking 2 L/day of drinking water. A 7-day SNARL of 24.5 mg/L was calculated by dividing the 24-hour SNARL by seven.

Table 1

Estimated tetrachloroethylene concentrations causing excess Cancer risks of 10^{-4}, 10^{-5} and 10^{-6}

Excess Lifetime Cancer Risk[a]	Tetrachloroethylene concentrations (μg/L) Basis for concentration estimates			
	CAG[b]	CAG[c]	NAS[d]	OHEA[e]
10^{-4}	90.0	65.8	350	(66.7)
10^{-5}	9.0	6.6	35	(6.7)
10^{-6}	0.9	0.7	3.5	(0.7)
1.5×10^{-6}				1.0

[a] Assumes 2 L of water consumed/day by 70-kg adult over a lifetime; number represents upper bound.
[b] U.S. EPA, 1980. Includes "fish factor," assumed daily consumption of 6.5 grams of contaminated fish and seafood.
[c] Anderson, 1983.
[d] NAS, 1977, 1980.
[e] U.S. EPA, 1985. Based on linear extrapolation from risk estimate based on concentrations of 1 μg/L.

Summary

The recommended HA values are listed below:

One-day	2.0 mg/L
Ten-day	2.0 mg/L
Longer-term (child)	1.4 mg/L
Longer-term (adult)	5.0 mg/L

A DWEL of 500 μg/L was calculated from which a lifetime HA value could be derived. The estimated excess upper bound cancer risk associated with lifetime exposure to drinking water containing tetrachloroethylene at 500 μg/L is approximately 1×10^{-3}. This estimate is derived from extrapolations using the linearized, multistage model.

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APPENDIX

Estimation of absorbed dose based on inhalation exposure

Species	Approx. weight (kg)	Approx. minute volume (l/min)	[PCE] (ppm)	Hours Exposed per day	Approx. dose (mg/kg/day)[a]	Reference
Human	70.0	10.0	100	7	20	Stewart et al., 1977
Guinea pig	0.50	0.222	100	7	63	Rowe et al., 1952
			200	7	130	Rowe et al., 1952
					190	Rowe et al., 1952
					240	Rowe et al., 1952
Rat	0.25	0.132	200	6	130	Savolainen et al., 1977; NTP, 1985
			400	6	260	Savolainen et al., 1977; NTP, 1985
			800	6	530	NTP, 1985
			1,600	6	1,100	NTP, 1985
			70	8	62	Carpenter, 1937
			230	8	200	Carpenter, 1937
			470	8	400	Carpenter, 1937
Mouse	0.025	0.024	100	6	120	NTP, 1985
			200	6	230	NTP, 1985
			400	6	650	NTP, 1985
			800	6	1,300	NTP, 1985
			1,600	6	2,600	NTP, 1985
			200	4	160	Kylin, 1963, 1965
Rabbit	2.5	0.742	2,280	4	680	Brancaccio et al., 1971
			2,790	4	840	Mazza, 1972

[a] $$\text{Dose} = \frac{[\text{tetrachloroethylene}(mg/m^3)][\text{lung vol}(m^3/hr)][\text{Time}(hr/day)][50\%\ \text{absorption}]}{\text{body weight (kg)}}$$

where:

$$[\text{tetrachloroethylene}(mg/m^3)] = (\text{ppm}) \times (6.78\ mg/m^3 - \text{ppm})$$

$$[\text{lung vol.}(m^3/hr)] = \frac{[2.1\ (\text{body weight in grams})^{.75}\ ml/min] \times 60\ min/hr}{(1{,}000\ ml/L)(1{,}000\ L/m^3)}$$