FICHE #

REF 0841

EIS PROJECT (ARXPF
Control # 3035

DCS INPUT FORM

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DCSN:	
Document Identification Number[1]:	
Document Title (or description)[2]:	Integrated Risk Assessment Information System (IRIS) - Selected Chemicals
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Integrated Risk Assessment Information System (IRIS) - *Selected Chemicals*

5 - IRIS
NAME - Acetaldehyde
RN - 75-07-0
IRSN - 284
DATE - 920122
UPDT - NO DATA
STAT - Oral RfD Assessment (RDO) no data
STAT - Inhalation RfC Assessment (RDI) on-line 10/01/91
STAT - Carcinogenicity Assessment (CAR) on-line 01/01/91
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 06/01/89 CARDR Secondary contact changed
IRH - 07/01/89 RDI Inhalation RfD now under review
IRH - 03/01/90 CAREV Citations clarified (1st paragraph)
IRH - 03/01/90 REFS Bibliography on-line
IRH - 01/01/91 CAR Text edited
IRH - 01/01/91 CARI Inhalation slope factor removed
IRH - 10/01/91 RDI Inhalation RfC summary on-line
IRH - 10/01/91 IREF Inhalation RfC references added
IRH - 01/01/92 EXSR Regulatory Action section on-line
RLEN - 39396
SY - ACETALDEHYD
SY - Acetaldehyde
SY - ACETIC ALDEHYDE
SY - ACETYLALDEHYDE
SY - ALDEHYDE ACETIQUE
SY - ALDEIDE ACETICA
SY - ETHANAL
SY - ETHYL ALDEHYDE
SY - NCI-C56326
SY - OCTOWY ALDEHYD
SY - RCRA WASTE NUMBER U001
SY - UN 1089
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA
VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

RDO - NO DATA

RDI -
o INHALATION RFD SUMMARY :

Critical Effect	Exposures*	UF	MF	RfC
Degeneration of olfactory epithelium	NOAEL: 273 mg/cu.m (150 ppm) NOAEL(ADJ): 48.75 mg/cu.m NOAEL(HEC): 8.7 mg/cu.m	1000	1	9E-3 mg/cu.m
Short-term Rat Inhalation Studies	LOAEL: 728 mg/cu.m (400 ppm) LOAEL(ADJ): 130 mg/cu.m			
Appleman et al., 1986;	LOAEL(HEC): 16.9 mg/cu.m			

*Conversion Factors: MW = 44.5.
Appleman et al., 1986: Assuming 25C and 760 mmHg, NOAEL(mg/cu.m) = 150 ppm x 44.5/24.45 = 273. NOAEL(ADJ) = 273 mg/cu.m x 6 hours/day x 5 days/7 days = 48.75 mg/cu.m. The NOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.23 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm, Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.18. NOAEL(HEC) = NOAEL(ADJ) x RGDR = 8.7 mg/cu.m.

Appleman et al., 1982: Assuming 25C and 760 mmHg, LOAEL(mg/cu.m) = 400 ppm x 44.5/24.45 = 130. LOAEL(ADJ) = 728 mg/cu. m x 6 hours/day x 5 days/7days = 130 mg/cu.m. The LOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.17 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm., Sh(ET) = 177 sq.cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.13. LOAEL(HEC) = LOAEL(ADJ) x RGDR = 16.9 mg/cu.m.

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o INHALATION RFD STUDIES :

Appleman, L.M., R.A. Woutersen, V.J. Feron, R.N. Hooftman and W.R.F. Notten. 1986. Effect of variable versus fixed exposure levels on the toxicity of acetaldehyde in rats. J. Appl. Toxicol. 6(5): 331-336.

Appleman, L.M., R.A. Woutersen, and V.J. Feron. 1982. Inhalation toxicity of acetaldehyde in rats. I. Acute and subacute studies. Toxicology. 23: 293-297.

Two short-term studies conducted by the same research group are the principal studies used. While these studies are short-term in duration, together they establish a concentration-response for lesions after only 4 weeks of exposure. These same types of lesions appear at longer exposure times and higher exposure levels in chronic studies (Wouterson et al., 1986; Wouterson and Feron, 1987; Kruysse et al., 1975). Under other circumstances, studies of short duration may not be considered appropriate, but for this chemical the observed effects are consistent with pathology seen in long-term studies. The 150-ppm exposure level was therefore established as the NOAEL from the Appleman et al. (1986) study and the LOAEL from the Appleman et al. (1982) study.

Appleman et al. (1986) conducted two inhalation studies on male Wistar rats (10/group) exposing them 6 hours/day, 5 days/week for 4 weeks to 0, 150, and 500 ppm (0, 273 and 910 mg/cu.m, respectively). Duration-adjusted concentrations are 0, 48.75, and 162.5 mg/cu.m, respectively. One group was exposed without interruption, a second group was interrupted for 1.5 hours between the first and second 3-hour period, and a third group was interrupted as described with a superimposed peak exposure profile of 4 peaks at 6-fold the basic concentration per 3-hour period. The purpose was to test intermittent and peak exposure effects. Urine samples were collected from all rats and lung lavage performed on 4-5 per group at the end of the experiment. Cell density, viability, number of phagocytosing cells, and phagocytic index were determined on the lavage fluid. Microscopic examination was performed on the nasal cavity, larynx, trachea with bifurcation and pulmonary lobes of all rats of all groups.

Continuous and interrupted exposure to 500 ppm did not induce any visible effect on general condition or behavior, but peak exposures at this level caused irritation. No behavioral differences were noted in the other groups. Mean body weights of the group exposed to 500 ppm with interruption and with peak exposures were statistically significantly lower than those of the controls. Body weights were similar to controls in the other exposure groups. Mean cell density and cell viability were significantly decreased in the group exposed to 500 ppm with or without peak exposures. The mean percentage of phagocytosing cells and the phagocytic index were significantly lower than controls in all groups exposed to 500 ppm, especially the group exposed to

superimposed peaks. Histopathological changes attributable to exposure were found only in the nasal cavity. Degeneration of the olfactory epithelium was observed in rats exposed to 500 ppm. Interruption of the exposure or interruption combined with peak exposure did not visibly influence this adverse effect. No compound-related effects were observed in rats interruptedly or uninterruptedly exposed to 150 ppm during the 4-week exposure period; therefore, the NOAEL is 150 ppm. The NOAEL(HEC) based on effects on the olfactory epithelium in the extrathoracic region is 8.7 mg/cu.m.

Appelman et al. (1982) exposed Wistar rats (10/sex/group) for 6 hours/day, 5 days/week for 4 weeks to 0, 400, 1000, 2200, or 5000 ppm acetaldehyde (0, 728, 1820, 4004 and 9100 mg/cu.m, respectively). Duration-adjusted concentrations are 0, 130, 325, 715 and 1625 mg/cu.m, respectively. The general condition and behavior of the rats were checked daily. Blood picture (Hb, Hct, RBC, total and differential WBC, and plasma protein) and chemistry were examined at the end of the treatment period. Activities of plasma glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, and alkaline phosphatase were also determined. Urine was analyzed for density, volume, pH, protein, glucose, occult blood, ketones, and appearance. The kidneys, lungs, liver, and spleen were weighed. Microscopic examination was performed on the lungs, trachea, larynx, and nasal cavity (3 transverse sections) of all animals and on the kidneys, liver, and spleen of all control and high-concentration groups.

During the first 30 minutes of each exposure at the 5000-ppm level, rats exhibited severe dyspnea that gradually became less severe during the subsequent exposure period. Two animals died at this level (1 female, 1 male) and one male died at the 2200-ppm level, but the cause of death could not be determined due to autolysis or cannibalism. Growth was retarded in males at the three highest exposure concentrations and in females at the 5000-ppm level. The percentage of lymphocytes in the blood was lower and the percentage of neutrophilic leukocytes higher in males and females of the 5000-ppm group than in controls. There were a few statistically significant differences in several blood chemistry parameters between the exposure groups and the control group but none of them were concentration-related. Statistically significant changes in organ-to-body weight ratios included decreased liver weights in both sexes and increased lung weights in males at the 5000-ppm level. Males in the 5000-ppm level produced less urine, but it was of higher density. Compound-related histopathological changes were observed only in the respiratory system. The nasal cavity was most severely affected and exhibited a concentration-response relationship. At the 400-ppm level, compound-related changes included: slight to severe degeneration of the nasal olfactory epithelium, without hyper- and metaplasia, and disarrangement of epithelial cells. At the 1000- and 2200-ppm levels, more severe degenerative changes occurred, with hyperplastic and metaplastic changes in the olfactory and respiratory epithelium of the nasal cavity. Degeneration with hyperplasia/metaplasia also occurred in the laryngeal and tracheal epithelium at these levels. At 5000 ppm changes included severe degenerative hyperplastic and metaplastic changes of the nasal, laryngeal, and tracheal epithelium. Based on the degenerative changes observed in the olfactory epithelium, the 400-ppm level is designated as a LOAEL. The LOAEL(HEC), based on the ventilation rates for female rats, is 16.9 mg/cu.m. No NOAEL was identified.

Woutersen et al.(1986) exposed Wistar rats (105/sex/group) for 6 hours/day, 5 days/week for up to 28 months to 0, 750, 1500 and 3000/1000 ppm (0, 1365, 2730, 5460/1820 mg/cu.m, respectively). The highest concentration was gradually decreased because of severe growth retardation, occasional loss of body weight, and early mortality in this group. The duration-adjusted concentrations are 0, 244, 488, and 975/325 mg/cu.m, respectively. The general condition and behavior of the rats were checked daily. Samples of a wide range (otherwise not specified) of tissues, including the nasal cavity, trachea with main bronchi, and lungs were examined by light microscopy. The rats in the high-exposure concentration showed excessive salivation, labored

respiration, and mouth breathing. The respiratory distress was still observed when the concentration was reduced to 1000 ppm, although fewer were dyspneic. Only a few rats died during the first 6 months of the study but thereafter a sharp increase in the numbers of deaths occurred in the high-concentration group. All top concentration rats had died by 25 months. When the study was terminated, only a few animals remained alive in the mid-concentration group. The cause of early death or moribund condition was nearly always partial or complete occlusion of the nose by excessive amounts of keratin and inflammatory exudate. Several showed acute bronchopneumonia occasionally accompanied by tracheitis. Growth retardation occurred in males of each test group and in females of the two highest concentrations. The only exposure-related histopathology occurred in the respiratory system and showed a concentration-response relationship. The most severe abnormalities were found in the nasal cavity. Basal cell hyperplasia of the olfactory epithelium was seen in the low- and mid-concentration rats. The decrease in these changes in the olfactory epithelium was attributed to the incidence of adenocarcinomas at the higher levels. The respiratory epithelium of the nasal cavity was involved (hyperplasia and squamous metaplasia with keratinization) at the mid and high concentrations. Hyperplasia and squamous metaplasia, occasionally accompanied by keratinization, occurred in the larynx of rats exposed at the mid and high concentrations. The tracheal epithelium was not visibly affected at any exposure level. Adenocarcinomas occurred at all exposure concentrations and squamous cell carcinoma at the mid and high concentrations only. It thus appeared that the nasal tumors could be distinguished into two major types: adenocarcinomas from olfactory epithelium, and squamous cell carcinoma from the respiratory epithelium. The lowest exposure concentration, 750 ppm, is clearly a LOAEL based on the above changes in the olfactory epithelium. The LOAEL(HEC) is 56 mg/cu.m. No NOAEL was identified.

Woutersen and Feron (1987) conducted an inhalation study in which Wistar rats (30 rats/sex/group) were exposed to 0, 750, 1500, or 3000/1500 ppm acetaldehyde (0, 1365, 2730, 5460/2730 mg/cu.m, respectively) for 6 hours/day, 5 days/week for 52 weeks with a 26- or 52-week recovery period. The highest concentration was gradually decreased because of severe growth retardation, occasional loss of body weight, and early mortality. Duration-adjusted concentrations are 0, 244, 488, and 975/488 mg/cu.m, respectively. The general condition and behavior of the rats were checked daily. Histopathology was performed as described for Wouterson et al. (1986).

At the end of the 52-week exposure period, most of the animals in the high-concentration group exhibited labored respiration and mouth breathing. The respiratory distress diminished during the recovery period but did not disappear completely. Adenocarcinoma and squamous cell carcinoma occurred at the mid and high concentrations. Degeneration of the olfactory epithelium was similar in rats terminated after 26 weeks of recovery and rats killed immediately after exposure termination. Histopathological changes found in the respiratory epithelium were comparable with, but less severe than, those observed immediately after exposure termination. After 52 weeks of recovery, the degeneration of the olfactory epithelium was still visible to a slight degree in animals from all exposure groups. Animals in the high-concentration group did not show restoration of the olfactory epithelium. At the low concentration, normal olfactory epithelium was present in some animals but replacement of olfactory epithelium by respiratory epithelium was frequently seen. Histopathological changes in the respiratory epithelium of the two females of the high-concentration group examined were essentially comparable with those found in rats terminated after 26 weeks of recovery. These data suggest that there is incomplete recovery of olfactory and respiratory epithelium changes induced at all exposure concentrations for periods as long as 52 weeks after exposure termination.

Kruysse et al. (1975) conducted a 90-day inhalation study in hamsters (10/sex/concentration). The hamsters were exposed to acetaldehyde vapor at concentrations of 0, 390, 1340, or 4560 ppm (0, 127, 435.5 or 1482 mg/cu.m, adjusted for duration, respectively), for 6 hours/day, 5 days/week for 90

days. Histopathological changes attributable to exposure were observed only in the respiratory tract. At 4560 ppm, body weights were significantly reduced and the relative weights of heart, kidney, brain, testicle, and lung were significantly increased. Histopathological changes of the nasal cavity, larynx, trachea, and bronchi included necrosis, inflammatory changes, and hyperplasia and metaplasia of the epithelium. Mild effects observed at 1340 ppm consisted of statistically significant increased kidney weight in males, and small areas of stratified epithelium in the trachea in both sexes (30% of the animals). At 390 ppm, with the exception of a tiny focus of metaplastic epithelium in the trachea of 1 out of the 20 animals examined, no adverse effects were observed. The 390-ppm concentration was identified by the authors as a NOAEL. The study by Appelman et al. (1982) identified a similar level (400 ppm) as a LOAEL [LOAEL(HEC) = 16.9 mg/cu.m] for Wistar rats, but surface area values in hamsters are not available so that a comparison on HEC values could not be made to determine the relative sensitivities of the species to acetaldehyde. The LOAEL for the extrarespiratory effects (effect on kidney weight) is 1340 ppm and the NOAEL also at 390 ppm. The NOAEL(HEC) for extrarespiratory effects is 127 mg/cu.m.

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o INHALATION RFD UNCERTAINTY :

UF = 1000. An uncertainty factor of 10 was applied to account for sensitive human populations. A factor of 10 was applied for both uncertainty in the interspecies extrapolation using dosimetric adjustments and to account for the incompleteness of the data base. A factor of 10 was applied to account for subchronic to chronic extrapolation.

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o INHALATION RFD MODIFYING :

MF = 1.
FACTOR

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o INHALATION RFD COMMENTS :

Saldiva et al. (1985) exposed male Wistar rats (12/group) to 0 or 243 ppm (442 mg/cu.m) of acetaldehyde 8 hours/day, 5 days/week for 5 weeks. Duration-adjusted values are 0 and 105 mg/cu.m., respectively. The animals were evaluated for pulmonary mechanics before and after the exposure period, and gross and paraffin-embedded sample observations were made after exposure, especially of the respiratory system. Increases in RF, FRC, RV, and TLC were significantly different from control values. Damage to distal airways was suggested since functional tests for damage to elasticity or for severe obstruction were not demonstrated. Histopathological investigation showed an intense inflammatory reaction with olfactory epithelium hyperplasia and polymorphonuclear and mononuclear infiltration of the submucosa. Cannulation precluded evaluation of tracheal effects and no differences between the control and exposed animals were observed for the lower respiratory tract. Although this study presents the pathology data in only a descriptive fashion, it identifies a LOAEL for nasal effects of 105 mg/cu.m (HEC = 13.7 mg/cu.m) that is consistent with the principal studies. The LOAEL(HEC) for thoracic effects on pulmonary function is 220.5 mg/cu.m.

Feron (1979) exposed Syrian golden hamsters (35 males/group) by inhalation to 1500 ppm acetaldehyde 7 hours/day, 5 days/week for 52 weeks. The duration-adjusted concentration is 487.5 mg/cu.m. Exposure to acetaldehyde vapor resulted in epithelial hyperplasia and metaplasia, accompanied by inflammation in the nasal cavity and trachea. No evidence of carcinogenicity was observed.

In an inhalation study Feron et al. (1982) exposed Syrian golden hamsters to 2500 ppm (948 mg/cu.m adjusted for duration) for the first 9 weeks, 2250 ppm, (853 mg/cu.m adjusted for duration) for weeks 10-20, 2000 ppm (758 mg/cu.m adjusted for duration) for weeks 21-29, 1800 ppm (682.5 mg/cu.m adjusted for duration) for weeks 30-44, and 1650 ppm (626 mg/cu.m adjusted for duration) for weeks 42-52, for 7 hours/day, 5 days/week for a total of 52

weeks. Compound-related changes included rhinitis, hyperplasia, and metaplasia of the nasal, laryngeal, and tracheal epithelium, and nasal and laryngeal carcinomas. No LOAEL was identified.

No inhalation studies for reproductive or developmental effects have been performed. No oral or inhalation developmental studies, nor any reproductive studies, exist.

Zorzano and Herrera (1989) studied the pattern of acetaldehyde appearance in maternal and fetal blood, maternal and fetal liver and placenta after oral ethanol administration or intravenous acetaldehyde administration (10 mg/kg) to pregnant Wistar rats. The study demonstrated that acetaldehyde was able to cross the placental barrier at high concentrations (fetal blood concentrations were only detectable when maternal blood concentrations were greater than 80 uM). The fetal oxidation capacity in liver and placenta was shown to be lower than that of the maternal liver. A threshold above which the removal capacity of acetaldehyde metabolism by the fetoplacental unit would be surpassed was estimated to be 80 uM (maternal blood concentration) in the 21-day pregnant rat and possibly lower at early pregnancy when aldehyde dehydrogenase is absent from fetal liver.

Retention of acetaldehyde in humans under "physiologic conditions" of breathing rate and tidal volume has been shown to be approximately 60% between 100 and 200 mg/cu.m for a few minutes (Egle, 1970), and retention was shown to decrease slightly at higher concentrations. Breathing rate and volume and exposure concentration were shown to influence retention. Retention has not been determined at lower concentrations comparable with the HEC estimates derived here, however. Retention of acetaldehyde from cigarette smoke was shown to be 99% (Dalhamn et al., 1968). Acetaldehyde has been shown to be absorbed via inhalation at high concentrations (9000-10,000) for 1 hour (Watanabe et al., 1986). Binding and metabolism in blood and rat nasal mucosa have been demonstrated (Hagihara et al., 1981; Casanova-Schmitz et al., 1984). Casanova-Schmitz et al. (1984) observed that rats exposed to 700 ppm for 2 hours demonstrated only 0.7 mM in circulating blood 5 minutes after exposure termination, suggesting that binding in the respiratory tract and rapid metabolism significantly reduces systemic circulation at steady state.

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o INHALATION RFD CONFIDENCE : Study: Medium Data Base: Low RfC: Low the principal studies is medium since appropriate histopathology was performed on an adequate number of animals and a NOAEL and LOAEL were identified, but the duration was short and only one species was tested. Confidence in the data base is low due to the lack of chronic data establishing NOAELs and due to the lack of reproductive and developmental toxicity data. Low confidence in the RfC results.

o INHALATION RFD SOURCE :

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA documentation -- U.S. EPA, 1991
DOCUMENT

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o REVIEW DATES : 05/18/89, 04/25/91
o VERIFICATION DATE : 04/25/91
o EPA CONTACTS :

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CAREV-

o CLASSIFICATION : B2; probable human carcinogen

o BASIS FOR CLASSIFICATION : Based on increased incidence of nasal tumors in male and female rats and laryngeal tumors in male and female hamsters after inhalation exposure.

o HUMAN CARCINOGENICITY DATA :

Inadequate. The only epidemiological study involving acetaldehyde exposure showed an increased crude incidence rate of total cancer in acetaldehyde production workers as compared with the general population (Bittersohl, 1974). Because the incidence rate was not age adjusted, and because this study has several other major methodological limitations (including concurrent exposure to other chemicals and cigarette exposure, short duration, small number of subjects, and lack of information on subject selection, age and sex distribution) it is considered inadequate to evaluate the carcinogenicity of acetaldehyde.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. Feron (1979) exposed groups of 35 male Syrian Golden hamsters to 0 or 1500 ppm acetaldehyde by inhalation 7 hours/day, 5 days/week, for 52 weeks. These animals were also exposed weekly by intratracheal instillation to increasing doses of benzo(a)pyrene (BaP) in 0.2 mL of 0.9% NaCl, or to NaCl alone. Animals were killed and autopsied after exposure and 26 weeks of recovery in air. No neoplastic effects due to acetaldehyde alone were found. The highest BaP dose (1 mg/week for 52 weeks) combined with acetaldehyde exposure produced twice the incidence of squamous cell carcinomas compared with the same dose of BaP alone. In the second part of this study, no respiratory tract tumors were found in groups of 25 male hamsters which were intratracheally instilled once a week with 0.2 mL of 2% or 4% acetaldehyde in 0.9% NaCl for 52 weeks.

Feron et al. (1982) studied male and female hamsters exposed by inhalation to acetaldehyde alone or in combination with intratracheally administered BaP or diethylnitrosamine. The animals were exposed for 7 hours/day, 5 days/week, for 52 weeks to a time weighted average concentration of 2028 ppm. They were killed and autopsied after a 29-week recovery period; that is, at week 81. A slight increase in nasal tumors and a significantly increased incidence of laryngeal tumors was observed in both male and female hamsters exposed to acetaldehyde alone. This study supported the observation of Feron (1979) that acetaldehyde treatment enhanced tumorigenicity (production of tracheobronchial carcinomas) of BaP.

The carcinogenicity of acetaldehyde was studied in 420 male and 420 female albino SPF Wistar rats (Woutersen and Appelman, 1984; Woutersen et al., 1985). After an acclimatization period of 3 weeks, these animals were randomly assigned to four groups of 105 males and 105 females each. The animals were then exposed by inhalation to atmospheres containing 0, 750, 1500, or 3000 ppm acetaldehyde for 6 hours/day, 5 days/week, for 27 months. The concentration in the highest dose group was gradually reduced from 3000 to 1000 ppm because of severe growth retardation, occasional loss of body weight and early mortality in this group. Interim sacrifices were carried out at 13, 26, and 52 weeks. One tumor was observed in the 52 week sacrifice group and none at earlier times. Exposure to acetaldehyde increased the incidence of tumors in an exposure-related manner in both male and female rats. In addition, there were exposure-related increases in the incidences of multiple respiratory tract tumors. Adenocarcinomas were increased significantly in both male and female rats at all exposure levels, whereas squamous cell carcinomas were increased significantly in male rats at middle and high doses and in female rats only at the high dose. The squamous cell carcinoma incidences showed a clear dose-response relationship. The incidence of adenocarcinoma was highest in the mid-exposure group (1500 ppm) in both male and female rats, but this was probably due to the high mortality and competing squamous cell carcinomas

at the highest exposure level. In the low-exposure group, the adenocarcinoma incidence was higher in males than in females.

In a concurrent study, 30 animals of each sex were exposed to the same concentrations of acetaldehyde for 52 weeks followed by a recovery period of 26 weeks (10 animals) or 52 weeks (20 animals). Significant increases in nasal tumors were observed in male and female rats, including adenocarcinomas and squamous cell carcinomas, in both recovery groups. These findings indicate that after 52 weeks of exposure to acetaldehyde, proliferative epithelial lesions of the nose may develop into tumors even without continued exposure.

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o SUPPORTING DATA :

Acetaldehyde has been shown by several laboratories to induce sister chromatid exchange (SCE) in cultured mammalian cells (Obe and Ristow, 1977; Obe and Beer, 1979; deRaat et al., 1983; Bohlke et al., 1983; Ristow and Obe, 1978; Jansson, 1982; Norrpa et al., 1985). A recent study provided evidence that SCE-inducing lesions may be persistent for several cell generations (He and Lambert, 1985). The in vitro SCE response did not require metabolic activation. The induction of SCE by acetaldehyde has also been detected in bone marrow cells of mice and hamsters in vivo (Obe et al., 1979; Korte and Obe, 1981). Acetaldehyde caused chromosomal aberrations in mammalian cell culture (Bird et al., 1981; Bohlke et al., 1983) and plants (Rieger and Michaelis, 1960), but not in Drosophila (Woodruff et al., 1985). Chromosome gaps and breaks were found in rat embryos after a single intraamniotic injection on day 13 of gestation (Barilyak and Kozachuk, 1983). Acetaldehyde produced sex-linked recessive lethal gene mutations after injection in Drosophila (Woodruff et al., 1985), but has been negative in testing in Salmonella (Commoner, 1976, Laumbach et al., 1976; Pool and Wiesler, 1981., Marnett et al., 1985, Mortelmans et al., 1986). Acetaldehyde has been shown to produce crosslinks between protein and DNA in the nasal respiratory mucosa (Lam et al., 1986).

Acetaldehyde is similar in stucture to formaldehyde (classified B1) which also produces nasal tumors in animals exposed by inhalation.

CARO - NO DATA
CARI -

o CLASSIFICATION	: B2; probable human carcinogen
o BASIS FOR CLASSIFICATION	: Based on increased incidence of nasal tumors in male and female rats and laryngeal tumors in male and female hamsters after inhalation exposure.
o INHALATION UNIT RISK	: 2.2E-6 per (ug/cu.m)
o DOSE EXTRAPOLATION METHOD	: Linearized multistage-variable exposure input form

o RISK/AIR CONCENTRATIONS :

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	5E+1 ug/cu.m
E-5 (1 in 100,000)	5E+0 ug/cu.m
E-6 (1 in 1,000,000)	5E-1 ug/cu.m

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o INHALATION DOSE-RESPONSE DATA :

Tumor Type -- nasal squamous cell carcinoma or adenocarcinoma
Test Animals -- rat/SPF Wistar, male

Route -- inhalation
Reference -- Woutersen and Appelman, 1984

Dose ----- Lifetime Average Administered (ppm)	Dose ----- Human Equivalent (ppm)	Tumor Incidence
0	0	1/94
750	130	20/95
1500	255	49/95
1540	279	47/92

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o ADDITIONAL COMMENTS :

Actual measured exposures on two occasions for the low and medium dose groups were 727/735 and 1438/1412 ppm, respectively. The highest dose administered is given as TWA. Low-dose extrapolation was performed using two forms of the linearized multistage model, the quantal model (Crump et al., 1977) and a form which allows analysis for a variable dose pattern, adjusts for intercurrent mortality, and is capable of estimating risk at any time from any dosing pattern (Crump and Howe, 1984). The latter model is referred to as the variable exposure form. Comparison of the results from the two models showed very little difference in the unit risk estimates. The variable exposure form was selected for the final unit risk estimate because it allows the combination of the lifetime study and the recovery study for risk estimation. The above estimates are from male rats; the unit risk calculated from data on female rats at 18 months was 1.6E-6 per (mg/cu.m). No difference was found in tumor incidence between animals exposed for a full lifetime and those exposed for 12 months and allowed to recover. At the end of 24 months, however, the tumor incidences in the recovery group were less than those in the lifetime exposure group.

The unit risk should not be used if the air concentration exceeds 5E+3 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

An adequate number of animals was observed in a lifetime study. Increases in nasal tumors were observed in both male and female rats, and similar unit risks were obtained using these data.

CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1987. Health Assessment Document for Acetaldehyde. Prepared by the Office of Health and Environmental Assessment, Research Triangle Park, NC for the Office of Air Quality Planning and Standards. EPA/600/8-86/015A. External Review Draft.

The Health Assessment Document is a final draft which has received both agency and external review.
DOCUMENT

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o REVIEW DATES : 01/13/88
o VERIFICATION DATE : 01/13/88

o EPA CONTACTS :

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HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE- NO DATA
BCF - NO DATA

CAA - NO DATA

WQCHU- NO DATA

WQCAQ- NO DATA

MCLG - NO DATA

MCL - NO DATA

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 1000 pounds (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for acetaldehyde is based on ignitability and reactivity as adjusted after consideration of the natural BHP processes. The available data indicate that the closed cup flash point is -38 degrees F and the boiling point is 70 degrees F. This chemical may also polymerize. After adjustment one level upward due to the BHP process, the final RQ is 1000 pounds.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA - NO DATA

TSCA -

No data available

OREF - None

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IREF - Appleman, L.M., R.A. Woutersen, V.J. Feron, R.N. Hooftman and W.R.F. Notten. 1986. Effect of variable versus fixed exposure levels on the toxicity of acetaldehyde in rats. J. Appl. Toxicol. 6(5): 331-336.

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IREF - Feron, V.J. 1979. Effects of exposure to acetaldehyde in Syrian hamsters simultaneously treated with benzo(:)pyrene or diethylnitrosamine. Prog. Exp. Tumor Res. 24: 162-176.

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IREF - Hagihara, S., Y. Sameshima, M. Kobayashi and F. Obo. 1981. Behavior of acetaldehyde transported in blood. Biochem. Pharmacol. 30: 657-661.

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IREF - Woutersen, R.A., L.M. Appelman, A.Van Garderen-Hoetmer, and V.J. Feron. 1986. Inhalation toxicity of acetaldehyde in rats. III. Carcinogenicity study. Toxicology. 41: 213-231.

IREF - Woutersen, R.A. and V.J. Feron. 1987. Inhalation toxicity of acetaldehyde in rats. IV. Progression and regression of nasal lesions after discontinuation of exposure. Toxicology. 47: 295-305.

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CREF - Feron, V.J. 1979. Effects of exposure to acetaldehyde in Syrian hamsters simultaneously treated with benzo(a)pyrene or diethylnitrosamine. Prog. Exp. Tumor Res. 24: 162-176.
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CREF - Wouterson, R., A. Van Garderen-Hoetmer and L.M. Appelman. 1985. Lifespan (27 months) inhalation carcinogenicity study of acetaldehyde in rats. Report No. V85.145/190172. CIVO-Institutes TNO, The Netherlands.
HAREF- None

2 - IRIS
NAME - Ammonia
RN - 7664-41-7
IRSN - 479
DATE - 920904
UPDT - 09/04/92, 3 fields
STAT - Oral RfD Assessment (RDO) no data
STAT - Inhalation RfC Assessment (RDI) on-line 05/01/91
STAT - Carcinogenicity Assessment (CAR) no data
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 05/01/91 RDI Inhalation RfC summary on-line
IRH - 05/01/91 REFS Bibliography on-line
IRH - 01/01/92 EXSR Regulatory Action section on-line
RLEN - 31303
SY - Ammonia
SY - AM-FOL
SY - AMMONIA GAS
SY - Ammonia Solution, Strong
SY - Ammoniac [French]
SY - Ammoniaca [Italian]
SY - Ammoniak [German]
SY - Amoniaco [Spanish]
SY - Amoniak [Polish]
SY - ANHYDROUS AMMONIA
SY - Aromatic Ammonia, Vaporole
SY - Caswell No. 041
SY - EPA Pesticide Chemical Code 005302
SY - HSDB 162
SY - Nitro-Sil
SY - R 717
SY - SPIRIT OF HARTSHORN
SY - UN 1005
SY - UN 2073
SY - UN 2672
MF - H3N
USE - Twenty-five percent of the ammonia produced is used as a direct application fertilizer; intermediate uses of ammonia include 10% used for urea fertilizer; 19% for ammonium nitrate fertilizer; 18% for all other fertilizers; 4% for ammonium nitrate-based commercial explosives; 7% for major fiber and plastic intermediates, and 14% for all other applications (SRI). Ammonia is also used as a bactericide (USEPA/Pesticide Index, 1985).
COFO - Colorless gas, liquid (Weast, 1979); sharp, cloying, repellant odor (Booth, 1982)
ODOR - Colorless gas, liquid (Weast, 1979); sharp, cloying, repellant odor (Booth, 1982)
BP - -28.03F, -33.35C (Merck, 1976)
MP - -107.9F, -77.7C (Merck, 1976)
MW - 17.03
DEN - Liquid 0.6818 at -33.35C (Merck, 1983; p. 74)
VAP - 400 at -45.4C (Weast, 1983)
VAPD - 0.6 (Weiss, 1980; p. 73)
EVAP - Not Found
SOLW - 31 g/100 g at 25C (Merck, 1983)
FLPT - Not Found
FLMT - Flammable Limits: LEL -- 16% (NFPA, 1978) UEL -- 25% (NFPA, 1978)
AVOI - Avoid mixing ammonia with other chemicals and water (Bretherick, 1979). Ammonia is incompatible with many materials including silver and gold salts, halogens, alkali metals, nitrogen trichloride, potassium chlorate, chromyl chloride, oxygen halides, acid vapors, azides, ethylene oxide (Bretherick, 1979), picric acid (Environment Canada, 1981), and many other chemicals (NFPA, 1978).
DCMP - Not Found

RDO - NO DATA

RDI -

o INHALATION RFD SUMMARY :

Critical Effect	Exposures*	UF	MF	RfC
Lack of evidence of decreased pulmonary function or changes in subjective syptomatology Occupational Study Holness et al., 1989	NOAEL: 6.4 mg/cu.m (9.2 ppm) NOAEL(ADJ): 2.3 mg/cu.m NOAEL(HEC): 2.3 mg/cu.m LOAEL: None	30	1	1E-1 mg/cu.m
Increased severity of rhinitis and pneumonia with respiratory lesions Rat Subchronic Inhalation Study Broderson et al., 1976	NOAEL: None LOAEL: 17.4 mg/cu.m (25 ppm) LOAEL(ADJ): 17.4 mg/cu.m LOAEL(HEC): 1.9 mg/cu.m			

*Conversion Factors: MW = 17.03
Holness et al., 1989: Assuming 25C and 760 mm Hg, NOAEL (mg/cu.m) = 9.2 ppm x 17.03/24.45 = 6.4 mg/cu.m. The NOAEL is based on an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. NOAEL(ADJ) = 6.4 mg/cu.m x (MVho/MVh) x 5 days/7 days = 2.3 mg/cu.m.

Broderson et al., 1976: Assuming 25C and 760 mm Hg, the LOAEL (mg/cu.m) = 25 ppm x 17.03/24.45 = 17.4 mg/cu.m. The LOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.14 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm., Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.1068. NOAEL(HEC) = 17.4 x RGDR = 1.9 mg/cu.m.

o INHALATION RFD STUDIES :

Holness, D.L., J.T. Purdham and J.R. Nethercott. 1989. Acute and chronic respiratory effects of occupational exposure to ammonia. Am. Ind. Hyg. Assoc. J. 50: 646-650.

Broderson, J.R., J.R. Lindsey and J.E. Crawford. 1976. The role of environmental ammonia in respiratory mycoplasmosis of rats. Am. J. Pathol. 85: 115-130.

Holness et al. (1989) investigated production workers exposed to ammonia in a soda ash facility. All of the available 64 production workers were invited to participate and 82% agreed to be evaluated. The control group consisted of 31 other plant workers from stores and office areas of the plant without previous exposure to ammonia. The mean age of the workers was 38.9 years and duration of exposure was 12.2 years. Weight was the only statistically significant difference in demographics found after comparing height, weight, years worked, % smokers and pack-years smoked. The mean TWA ammonia exposures based on personal sampling over one work shift (average sample collection 8.4 hours) of the exposed and control groups were 9.2 ppm (6.4 mg/cu.m) and 0.3 ppm (0.21 mg/cu.m), respectively.

A questionnaire was administered to obtain information on exposure and

work histories and to determine eye, skin and respiratory symptomatology (based on the American Thoracic Society [ATS] questionnaire [Ferris, 1978]). Spirometry (FVC, FEV-1, FEF50 and FEF75) was performed according to ATS criteria at the beginning and end of each work shift on the first workday of the week (day 1) and the last workday of the week (day 2). Differences in reported symptoms and lung function between groups were evaluated using the actual values and with age, height and pack-years smoked as covariates in linear regression analysis. Baseline lung function results were expressed as percent of predicted values calculated from Crapo et al. (1981) for FVC and FEV-1 and from Lapp and Hyatt (1967) for FEF50 and FEF75.

No statistical difference in the prevalence of the reporting symptoms was evident between the exposed and control groups, although workers reported that exposure at the plant had aggravated specific symptoms including coughing, wheezing, nasal complaints, eye irritation, throat discomfort and skin problems. The percentage of exposed workers reporting hay fever or familial history of hay fever was significantly less than controls, suggesting possible self-selection of atopic individuals out of this work force. The atopic status of the worker and control groups was not determined by skin prick tests to common aeroallergens. Furthermore, the workers complained that their symptomatology was exacerbated even though there was no statistical difference between groups. Since the study was cross-sectional in design with a small population, it is possible that selection bias may have occurred.

Baseline lung functions (based on the best spirometry values obtained during the four testing sessions) were similar in the exposed and control groups. No changes in lung function were demonstrated over either work shift (days 1 or 2) or over the workweek in the exposed group compared with controls. No relationship was demonstrated between chronic ammonia exposure and baseline lung function changes either in terms of the level or duration of exposure, probably due to lack of adequate exposure data for categorizing exposures and thus precluding development of a meaningful index accounting for both level and length of exposure.

Based on the lack of subjective symptomatology and changes in spirometry, this study establishes a free-standing TWA NOAEL of 9.2 ppm (6.4 mg/cu.m). Adjustment for the TWA occupational scenario results in a NOAEL(HEC) of 2.3 mg/cu.m.

Broderson et al. (1976) exposed groups of F344 rats (6/sex/dose) continuously to 25, 50, 150 or 250 ppm ammonia (HEC = 1.9, 3.7, 11.2 or 18.6 mg/cu.m, respectively) for 7 days prior to inoculation with Mycoplasma pulmonis and from 28-42 days following M. pulmonis exposure. Each treatment group had a corresponding control group exposed only to background ammonia and inoculated with M. pulmonis in order to produce murine respiratory mycoplasmosis (MRM). The following parameters were used to assess toxicity: clinical observations and histopathological examination of nasal passages, middle ear, trachea, lungs, liver and kidneys. All levels of ammonia, whether produced naturally or derived from a purified source, significantly increased the severity of rhinitis, otitis media, tracheitis and pneumonia characteristic of M. pulmonis. Furthermore, there was a significant concentration response between observed respiratory lesions and increasing environmental ammonia concentration for gross and microscopic lesions. All lesions observed were characteristic of MRM. Gross bronchiectasis and/or pulmonary abscesses and the extent of gross atelectasis and consolidation was consistently more prevalent in exposed animals at all concentrations than in their corresponding controls. The severity of the microscopic lesions in the nasal passages, middle ears, tracheas and lungs was significantly greater in all exposed groups compared with controls. Increasing ammonia concentration was not associated with an increasing frequency of M. pulmonis isolations. Additionally, rats not exposed to M. pulmonis and exposed to ammonia at 250 ppm developed nasal lesions (epithelial thickening and epithelial hyperplasia) unlike those observed in inoculated rats. Based upon these data in M. pulmonis exposed rats, a LOAEL(HEC) of 1.9 mg/cu.m was identified.

A group of 295 pathogen free F344 rats was inoculated with M. pulmonis and exposed to either trace or 100 ppm ammonia (HEC=7.4 mg/cu.m) (Schoeb et al., 1982). Growth of M. pulmonis was greater in exposed rats than in controls. Similarly, serum immunoglobulin antibody responses to the inoculum were greater in the exposed population. It was further demonstrated that the nasal passages absorbed virtually all the ammonia at concentrations <500 ppm, indicating that the increased numbers of M. pulmonis in the lungs and the consequent exacerbation of lung lesions in MRM are secondary to events in the nasal passages rather than a direct effect of ammonia in the lung itself. These results are consistent with those of Broderson et al. (1976) detailed above.

The use of Holness et al. (1989) as the principal study can only be supported in the context of the data array. It is not surprising that no effects were seen on screening spirometry since the exposure levels were low. Comparing the 9.2 TWA of Holness et al. (1989) with other data on the respiratory effects of ammonia, a trend is observed that at lower concentrations the extrathoracic region of the respiratory system is affected due to the chemical's solubility and reactivity; while at higher concentrations, the lower part of the respiratory system is involved in both experimental animals (Dahlman, 1956; Gamble and Clough, 1976) and humans (Flury et al., 1983). Thus, no effects were observed in the lower respiratory system as reflected by pulmonary function. Pulmonary function may not be a particularly sensitive test because exposure to this type of agent at low concentrations is not expected to result in significant exposure of the lower respiratory region. No objective investigation of the workers' nasal epithelium was performed and the complaint of exacerbated upper respiratory symptoms suggests sensory irritation and supports the extrathoracic region as the critical region for an effect. The possibility of selection bias against atopic predispositions in the population is suggested by the significantly lower prevalence of hay fever in the exposed versus control cohort. Thus, there is a concentration-response in the extrathoracic region in experimental animals beginning at a LOAEL at essentially the same HEC as the NOAEL in Holness et al. (1989) and the NOAEL may be based on a less sensitive endpoint. Also the apparent discrepancy of a lower LOAEL(HEC) from Broderson et al. (1976) and the identified NOAEL(HEC) of the Holness et al. (1989) study may be the result of differences in air flow patterns since rats are obligate nose-breathers and humans breathe oronasally. The use of the NOAEL from Holness et al. (1989) can be supported as marginal in this context due to the symptomatology complaints and because human data engenders less uncertainty than extrapolation from the experimental animal data.

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o INHALATION RFD UNCERTAINTY :

UF = 30. An uncertainty factor of 10 is used to allow for the protection of sensitive individuals. A factor of 3 was used to account for several data base deficiencies including the lack of chronic data, the proximity of the LOAEL to the NOAEL and the lack of reproductive and developmental toxicology studies. This factor is not larger than 3, however, since studies in rats (Schaerdel et al., 1983) have shown no increases in blood ammonia levels at exposures 32 ppm and only minimal increases at 300-1000 ppm, suggesting that no significant distribution is likely to occur at the HEC level calculated.

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o INHALATION RFD MODIFYING :

MF = 1.
FACTOR

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o INHALATION RFD COMMENTS :

Groups of four healthy human volunteers were exposed weekly (5 days/week) to 25 (2 hours/day), 50 (4 hours/day) or 100 (6 hours/day) ppm ammonia (1.0,

4.1 or 12.1 mg/cu.m) for 6 weeks; or to 50 ppm (6.2 mg/cu.m) 6 hours/day for 6 weeks. Subjective and objective indications of eye and respiratory tract irritation, pulse rate, respiration rate, FVC, FEV and difficulty in performing simple cognitive tasks were used to assess toxicity. No abnormalities of the chest, heart, vital organs, neurological response, apparent motor function, or significant weight changes were observed during weekly medical examinations. Transient irritation of the nose and throat was observed at 50 ppm (duration-adjusted to 4.1 mg/cu.m) or greater (Ferguson et al., 1977).

Flury et al. (1983) reported on a 5-year follow-up case study of a 50-year-old male patient who sustained a high-concentration exposure to ammonia fumes when a refrigerator coolant tank exploded. The patient had no prior history of smoking, pulmonary disease, wheezing or atopy and no family history of atopy or asthma before the industrial accident. The patient was hospitalized with acute respiratory failure. Laryngoscopy demonstrated membranous formation involving the entire tracheal wall. Chest examination revealed bilateral rhonchi, and chest x-rays on admission revealed bilateral perihilar infiltrates. Subsequent serial pulmonary function testing (spirometry and diffusion capacity) was performed and although the initial peripheral airway abnormality resolved over the 5-year period, a persistent expiratory obstruction and recurrent bronchospasm, suggestive of hyperreactive airways, was demonstrated. It is proposed that reepithelialization and probable reinnervation of the bronchial mucosa following the initial inflammation resulted in drastically altered irritant receptors.

Eight human volunteers were exposed to 50, 80, 110 and 140 ppm ammonia (35, 56, 76 and 97 mg/cu.m, respectively) for 2 hours, with a 1-week interval between exposures. The subjects tolerated a concentration of 76 mg/cu.m, although they rated the throat irritation as a nuisance. An ammonia concentration of 97 mg/cu.m was intolerable, and all of the subjects left the exposure chamber prematurely (Verberk, 1977).

Human volunteers were exposed to 21 or 35 mg/cu.m ammonia for 10 minutes. At 35 mg/cu.m, the irritation was not found to be "discomforting or painful" and was rated "moderate" by 4/6 volunteers, "faint" by 1/6 and "none" by 1/6; at 21 mg/cu.m, irritation was rated "faint" by 2/5 and "none" by 3/5 (MacEwen et al., 1970).

Six volunteers were exposed to 500 ppm ammonia (348 mg/cu.m) for 30 minutes. Nasal and throat irritation was reported. An increase in minute volume ranging from 50-250% over control values was observed (Silverman et al., 1949).

Kane et al. (1979) determined an RD50 value (exposure concentration to evoke a 50% decrease in respiratory rate) for sensory irritation in Swiss-Webster mice for ammonia of 303 ppm (95% C.I. 159-644) by plotting the percent decrease in respiratory rate versus the logarithm of the exposure concentration. A minimal irritation level for humans was predicted at 0.01RD50 (3 ppm).

Dahlman (1956) microscopically monitored the ciliary movement in the tracheas of rats exposed to ammonia via mouth-piece continuously for 8 minutes to concentrations of 90, 45, 20 and 10 ppm (3 rats/dose); and 6.5 and 3 ppm (2 rats/dose). Ciliary activity ceased in a concentration-dependent rate upon exposure to ammonia. Time to ciliary stasis was 5, 10, 20 and 150 seconds at concentrations of 90, 45, 20 and 6.5 ppm, respectively. Time to ciliary stasis was 7-8 minutes at the 3 ppm concentration.

Gamble and Clough (1976) whole-body exposed female Porton rats to ammonia concentrations of 200 (+/- 50) ppm for 4, 8 or 12 days or 435 (+/- 135) ppm for 7 days. Duration of exposure was not otherwise specified. The total number of animals was 16, but the apportionment into exposure groups was not provided. Hyperplasia of the tracheal epithelium was shown to be

concentration- and time-dependent. At 4 days of exposure to 200 ppm, the epithelium had changed to transitional-stratified and by 8 days there was gross change: disappearance of cilia and stratification increasing to folds forming on the luminal surface. A mucilaginous exudate was also evident with a slight increase in submucosal cellularity. At 12 days at the 200 ppm concentration, the epithelialization had increased in thickness. Rats exposed for 7 days to 435 ppm showed acute inflammatory reactions with infiltration of neutrophils, large mononucleated cells, monocytes and immature fibroblasts in the trachea. Evidence of necrotic changes at the luminal surface included pyknotic nuclei and karyorrhectic cells.

Groups of 10 guinea pigs and 20 Swiss albino mice were exposed continuously to an ammonia-air concentration of 20 ppm (13.9 mg/cu.m) for up to 6 weeks. A separate group of six guinea pigs was similarly exposed to an ammonia concentration of 50 ppm (35 mg/cu.m) for 6 weeks, and a group of 21 Leghorn chickens was exposed to a 20 ppm concentration for up to 12 weeks. Controls (number not specified) were maintained under identical conditions, except for the ammonia. Smaller groups of chickens were exposed continually to either 200 ppm for up to 3 weeks or 1000 ppm for up to 2 weeks. The effects of ammonia were found to be both time- and concentration-dependent. While no effects were observed in guinea pigs, mice, or chickens sacrificed after 1, 2, 3 or 4 weeks of exposure at 20 ppm, darkening/reddening, edema, congestion, and hemorrhage were seen in the lungs of all three species at sacrifice after 6 weeks of exposure at that concentration. In guinea pigs exposed to 50 ppm ammonia for 6 weeks, grossly enlarged and congested spleens, congested livers and lungs, and pulmonary edema were seen. In chickens exposed to 200 ppm for 17-21 days, liver congestion and slight clouding of the cornea were observed in addition to those effects observed in the chickens exposed to 20 ppm ammonia for 6 weeks. At 1000 ppm, the same effects, in addition to congestion of the spleen, were seen in chickens after just 2 weeks of exposure, and corneal opacities developed within just 8 days of exposure. In a second series of experiments, it was found that a 72-hour exposure to 20 ppm ammonia significantly increased the infection rate of chickens subsequently exposed to an aerosol of Newcastle disease virus, while the same effect was observed in just 48 hours in chickens exposed to 50 ppm. Changes in gross and micropathology did not accompany the change in disease rate (Anderson et al., 1964).

Guinea pigs were exposed to 0 or 170 ppm (118 mg/cu.m) 6 hours/day, 5 days/week for up to 18 weeks. No adverse effects were observed in animals exposed to ammonia for 6-12 weeks (HEC=21 mg/cu.m). Mild changes in the spleen, kidney suprarenal glands and livers were observed (HEC=19 mg/cu.m) in guinea pigs exposed for 18 weeks. No effects on the lungs were observed. The upper respiratory tract was not examined (Weatherby, 1952).

Swiss-Webster mice (16-24/group) were exposed to 0 or 305 ppm ammonia (212 mg/cu.m) 6 hours/day for 5 days. Nasal lesions were observed at 212 mg/cu.m which when dose duration adjusted for the RGDR, equals a LOAEL(HEC) of 4.5 mg/cu.m (Buckley et al., 1984).

Continuous exposure of rats to ammonia at 0, 40, 127, 262, 455 or 470 mg/cu.m for a minimum of 90 days (114 days for the 40 mg/cu.m group) was conducted in male and female Sprague-Dawley and Long-Evans rats. A LOAEL of 262 mg/cu.m (HEC=28 mg/cu.m) was determined based upon nasal discharge in 25% of the rats, and nonspecific circulatory and degenerative changes in the lungs and kidneys that were difficult to relate specifically to ammonia inhalation. A frank-effect-level of 455 mg/cu.m (HEC=48.7 mg/cu.m) was observed due to high mortality in the rats (90-98%). Nasal passages were not histologically examined (Coon et al., 1970).

Duroc pigs were exposed to ammonia concentrations of 10, 50, 100 and 150 ppm. Exposure to ammonia significantly decreased both food intake and body weight gain. Higher concentrations caused nasal, lacrimal and mouth secretions, which became less severe over time. No treatment-related gross or

microscopic changes were observed in the bronchi, lungs or turbinates at necropsy (Stombaugh et al., 1969).

Various animal species were exposed to 0, 155 and 770 mg/cu.m for 8 hours/day, 5 days/week for 30 exposures (rats, guinea pigs, rabbits, dogs and monkeys). The LOAEL for lung inflammation is 770 mg/cu.m for rats (HEC=82.4 mg/cu.m) and guinea pigs. Ocular and nasal irritation was observed at 770 mg/cu.m in rabbits and dogs. The upper respiratory tract was not examined (Coon et al., 1970).

Atmospheric ammonia is present in relatively low concentrations in both urban and nonurban environments. Typical levels of ammonia are on the order of 5 and 20 ug/cu.m for nonurban and urban sites, respectively (WHO, 1986). The total intake of ammonia by inhalation is approximately 0.1-0.5 mg/day. Ammonia also may be excreted through expired air. Estimates of ammonia expired by humans during mouth breathing have been reported to be between 90 and 1509 ug/cu.m (Hunt and Williams, 1977) and 29-518 ug/cu.m (Larson et al., 1977). These measured values are considerably higher than the expected values from the equilibration concentrations of plasma and lung parenchyma ammonia levels (28-49 ug/cu.m). The higher-than-expected levels of ammonia in air expired by humans and other experimental animals suggests that ammonia may be synthesized by oral microflora. Furthermore, reaction products may be formed from the expired ammonia and other ambient chemicals thereby altering the toxicity and reactivity of this endogenous ammonia source. Barrow and Steinhagen (1980) measured the average expired air ammonia concentration in nose breathing rats (mean=54 ug/cu.m) and found the concentration to be in reasonable agreement with the values measured by Larson et al. (1977) in humans. However, comparison of tracheal cannulated animals to humans is not possible because in the Larson et al. (1977) study only one subject was sampled (29 ug/cu.m). Also, due to the inadequate sample size and inherent variability of breath ammonia values, some caution must be expressed in accepting the validity of the human values. Furthermore, because the oral cavity can be a "sink" or source of ammonia, comparisons to mouth breathing humans should not be made.

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o INHALATION RFD CONFIDENCE : Study: Medium Data Base: Medium RfC: Medium Confidence in the principal study is medium. Although a relatively small sample size (males only) was studied and a free standing NOAEL was determined, mild extrathoracic effects were observed in rats near the same HEC as reported in the Holness study. Additional human subchronic and acute studies support the NOAEL. Confidence in the data base is medium to high. Although developmental, reproductive or chronic toxicity following ammonia exposure has not been adequately tested, pharmacokinetic data suggests systemic distribution at the HEC level is unlikely. Reflecting medium confidence in the principal studies and medium to high confidence in the data base, confidence in the RfD is medium.

o INHALATION RFD SOURCE :

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1987; U.S. EPA, 1989
DOCUMENT

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o REVIEW DATES : 10/13/88, 09/19/89, 05/16/90, 09/19/90, 02/20/91

o VERIFICATION DATE : 02/20/91

o EPA CONTACTS :

Kenneth A. Poirier / ORD -- (513)569-7531 / FTS 684-7531

Annie M. Jarabek / ORD -- (919)541-4847 / FTS 629-4847

CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE-
o ACUTE TOXICITY :

Ammonia vapors cause irritation of eyes and respiratory tract (Gosselin, 1976). Liquid ammonia will burn skin and eyes (CHRIS, 1978). Ammonia is poisonous and may be fatal if inhaled. Contact with ammonia may cause burns to skin and eyes. Contact with liquid ammonia may cause frostbite (DOT, 1984; Guide 15).

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o SIGNS AND SYMPTOMS :

Ammonia vapors cause irritation of the eye and respiratory tract. High concentrations of ammonia cause conjunctivitis, laryngitis and pulmonary edema, possibly accompanied by a feeling of suffocation. Contact with the skin causes burns and blistering. Extensive absorption of ammonia may result in convulsions followed by coma (Gosselin, 1976). Ammonia has a greater tendency than other alkalies to penetrate and damage the eye, and to cause cataracts (Grant, 1974).

BCF - NO DATA

CAA - NO DATA

WQCHU-

No data available

WQCAQ-

Freshwater:

Acute -- (total NH3) Criteria are pH and temperature dependent
Chronic -- (total NH3) Criteria are pH and temperature dependent

Marine:

Acute -- None
Chronic -- None

Considers technological or economic feasibility? -- NO

Discussion -- The freshwater criteria for NH3 are pH and temperature dependent. Methodology for calculating these values can be found in the reference to the Federal Register.

Reference -- 54 FR 19227 (05/04/89)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG - NO DATA

MCL - NO DATA

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 100 pounds (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for ammonia is based on aquatic toxicity as established under CWA Section (40 CFR 117.3). The available data indicate that the aquatic 96-Hour Median Threshold Limit is between 0.1 and 1 ppm, which corresponds to an RQ of 10 pounds. Consideration of the BHP process adjusts the RQ upwards to a 100 pound RQ.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA Superfund Hotline
(800) 424-9346 / (703) 920-9810 / FTS 260-3000

SARA - NO DATA

RCRA - NO DATA

TSCA -

No data available

OREF - None
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IREF - Barrow, C.S. and W.H. Steinhagen. 1980. NH3 concentrations in the

expired air of the rat: Importance to inhalation toxicology. Toxicol. Appl. Pharmacol. 53: 116-121.
IREF - Broderson, J.R., J.R. Lindsey and J.E. Crawford. 1976. The role of environmental ammonia in respiratory mycoplasmosis of rats. Am. J. Pathol. 85(1): 115-130.
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IREF - Coon, R.A., R.A. Jones, L.J. Jenkins Jr. and J. Siegel. 1970. Animal inhalation studies on ammonia, ethylene glycol, formaldehyde, dimethylamine and ethanol. Toxicol. Appl. Pharmacol. 16: 646-655.
IREF - Crapo, R.O., A.H. Morris and R.M. Gardner. 1981. Reference spirometric values using techniques and equipment that meets ATS recommendations. Am. Rev. Respir. Dis. 123: 659-664.
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IREF - Gamble, M.R. and G. Clough. 1976. Ammonia build-up in animal boxes and its effect on rat tracheal epithelium. Lab. Anim. 10: 93-104.
IREF - Holness, D.L., J.T. Purdham and J.R. Nethercott. 1989. Acute and chronic respiratory effects of occupational exposure to ammonia. Am. Ind. Hyg. Assoc. J. 50(12): 646-650.
IREF - Hunt, R.D. and D.T. Williams. 1977. Spectrometric measurements of ammonia in normal human breath. Am. Lab. 9: 10-23.
IREF - Kane, L.E., C.S. Barrow and Y. Alarie. 1979. A short-term test to predict acceptable levels of exposure to airborne sensory irritants. Am. Ind. Hyg. Assoc. J. 40: 207-229.
IREF - Lapp, N.L. and R.E. Hyatt. 1967. Some factors affecting the relationship of maximal expiratory flow to lung volume in health and disease. Dis. Chest. 51: 475-481.
IREF - Larson, T.V., D.S. Covert, R. Frank and R.J. Charlson. 1977. Ammonia in the human airways: Neutralization of inspired acid sulfate aerosols. Science. 197: 161-163.
IREF - MacEwen, J.D., J. Theodore and E.H. Vernot. 1970. Human exposure to EEL concentrations of monomethylhydrazine. In: Proc. 1st Ann. Conf. Environmental Toxicology, Wright-Patterson Air Force Base, OH, Sept. 9-11, 1970. Aerospace Medical Research Laboratory. (AMRL-TR-70-102, Paper 23). NTIS AD727022. p. 355-363.
IREF - Schaerdel, A.D., W.J. White, C.M. Lane, B.H. Dvorchik and K. Bohner. 1983. Localized and systemic effects of environmental ammonia in rats. Lab. Anim. Sci. 33(1): 40-45.
IREF - Schoeb, T.R., M.K. Davidson and J.R. Lindsey. 1982. Intracage ammonia promotes growth of Mycoplasma pulmonis in the respiratory tract of rats. Infect. Immun. 38: 212-217.
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IREF - Stombaugh, D.P., H.S. Teague and W.L. Roller. 1969. Effects of atmospheric ammonia on the pig. J. Animal Sci. 28: 844-847.
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IREF - U.S. EPA. 1989. Health Issue Assessment: Summary Review of Health Effects Associated with Ammonia. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-89-052F.
IREF - Verberk, M.M. 1977. Effects of ammonia in volunteers. Int. Arch. Occup. Environ. Health. 39: 73-81.
IREF - Weatherby, J.H. 1952. Chronic toxicity of ammonia fumes by inhalation. Proc. Soc. Exp. Biol. Med. 81: 300-301.
IREF - WHO (World Health Organization). 1986. Environmental Health Criteria 54: Ammonia. (IPCS International Programme on Chemical Safety). Geneva.
CREF - None
HAREF- None

4 - IRIS
NAME - Arsenic, inorganic
RN - 7440-38-2
IRSN - 272
DATE - 930303
UPDT - 03/03/93, 3 fields
STAT - Oral RfD Assessment (RDO) on-line 02/01/93
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 08/01/92
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 06/30/88 CARO Revised last paragraph
IRH - 06/30/88 CARI Inhalation slope factor changed
IRH - 06/30/88 CARI Paragraph 2 added
IRH - 09/07/88 CARO Major text changes
IRH - 12/01/88 CAREV Mabuchi et al. citation year corrected
IRH - 12/01/88 CAREV Pershagen et al. citation year corrected
IRH - 09/01/89 CARI Citations added to anacondor smelter
IRH - 09/01/89 REFS Bibliography on-line
IRH - 06/01/90 CAREV 2nd & 3rd paragraph - Text revised
IRH - 06/01/90 CAREV Text corrected
IRH - 06/01/90 CARI Inhalation slope factor removed (format change)
IRH - 06/01/90 RCRA EPA contact changed
IRH - 06/01/90 CREF References added
IRH - 12/01/90 CARO Changed slope factor to "unit risk", 2nd para, 1st sen
IRH - 02/01/91 CARI Text edited
IRH - 09/01/91 RDO Oral RfD summary now on-line
IRH - 09/01/91 RDO Oral RfD bibliography added
IRH - 10/01/91 RDO Conversion factor text clarified
IRH - 10/01/91 MCLG MCLG noted as pending change
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 08/01/92 CAR Note added to indicate text in oral quant. estimate
IRH - 10/01/92 CREF Missing reference added to bibliography
IRH - 02/01/93 RDO Citations added to second paragraph
IRH - 02/01/93 OREF References added to bibliography
IRH - 03/01/93 OREF Corrections to references
RLEN - 38096
SY - Arsenic
SY - Arsenic, inorganic
SY - gray-arsenic
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA
VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Hyperpigmentation, keratosis and	NOAEL: 0.009 mg/L converted to 0.0008	3	1	3E-4 mg/kg-day

possible vascular complications	mg/kg-day	
	LOAEL: 0.17 mg/L converted	
Human chronic oral exposure	to 0.014 mg/kg-day	

Tseng, 1977;
Tseng et al., 1968

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*Conversion Factors: NOAEL was based on an arithmetic mean of 0.009 mg/L in a range of arsenic concentration of 0.001 to 0.017 mg/L. This NOAEL also included estimation of arsenic from food. Since experimental data were missing, arsenic concentrations in sweet potatoes and rice were estimated as 0.002 mg/day. Other assumptions included consumption of 4.5 L water/day and 55 kg bw (Abernathy et al., 1989). NOAEL = [(0.009 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.0008 mg/kg-day. The LOAEL dose was estimated using the same assumptions as the NOAEL starting with an arithmetic mean water concentration from Tseng (1977) of 0.17 mg/L. LOAEL = [(0.17 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.014 mg/kg-day.

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o ORAL RFD STUDIES :

Tseng, W.P. 1977. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19: 109-119.

Tseng, W.P., H.M. Chu, S.W. How, J.M. Fong, C.S. Lin and S. Yeh. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J. Natl. Cancer Inst. 40: 453-463.

The data reported in Tseng (1977) show an increased incidence of blackfoot disease that increases with age and dose. Blackfoot disease is a significant adverse effect. The prevalences (males and females combined) at the low dose are 4.6 per 1000 for the 20-39 year group, 10.5 per 1000 for the 40-59 year group, and 20.3 per 1000 for the >60 year group. Moreover, the prevalence of blackfoot disease in each age group increases with increasing dose. However, a recent report indicates that it may not be strictly due to arsenic exposure (Lu, 1990). The data in Tseng et al. (1968) also show increased incidences of hyperpigmentation and keratosis with age. The overall prevalences of hyperpigmentation and keratosis in the exposed groups are 184 and 71 per 1000, respectively. The text states that the incidence increases with dose, but data for the individual doses are not shown. These data show that the skin lesions are the more sensitive endpoint. The low dose in the Tseng (1977) study is considered a LOAEL.

The control group described in Tseng et al. (1968; Table 3) shows no evidence of skin lesions and presumably blackfoot disease, although this latter point is not explicitly stated. This group is considered a NOAEL.

The arithmetic mean of the arsenic concentration in the wells used by the individuals in the NOAEL group is 9 ug/L (range: 1-17 ug/L) (Abernathy et al., 1989). The arithmetic mean of the arsenic concentration in the wells used by the individuals in the LOAEL group is 170 ug/L (Tseng, 1977; Figure 4). Using estimates provided by Abernathy et al. (1989), the NOAEL and LOAEL doses for both food and water are as follows: LOAEL - [170 ug/L x 4.5 L/day + 2 ug/day (contribution of food)] x (1/55 kg) = 14 ug/kg/day; NOAEL - [9 ug/L x 4.5 L/day + 2 ug/day (contribution of food)] x (1/55 kg) = 0.8 ug/kg/day.

Although the control group contained 2552 individuals, only 957 (approximately 38%) were older than 20, and only 431 (approximately 17%) were older than 40. The incidence of skin lesions increases sharply in individuals above 20; the incidence of blackfoot disease increases sharply in individuals above 40 (Tseng, 1968; Figures 5, 6 and 7). This study is less powerful than it appears at first glance. However, it is certainly the most powerful study available on arsenic exposure to people.

This study shows an increase in skin lesions, 22% (64/296) at the high dose vs. 2.2% (7/318) at the low dose. The average arsenic concentration in the wells at the high dose is 410 ug/L and at the low dose is 5 ug/L (Cebrian et al., 1983; Figure 2 and Table 1) or 7 ug/L (cited in the abstract). The average water consumption is 3.5 L/day for males and 2.5 L/day for females. There were about an equal number of males and females in the study. For the dose estimates given below we therefore assume an average of 3 L/day. No data are given on the arsenic exposure from food or the body weight of the participants (we therefore assume 55 kg). The paper states that exposure times are directly related to chronological age in 75% of the cases. Approximately 35% of the participants in the study are more than 20 years old (Figure 1).

Exposure estimates (water only) are: high dose - 410 ug/L x 3 L/day x (1/55 kg) = 22 ug/kg/day; low dose - 5-7 ug/L x 3 L/day x (1/55 kg) = 0.3-0.4 ug/kg/day.

The high-dose group shows a clear increase in skin lesions and is therefore designated a LOAEL. There is some question whether the low dose is a NOAEL or a LOAEL since there is no way of knowing what the incidence of skin lesions would be in a group where the exposure to arsenic is zero. The 2.2% incidence of skin lesions in the low-dose group is higher than that reported in the Tseng et al. (1968) control group, but the dose is lower (0.4 vs. 0.8 ug/kg/day).

The Southwick et al. (1983) study shows a marginally increased incidence of a variety of skin lesions (palmar and plantar keratosis, diffuse palmar or plantar hyperkeratosis, diffuse pigmentation, and arterial insufficiency) in the individuals exposed to arsenic. The incidences are 2.9% (3/105) in the control group and 6.3% (9/144) in the exposed group. There is a slight, but not statistically significant increase in the percent of exposed individuals that have abnormal nerve conduction (8/67 vs. 13/83, or 12% vs. 16% (Southwick et al., 1983; Table 8). The investigators excluded all individuals older than 47 from the nerve conduction portion of the study. These are the individuals most likely to have the longest exposure to arsenic.

Although neither the increased incidence of skin lesions nor the increase in abnormal nerve conduction is statistically significant, these effects may be biologically significant because the same abnormalities occur at higher doses in other studies. The number of subjects in this study was insufficient to establish statistical significance.

Table 3 (Southwick et al., 1983) shows the annual arsenic exposure from drinking water. No data are given on arsenic exposure from food or the body weight (assume 70 kg). Exposure times are not clearly defined, but are >5 years, and dose groups are ranges of exposure.

Exposure estimates (water only) are: dosed group - 152.4 mg/year x 1 year/365 days x (1/70) kg = 6 ug/kg/day; control group - 24.2 mg/year x year/365 days x (1/70) kg = 0.9 ug/kg/day.

Again because there are no data for a group not exposed to arsenic, there is some question if the control group is a NOAEL or a LOAEL. The incidence of skin lesions in this group is about the same as in the low-dose group from the Cebrian et al. (1983) study; the incidence of abnormal nerve conduction in the control group is higher than that from the low-dose group in the Hindmarsh et al. (1977) study described below. The control dose is comparable to the dose to the control group in the Tseng et al. (1968) and Hindmarsh et al. (1977) studies. The dosed group may or may not be a LOAEL, since it is does not report statisically significant effects when compared to the control.

This study shows an increased incidence of abnormal clinical findings and abnormal electromyographic findings with increasing dose of arsenic (Hindmarsh

et al., 1977; Tables III and VI). However, the sample size is extremely small. Percentages of abnormal clinical signs possibly attributed to As were 10, 16, and 40% at the low, mid and high doses, respectively. Abnormal EMG were 0, 17 and 53% in the same three groups.

The exact doses are not given in the Hindmarsh et al. (1977) paper; however, some well data are reported in Table V. The arithmetic mean of the arsenic concentration in the high-dose and mid-dose wells is 680 and 70 ug/L, respectively. Figure 1 (Hindmarsh et al., 1977) shows that the average arsenic concentration of the low-dose wells is about 25 ug/L. No data are given on arsenic exposure from food. We assume daily water consumption of 2 liters and body weight of 70 kg. Exposure times are not clearly stated.

Exposure estimates (water only) are: low - 25 ug/L x 2 L/day x (1/70) kg = 0.7 ug/kg/day; mid - 70 ug/L x 2 L/day x (1/70) kg = 2 ug/kg/day; high - 680 ug/L x 2 L/day x (1/70) kg = 19 ug/kg/day.

The low dose is a no-effect level for abnormal EMG findings. However, because there is no information on the background incidence of abnormal clinical findings in a population with zero exposure to arsenic, there is no way of knowing if the low dose is a no-effect level or another marginal effect level for abnormal clinical findings. The low dose is comparable to the dose received by the control group in the Tseng (1977) and Southwick et al. (1983) studies.

The responses at the mid dose do not show a statistically significant increase but are part of a statistically significant trend and are biologically significant. This dose is an equivocal NOAEL/LOAEL. The high dose is a clear LOAEL for both responses.

As discussed previously there is no way of knowing whether the low doses in the Cebrian et al. (1983), Southwick et al. (1983) and Hindmarsh et al. (1977) studies are NOAELs for skin lesions and/or abnormal nerve conduction. However, because the next higher dose in the Southwick and Hindmarsh studies only shows marginal effects at doses 3-7 times higher, the Agency feels comfortable in assigning the low doses in these studies as NOAELs.

The Tseng (1977) and Tseng et al. (1968) studies are therefore considered superior for the purposes of developing an RfD and show a NOAEL for a sensitive endpoint. Even discounting the people <20 years of age, the control group consisted of 957 people that had a lengthy exposure to arsenic with no evidence of skin lesions.

The following is a summary of the defined doses in mg/kg-day from the principal and supporting studies:

1) Tseng (1977): NOAEL = 8E-4; LOAEL = 1.4E-2

2) Cebrian et al. (1983): NOAEL = 4E-4; LOAEL = 2.2E-2

3) Southwick et al. (1983): NOAEL = 9E-4; LOAEL = none (equivocal effects at 6E-3)

4) Hindmarsh et al., 1977: NOAEL = 7E-4; LOAEL = 1.9E-2 (equivocal effects at 2E-3)

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o ORAL RFD UNCERTAINTY :

UF -- The UF of 3 is to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals.

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o ORAL RFD MODIFYING FACTOR :

MF -- None

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o ORAL RFD COMMENTS :

Ferm and Carpenter (1968) produced malformations in 15-day hamster fetuses via intravenous injections of sodium arsenate into pregnant dams on day 8 of gestation at dose levels of 15, 17.5, or 20 mg/kg bw. Exencephaly, encephaloceles, skeletal defects and genitourinary systems defects were produced. These and other terata were produced in mice and rats all at levels around 20 mg/kg bw. Minimal effects or no effects on fetal development have been observed in studies on chronic oral exposure of pregnant rats or mice to relatively low levels of arsenic via drinking water (Schroeder and Mitchner, 1971). Nadeenko et al. (1978) reported that intubation of rats with arsenic solution at a dose level of 25 ug/kg/day for a period of 7 months, including pregnancy, produced no significant embryotoxic effects and only infrequent slight expansion of ventricles of the cerebrum, renal pelves and urinary bladder. Hood et al. (1977) reported that very high single oral doses of arsenate solutions (120 mg/kg) to pregnant mice were necessary to cause prenatal fetal toxicity, while multiple doses of 60 mg/kg on 3 days had little effect.

Extensive human pharmacokinetic, metabolic, enzymic and long-term information is known about arsenic and its metabolism. Valentine et al. (1987) established that human blood arsenic levels did not increase until daily water ingestion of arsenic exceeded approximately 250 ug/day (approximately 120 ug of arsenic/L. Methylated species of arsenic are successively 1 order of magnitude less toxic and less teratogenic (Marcus and Rispin, 1988). Some evidence suggests that inorganic arsenic is an essential nutrient in goats, chicks, minipigs and rats (NRC, 1989). No comparable data are available for humans.

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o ORAL RFD CONFIDENCE :

Study -- Medium
Data Base -- Medium
RfD -- Medium

Confidence in the chosen study is considered medium. An extremely large number of people were included in the assessment (>40,000) but the doses were not well-characterized and other contaminants were present. The supporting human toxicity data base is extensive but somewhat flawed. Problems exist with all of the epidemiological studies. For example, the Tseng studies do not look at potential exposure from food or other source. A similar criticism can be made of the Cebrian et al. (1983) study. The U.S. studies are too small in number to resolve several issues. However, the data base does support the choice of NOAEL. It garners medium confidence. Medium confidence in the RfD follows.

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o ORAL RFD SOURCE DOCUMENT :

Source Document -- This assessment is not presented in any existing U.S. EPA document.

This analysis has been reviewed by EPA's Risk Assessment Council on 11/15/90. This assessment was discussed by the Risk Assessment Council of EPA on 11/15/90 and verified through a series of meetings during the 1st, 2nd and 3rd quarters of FY91.

Other EPA Documentation -- U.S. EPA, 1984, 1988

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o REVIEW DATES : 03/24/88, 05/25/88, 03/21/89, 09/19/89, 08/22/90, 09/20/90

o VERIFICATION DATE : 11/15/90

o EPA CONTACTS :

Charles Abernathy / OST -- (202)260-5374

Michael Dourson / OHEA -- (513)569-7533

RDI - NO DATA
CAREV-

o CLASSIFICATION	: A; human carcinogen
o BASIS FOR CLASSIFICATION	: based on observation of increased lung cancer mortality in populations exposed primarily through inhalation and on increased skin cancer incidence in several populations consuming drinking water with high arsenic concentrations.

o HUMAN CARCINOGENICITY DATA :

Studies of smelter worker populations (Tacoma, WA; Magma, UT; Anaconda, MT; Ronnskar, Sweden; Saganoseki-Machii, Japan) have all found an association between occupational arsenic exposure and lung cancer mortality (Enterline and Marsh, 1982; Lee-Feldstein, 1983; Axelson et al., 1978; Tokudome and Kuratsune, 1976; Rencher et al., 1977). Both proportionate mortality and cohort studies of pesticide manufacturing workers have shown an excess of lung cancer deaths among exposed persons (Ott et al., 1974; Mabuchi et al., 1979). One study of a population residing near a pesticide manufacturing plant revealed that these residents were also at an excess risk of lung cancer (Matanoski et al., 1981). Case reports of arsenical pesticide applicators have also demonstrated an association between arsenic exposure and lung cancer (Roth, 1958).

A cross-sectional study of 40,000 Taiwanese exposed to arsenic in drinking water found significant excess skin cancer prevalence by comparison to 7500 residents of Taiwan and Matsu who consumed relatively arsenic-free water (Tseng et al., 1968). This study design limited its usefulness in risk estimation. Arsenic-induced skin cancer has also been attributed to water supplies in Chile, Argentina and Mexico (Borgono and Greiber, 1972; Bergoglio, 1964; Cebrian et al., 1983). No excess skin cancer incidence has been observed in U.S. residents consuming relatively high levels of arsenic in drinking water (Morton et al., 1976; Southwick et al., 1981). The results of these U.S. studies, however, are not necessarily inconsistent with the existing findings from the foreign populations. The statistical powers of the U.S. studies are considered to be inadequate because of the small sample size.

A follow-up study (Tseng, 1977) of the population living in the same area of Taiwan, where arsenic contamination of the water supply was endemic, found significantly elevated standard mortality ratios for cancer of the bladder, lung, liver, kidney, skin and colon. This study of bladder, liver and lung cancer cases in the endemic area found a significant association with arsenic exposure that was dose-related. The association of arsenic ingestion and cancer of various internal organs has also been cited in a number of case reports (Chen et al., 1985, 1986). Persons treated with arsenic-containing medicinals have also been shown to be at a risk of skin cancer (Sommers and McManus, 1953).

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o ANIMAL CARCINOGENICITY DATA :

None. There has not been consistent demonstration of arsenic carcinogenicity in test animals for various chemical forms administered by different routes to several species (IARC, 1980). There are some data to indicate that arsenic may produce animal tumors if retention time in the lung

can be increased (Pershagen et al., 1982, 1984).

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o SUPPORTING DATA :

Sodium arsenate has been shown to transform Syrian hamster embryo cells (Dipaolo and Casto, 1979) and to produce sister-chromatid-exchange in DON cells, CHO cells and human peripheral lymphocytes exposed in vitro (Wan et al., 1982; Ohno et al., 1982; Larramendy et al., 1981; Andersen, 1983; Crossen, 1983). While arsenic compounds have not been shown to mutate bacterial strains, it produces preferential killing of repair deficient strains (Rossman, 1981).

CARO -

o CLASSIFICATION	: A; human carcinogen
o BASIS FOR CLASSIFICATION	: based on observation of increased lung cancer mortality in populations exposed primarily through inhalation and on increased skin cancer incidence in several populations consuming drinking water with high arsenic concentrations.
o ORAL SLOPE FACTOR	: none
o ADDITIONAL COMMENTS :	

The Risk Assessment Forum has completed a reassessment of the carcinogenicity risk associated with ingestion of inorganic arsenic. This report, which has been extensively peer-reviewed by outside reviewers (including SAB review) concluded that the most appropriate basis for an oral quantitative estimate was the study by Tseng et al. (1977), which reported increased prevalence of skin cancers in humans as a consequence of arsenic exposure in drinking water. Based on this study a unit risk of 5E-5/ug/L was proposed.

A recent memorandum by the Administrator of the EPA recommended that the above unit risk be adopted. The memorandum further counsels that "in reaching risk management decisions in a specific situation, risk managers must recognize and consider the qualities and uncertainties of risk estimates. The uncertainties associated with ingested inorganic arsenic are such that estimates could be modified downwards as much as an order of magnitude, relative to risk estimates associated with most other carcinogens. In such instances, the management document must clearly articulate this fact and state the factors that influenced such a decision."

CARI -

o CLASSIFICATION	: A; human carcinogen
o BASIS FOR CLASSIFICATION	: based on observation of increased lung cancer mortality in populations exposed primarily through inhalation and on increased skin cancer incidence in several populations consuming drinking water with high arsenic concentrations.
o INHALATION UNIT RISK	: 4.3E-3/ug/cu.m
o DOSE EXTRAPOLATION METHOD	: absolute-risk linear model
o RISK/AIR CONCENTRATIONS :	

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration

E-4 (1 in 10,000)	2E-2 ug/cu.m
E-5 (1 in 100,000)	2E-3 ug/cu.m
E-6 (1 in 1,000,000)	2E-4 ug/cu.m

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o INHALATION DOSE-RESPONSE DATA :

Tumor Type -- lung cancer
Test Animals -- human, male
Route -- inhalation, occupational exposure
Reference -- Brown and Chu, 1983a,b,c; Lee-Feldstein, 1983; Higgins, 1982; Enterline and Marsh, 1982

Ambient Unit Risk Estimates

Exposure Source	Study	Unit Risk	Geometric Mean Unit Risk	Final Estimates Unit Risk
Anaconda smelter	Brown and Chu, 1983a,b,c	1.25 E-3		
	Lee-Feldstein, 1983	2.80 E-3	2.56 E-3	
	Higgins, 1982; Higgins et al., 1982; Welch et al., 1982	4.90 E-3		4.29 E-3
ASARCO smelter	Enterline and Marsh, 1982	6.81 E-3	7.19 E-3	
		7.60 E-3		

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o ADDITIONAL COMMENTS :

A geometric mean was obtained for data sets obtained within distinct exposed populations (U.S. EPA, 1984). The final estimate is the geometric mean of those two values. It was assumed that the increase in age-specific mortality rate of lung cancer was a function only of cumulative exposures.

The unit risk should not be used if the air concentration exceeds 2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

Overall a large study population was observed. Exposure assessments included air measurements for the Anaconda smelter and both air measurements and urinary arsenic for the ASARCO smelter. Observed lung cancer incidence was significantly increased over expected values. The range of the estimates derived from data from two different exposure areas was within a factor of 6.

CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1984. Health Assessment Document for Inorganic Arsenic. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-83-021F.

The 1984 Health Assessment Document for Inorganic Arsenic received Agency and external review including a review by SAB.
DOCUMENT

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o REVIEW DATES : 01/13/88

o VERIFICATION DATE : 01/13/88
o EPA CONTACTS :

Herman J. Gibb / OHEA -- (202)260-5898

Chao W. Chen / OHEA -- (202)260-5898

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE- NO DATA
BCF - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption -- 2.2E-3 ug/L

Fish Consumption Only -- 1.75E-2 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, zero may not be attainable at this time, so the recommended criteria represents a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute -- 3.6E+2 ug/L (Arsenic III)
Chronic -- 1.9E+2 ug/L (Arsenic III)

Marine:

Acute -- 6.9E+1 ug/L (Arsenic III)
Chronic -- 3.6E+1 ug/L (Arsenic III)

Considers technological or economic feasibility? -- NO

Discussion -- The criteria given are for Arsenic III. Much less data are available on the effects of Arsenic V to aquatic organisms, but the toxicity seems to be less. A complete discussion may be found in the referenced notice.

Reference -- 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 0.05 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.05 mg/L for arsenic is proposed based on the current MCL of 0.05 mg/L. Even though arsenic is potentially carcinogenic in humans by inhalation and ingestion, its potential essential nutrient value was considered in determination of an MCLG. The basis for this evaluation is nutritional requirements by NAS (NAS, 1983, Vol. 5, Drinking Water and Health, National Academy of Sciences Press, Washington, DC.)

Reference -- 50 FR 46936 (11/13/85)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value (status) -- 0.05 mg/L (Interim, 1980)

Considers technological or economic feasibility? -- YES

Discussion -- As an interim measure the U.S. EPA is using the value previously derived by the Public Health Service.

Monitoring requirements -- Ground water systems every three years; surface water systems annually.

Analytical methodology -- Atomic absorption/furnace technique (EPA 206.2; SM 304); atomic absorption/gaseous hydride (EPA 206.3; SM 303E; ASTM D-2972-78B)

Best available technology -- No data available.

Reference -- 45 FR 57332 (08/27/80); 50 FR 46936 (11/13/85)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD-

Status -- Issued (1988)

Reference -- Arsenic, Chromium and Chromated Arsenical Compounds Pesticide Registration Standard. June, 1988. [NTIS# PB89-102842]

EPA Contact -- Registration Branch / OPP
(703)557-7760 / FTS 557-7760

FIREV-

Action -- Final regulatory decision - PD4 (1988)

Considers technological or economic feasibility? -- NO

Summary of regulatory action -- Cancellation of specified non-wood uses. Registrant of lead arsenate voluntarily canceled 09/87. Registrant of calcium arsenate voluntarily canceled 02/14/89. Use of sodium arsenate as ant bait canceled on 07/26/89. Criterion of concern: oncogenicity, mutagenicity and teratogenicity. Previous actions: 1) Voluntary cancellation of sodium arsenite (1978). Voluntary cancellation of two products. Criterion of concern: oncogenicity, mutagenicity and teratogenicity; 2) PD4 (1984). Requires label changes for wood use including a restricted use classification. Criterion of concern: oncogenicity, mutagenicity and teratogenicity; 3) Voluntary cancellation of copper arsenate (1977). Criterion of concern: oncogenicity.

Reference -- 53 FR 24787 (06/30/88); 43 FR 48267 (10/18/78); 42 FR 18422 (04/07/77); 49 FR 28666 (07/13/84) [NTIS# PB84-241538]; 49 FR 43772 (10/31/84); 50 FR 4269 (01/30/85)

EPA Contact -- Special Review Branch / OPP
(703)557-7400 / FTS 557-7400

CERC -

Value (status) -- 1 pound (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The 1-pound RQ for arsenic is based on its potential carcinogenicity. Available data indicate a hazard ranking of high based on a potency factor of 142.31/mg/kg/day and a weight-of-evidence group A, which corresponds to an RQ of 1 pound. Evidence found in "Water-Related Environmental Fate of 129 Priority Pollutants" (EPA 440/4-79-029a) also indicates that this material, or a constituent of this material, is bioaccumulated to toxic levels in the tissue of aquatic and marine organisms,

and has the potential to concentrate in the food chain. Reporting of releases of massive forms of this hazardous substance is not required if the diameter of the pieces released exceeds 100 micrometers (0.004 inches).

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

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OREF - Nadeenko, V.G., V. Lenchenko, S.B. Genkina and T.A. Arkhipenko. 1978. The influence of tungsten, molibdenum, copper and arsenic on the intrauterine development of the fetus. TR-79-0353. Farmakologiya i Toksikologiya. 41: 620-623.

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OREF - U.S. EPA. 1984. Health Assessment Document for Inorganic Arsenic. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-83-021F.
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CREF - U.S. EPA. 1984. Health Assessment Document for Inorganic Arsenic. Prepared by Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-83/021F.
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HAREF- None

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USER:

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[IRIS] SS 2 /cf?
USER:
asbestos

    Search in progress

ASBESTOS APPEARS IN THE FOLLOWING CATEGORIES IN IRIS:
   #       CATEGORY      POSTINGS
   1       ID     **           1
   2       CAR    **           2
   3       EXSR   **           1
   4       REFS   **           2
SPECIFY NUMBERS, EXPAND, ALL OR NONE-
USER:
2

SS (2) PSTG (2)

[IRIS] SS 3 /cf?
USER:
print dl



1     - IRIS
IRSN - 370
I   E - 930701
U.  T - 07/01/93, 2 fields
STAT - Oral RfD Assessment (RDO) no data
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 07/01/93
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH  - 09/26/88 CAR Carcinogen summary on-line
IRH  - 05/01/89 CAR Carcinogen summary noted as pending change
IRH  - 12/01/89 REFS Bibliography on-line
IRH  - 03/01/91 CAREV Text revised
IRH  - 07/01/91 CARI Last paragraph units changed from ug/cu.m to fibers/ml
IRH  - 01/01/92 EXSR Regulatory Action section on-line
IRH  - 07/01/93 CARDR EPA Documentation clarified
IRH  - 07/01/93 CREF References alphabetized correctly
RLEN - 27858
CONTINUE PRINTING? (YES/NO/CONT)
USER:
cont

NAME - Asbestos
RN   - 1332-21-4
SY   - Asbestos
SY   - calidria-asbestos
CAREV-
o CLASSIFICATION                : A; human carcinogen
(  ASIS FOR CLASSIFICATION      : Observation of increased mortality and
                                  incidence of lung cancer, mesotheliomas and
                                  gastrointestinal cancer in occupationally
                                  exposed workers are consistent across
                                  investigators and study populations. Animal
                                  studies by inhalation in two strains of rats
                                  showed similar findings for lung cancer and
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mesotheliomas. Animal evidence for carcinogenicity via ingestion is limited (male rats fed intermediate-range chrysotile fibers; i.e., >10 um length, developed benign polyps), and epidemiologic data in this regard are inadequate.

o HUMAN CARCINOGENICITY DATA :

Sufficient. Numerous epidemiologic studies have reported an increased incidence of deaths due to cancer, primarily lung cancer and mesotheliomas associated with exposure to inhaled asbestos. Among 170 asbestos insulation workers in North Ireland followed for up to 26 years, an increased incidence of death was seen due to all cancers (SMR=390), cancers of the lower respiratory tract and pleura (SMR=1760) (Elmes and Simpson, 1971) and mesothelioma (7 cases). Exposure was not quantified.

Selikoff (1976) reported 59 cases of lung cancer and 31 cases of mesothelioma among 1249 asbestos insulation workers followed prospectively for 11 years. Exposure was not quantified. A retrospective cohort mortality study (Selikoff et al., 1979) of 17,800 U.S. and Canadian asbestos insulation workers for a 10-year period using best available information (autopsy, surgical, clinical) reported an increased incidence of cancer at all sites (319.7 expected vs. 995 observed, SMR=311) and cancer of the lung (105.6 expected vs. 486 observed, SMR=460). A modest increase in deaths from gastrointestinal cancer was reported along with 175 deaths from mesothelioma (none expected). Years of exposure ranged from less than 10 to greater than or equal to 45. Levels of exposure were not quantified. In other epidemiologic studies, the increase for lung and pleural cancers has ranged from a low of 1.9 times the expected rate, in asbestos factory workers in England (Peto et al., 1977), to a high of 28 times the expected rate, in male asbestos textile workers in England (Newhouse et al., 1972). Other occupational studies have demonstrated asbestos exposure-related increases in lung cancer and mesothelioma in several industries including textile manufacturing, friction products manufacture, asbestos cement products, and in the mining and milling of asbestos. The studies used for the inhalation quantitative estimate of risk are listed in the table in CARI.

A case-control study (Newhouse and Thompson, 1965) of 83 patients with mesothelioma reported 52.6% had occupational exposure to asbestos or lived with asbestos workers compared with 11.8% of the controls. Of the remaining subjects, 30.6% of the mesothelioma cases lived within one-half mile of an asbestos factory compared with 7.6% of the controls.

The occurrence of pleural mesothelioma has been associated with the presence of asbestos fibers in water, fields and streets in a region of Turkey with very high environmental levels of naturally-occurring asbestos (Baris et al., 1979).

Kanarek et al. (1980) conducted an ecologic study of cancer deaths in 722 census tracts in the San Francisco Bay area, using cancer incidence data from the period of 1969-1971. Chrysotile asbestos concentrations in drinking water ranged from nondetectable to 3.6E+7 fibers/L. Statistically significant dose-related trends were reported for lung and peritoneal cancer in white males and for gall bladder, pancreatic and peritoneal cancer in white females. Weaker correlations were reported between asbestos levels and female esophageal, pleural and kidney cancer, and stomach cancer in both sexes. In an extension of this study, Conforti et al. (1981) included cancer incidence data from the period of 1969-1974. Statistically significant positive associations were found between asbestos concentration and cancer of the digestive organs in white females, cancers of the digestive tract in white males and esophageal, pancreatic and stomach cancer in both sexes. These associations appeared to be independent of socioeconomic status and occupational exposure to asbestos.

Marsh (1983) reviewed eight independent ecologic studies of asbestos in drinking water carried out in five geographic areas. It was concluded that even though one or more studies found an association between asbestos in water and cancer mortality (or incidence) due to neoplasms of various organs, no individual study or aggregation of studies exists that would establish risk levels from ingested asbestos. Factors confounding the results of these studies include the possible underestimates of occupational exposure to asbestos and the possible misclassification of peritioneal mesothelioma as GI cancer.

Polissar et al. (1984) carried out a case-control study which included better control for confounding variables at the individual level. The authors concluded that there was no convincing evidence for increased cancer risk from asbestos ingestion. At the present time, an important limitation of both the case-control and the ecologic studies is the short follow-up time relative to the long latent period for the appearance of tumors from asbestos exposure.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. There have been about 20 animal bioassays of asbestos. Gross et al. (1967) exposed 61 white male rats (strain not reported) to 86 mg chrysotile asbestos dust/cu.m for 30 hours/week for 16 months. Of the 41 animals that survived the exposure period, 10 had lung cancer. No lung cancer was observed in 25 controls.

Reeves (1976) exposed 60-77 rats/group for 4 hours/day, 4 days/week for 2 years to doses of 48.7-50.2 mg/cu.m crocidolite, 48.2-48.6 mg/cu.m amosite and 47.4-47.9 mg/cu.m chrysotile. A 5-14% incidence of lung cancer was observed among concentration groups and was concentration-dependent.

Wagner et al. (1974) exposed CD Wistar rats (19-52/group) to 9.7-14.7 mg/cu.m of several types of asbestos for 1 day to 24 months for 7 hours/day, 5 days/week. A duration-dependent increased incidence of lung carcinomas and mesotheliomas was seen for all types of asbestos after 3 months of exposure compared with controls.

F344 rats (88-250/group) were exposed to intermediate range chrysotile asbestos (1291E+8 f/g) in drinking water by gavage to dams during lactation and then in diet throughout their lifetime (NTP, 1985). A statistically significant increase in incidence of benign epithelial neoplasms (adenomatous polyps in the large intestine) was observed in male rats compared with pooled controls of all NTP oral lifetime studies (3/524). In the same study, rats exposed to short range chrysotile asbestos (6081E+9 f/g) showed no significant increase in tumor incidence.

Ward et al. (1980) administered 10 mg UICC amosite asbestos 3 times/week for 10 weeks by gavage to 50 male F344 rats. The animals were observed for an additional 78-79 weeks post-treatment. A total of 17 colon carcinomas were observed. This result was statistically significant compared with historical controls; no concurrent controls were maintained.

Syrian golden hamsters (126-253/group) were exposed to short and intermediate range chrysotile asbestos at a concentration of 1% in the diet for the lifetime of the animals (NTP, 1983). An increased incidence of neoplasia of the adrenal cortex was observed in both males and females exposed to intermediate range fibers and in males exposed to short range fibers. This increase was statistically significant by comparison to pooled controls but not by comparison to concurrent controls. NTP suggested that the biologic importance of adrenal tumors in the absence of target organ (GI tract) neoplasia was questionable.

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o SUPPORTING DATA :

Sincock (1977) reported an increased number of chromosomes and chromosome breaks after passive inclusion of asbestos with CHO-K1 cells. Chamberlain and Tarmy (1977) reported asbestos not to be mutagenic for E. coli or S. typhimurium. A positive response was unlikely, however, since prokaryotic cells do not phagocytize particles as do eukaryotic cells.

CARI -

- o CLASSIFICATION : A; human carcinogen
- o BASIS FOR CLASSIFICATION : Observation of increased mortality and incidence of lung cancer, mesotheliomas and gastrointestinal cancer in occupationally exposed workers are consistent across investigators and study populations. Animal studies by inhalation in two strains of rats showed similar findings for lung cancer and mesotheliomas. Animal evidence for carcinogenicity via ingestion is limited (male rats fed intermediate-range chrysotile fibers; i.e., >10 um length, developed benign polyps), and epidemiologic data in this regard are inadequate.
- o INHALATION UNIT RISK : 2.3E-1 per (f/mL)
- o DOSE EXTRAPOLATION METHOD : Additive risk of lung cancer and mesothelioma, using

o RISK/AIR CONCENTRATIONS :

Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	4E-4 f/mL
E-5 (1 in 100,000)	4E-5 f/mL
E-6 (1 in 1,000,000)	4E-6 f/mL

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o INHALATION DOSE-RESPONSE DATA :

Human Data Occupational Group	Fiber Type	Reported Average Exposure (fiber-yr/mL)	% Increase in Cancer per fiber-yr/mL	Reference
Lung Cancer:				
Textile Products	Predominantly Chrysotile	44	2.8	Dement et al., 1983b
Textile Products	Chrysotile	31	2.5	McDonald et al., 1983a
Textile Products	Chrysotile	200	1.1	Peto, 1980
Textile Products	Chrysotile	51	1.4	McDonald et al., 1983b
Friction Products	Chrysotile	32	0.058	Berry and Newhouse, 1983
Friction Products	Chrysotile	31	0.010	McDonald et al., 1984
Insulation Products	Amosite	67	4.3	Seidman, 1984

Textile Products	Chrysotile	31	2.5	McDonald et al., 1983a
Textile Products	Chrysotile	200	1.1	Peto, 1980
Textile Products	Chrysotile	51	1.4	McDonald et al., 1983b
Friction Products	Chrysotile	32	0.058	Berry and Newhouse, 1983
Friction Products	Chrysotile	31	0.010	McDonald et al., 1984
Insulation Products	Amosite	67	4.3	Seidman, 1984
Insulation Workers	Mixed (Chrysotile, Crocidolite and Amosite)	300	0.75	Selikoff et al., 1979
Asbestos Products		374	0.49	Henderson and Enterline, 1979
Cement Products		89	0.53	Weill et al., 1979
		112	6.7	Finkelstein, 1983
Mesothelioma:				
Insulation workers	Mixed	375	1.5E-6	Selikoff et al., 1979; Peto et al., 1982
Insulation Products	Amosite	400	1.0E-6	Seidman et al., 1979
Textile Products Manufacturer	Chrysotile	67	3.2E-6	Peto, 1980; Peto et al., 1982
Cement Products	Mixed	108	1.2E-5	Finkelstein, 1983

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o ADDITIONAL COMMENTS :

Risks have been calculated for males and females according to smoking habits for a variety of exposure scenarios (U.S. EPA, 1986). The unit risk value is calculated for the additive combined risk of lung cancer and mesothelioma, and is calculated as a composite value for males and females. The epidemiological data show that cigarette smoking and asbestos exposure interact synergistically for production of lung cancer and do not interact with regard to mesothelioma. The unit risk value is based on risks calculated using U.S. general population cancer rates and mortality patterns without consideration of smoking habits. The risks associated with occupational exposure were adjusted to continuous exposure by applying a factor of 140 cu.m/50 cu.m based on the assumption of 20 cu.m/day for total ventilation and 10 cu.m/8-hour workday in the occupational setting.

The unit risk is based on fiber counts made by phase contrast microscopy (PCM) and should not be applied directly to measurements made by other analytical techniques. The unit risk uses PCM fibers because the measurements made in the occupational environment use this method. Many environmental monitoring measurements are reported in terms of fiber counts or mass as determined by transmission electron microscopy (TEM). PCM detects only fibers longer than 5 um and >0.4 um in diameter, while TEM can detect much smaller fibers. TEM mass units are derived from TEM fiber counts. The correlation between PCM fiber counts and TEM mass measurements is very poor. Six data sets which include both measurements show a conversion between TEM mass and PCM fiber count that range from 5-150 (ug/cu.m)/(f/mL). The geometric mean of these results, 30 (ug/cu.m)/(f/mL), was adopted as a

conversion factor (U.S. EPA, 1986), but it should be realized that this value is highly uncertain. Likewise, the correlation between PCM fiber counts and TEM fiber counts is very uncertain and no generally applicable conversion factor exists for these two measurements.

In some cases TEM results are reported as numbers of fibers <5 um long and of fibers longer than 5 um. Comparison of PCM fiber counts and TEM counts of fibers >5 um show that the fraction of fibers detected by TEM that are also >0.4 um in diameter (and detectable by PCM) varies from 22-53% (U.S. EPA, 1986).

It should be understood that while TEM can be specific for asbestos, PCM is a nonspecific technique and will measure any fibrous material. Measurements by PCM which are made in conditions where other types of fibers may be present may not be reliable.

In addition to the studies cited above, there were three studies of asbestos workers in mining and milling which showed an increase in lung cancer (McDonald et al., 1980, Nicholson et al., 1979; Rubino et al., 1979). The slope factor calculated from these studies was lower than the other studies, possibly because of a substantially different fiber size distribution, and they were not included in the calculation. The slope factor was calculated by life table methods for lung cancer using a relative risk model, and for mesothelioma using a absolute risk model. The final slope factor for lung cancer was calculated as the weighted geometric mean of estimates from the 11 studies cited in CARI. The final slope factor for mesothelioma is based on the calculated values from the studies of Selikoff et al. (1979), Peto et al. (1982), Seidman et al. (1979), Peto (1980) and Finkelstein (1983) adjusted for the mesothelioma incidence from several additional studies cited previously.

There is some evidence which suggests that the different types of asbestos fibers vary in carcinogenic potency relative to one another and site specificity. It appears, for example, that the risk of mesothelioma is greater with exposure to crocidolite than with amosite or chrysotile exposure alone. This evidence is limited by the lack of information on fiber exposure by mineral type. Other data indicates that differences in fiber size distribution and other process differences may contribute at least as much to the observed variation in risk as does the fiber type itself.

The unit risk should not be used if the air concentration exceeds 4E-2 fibers/ml, since above this concentration the slope factor may differ from that stated.

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o DISCUSSION OF CONFIDENCE :

A large number of studies of occupationally-exposed workers have conclusively demonstrated the relationship between asbestos exposure and lung cancer or mesothelioma. These results have been corroborated by animal studies using adequate numbers of animals. The quantitative estimate is limited by uncertainty in the exposure estimates, which results from a lack of data on early exposure in the occupational studies and the uncertainty of conversions between various analytical measurements for asbestos.

RDR-

o CARCINOGENICITY SOURCE :

Source Document -- U.S. EPA, 1985

The 1985 Drinking Water Criteria Document for Asbestos and the 1986 Airborne

Asbestos Health Assessment Update have received Agency review.
DOCUMENT

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o REVIEW DATES : 09/15/87, 12/02/87
o VERIFICATION DATE : 12/02/87
o EPA CONTACTS :

Steven P. Bayard / OHEA -- (202)260-5722

Dan Guth / OHEA -- (919)541-4930

WQCHU-

Water and Fish Consumption: 3.0E+4 fibers/L

Fish Consumption Only: None

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, since zero may not be attainable at this time, the recommended criteria represents a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

None available

MCLG -

Value -- 7E+6 fibers/liter [longer than 10 um] (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- EPA has promulgated a MCLG for asbestos of 7 million fibers/ liter (longer than 10 um) based on potential adverse effects (carcinogenicity) reported in a National Toxicology Program (NTP) bioassay of rats and statements by the EPA Science Advisory Board.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 7E+6 fibers/liter (longer than 10 um) (Final, 1991)

Considers technological or economic feasibility? -- YES

Discussion -- EPA has promulgated a MCL equal to the MCLG of 7 million fibers/liter (longer than 10 um).

Monitoring requirements -- Ground water systems monitored every three years; surface water systems monitored annually; systems out of compliance must begin monitoring quarterly until system is reliably and consistently below MCL.

Analytical methodology -- Transmission electron microscopy (EPA-600/4-83-043, September, 1983).

Best available technology -- Coagulation/filtration; direct and diatomite filtration; corrosion control.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

CERC -

Value (status) -- 1 pound (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for asbestos (friable forms only) is based on potential carcinogenicity. Available data indicate a hazard ranking of high and a weight of evidence classification of Group A, which corresponds to an RQ of 1 pound.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline (800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

___IV.E.1. TSCA, SECTION 6

Status -- Final Rule (1987)

Discussion -- Inspection and response actions under the Asbestos Hazard Emergency Response Act.

Reference -- 52 FR 41826 (10/30/87)

EPA Contact -- Chemical Control Division / OTS
(202) 260-3749 / FTS 260-3749

OREF - None
IREF - None
CREF - Baris, Y.I., M. Artivinli and A.A. Sahin. 1979. Environmental mesothelioma in Turkey. Ann. N.Y. Acad. Sci. 330: 423-432.
CREF - Berry, G. and M.L. Newhouse. 1983. Mortality of workers manufacturing friction materials using asbestos. Br. J. Ind. Med. 40: 1-7.
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CREF - Conforti, P.M., M.S. Kanarek, L.A. Jackson, R.C. Cooper and J.C. Murchio. 1981. Asbestos in drinking water and cancer in the San Francisco Bay Area: 1969-1974 incidence. J. Chr. Dis. 34: 211-224.
CREF - Dement, J.M., R.L. Harris Jr., M.J. Symons and C.M. Shy. 1983. Exposures and mortailty among chrysotile asbestos workers. Part II: Mortality. Am. J. Ind. Med. 4: 421-433.
CREF - Elmes, P.C. and M.J. Simpson. 1971. Insulation workers in Belfast. III. Mortality 1940-1966. Br. J. Ind. Med. 28: 226-236.
CREF - Finkelstein, M.M. 1983. Mortality among long-term employees of an Ontario asbestos-cement factory. Br. J. Ind. Med. 40: 138-144.
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CREF - Kanarek, M.S., P.M. Conforti, L.A. Jackson, R.C. Cooper and J.C. Murchio. 1980. Asbestos in drinking water and cancer incidence in the San Francisco bay area. Am. J. Epidemiol. 12-1: 54-72.
CREF - Marsh, G.M. 1983. Critical review of epidemiologic studies related to ingested asbestos. Environ. Health. Perspect. 53: 49-56.
CREF - McDonald, J.C., F.D.K. Liddell, G.W. Gibbs, G.E. Eyssen and A.D. McDonald. 1980. Dust exposure and mortality in chrysotile mining, 1910-1975. Br. J. Ind. Med. 37: 11-24.
CREF - McDonald, A.D., J.S. Fry, A.J. Wooley and J.C. McDonald. 1983a. Dust exposure and mortality in an American chrysotile textile plant. Br. J. Ind. Med. 40: 361-367.
CREF - McDonald, A.D., J.S. Fry, A.J. Wooley and J.C. McDonald. 1983b. Dust exposure and mortality in an American factory using chrysotile, amosite and crocidolite in mainly textile manufacturing. Br. J. Ind. Med. 40: 368-374.
CREF - McDonald, A.D., J.S. Fry, A.J. Wooley and J.C. McDonald. 1984. Dust exposure and mortality in an American chrysotile asbestos friction products plant. Br. J. Ind. Med. 41: 151-157.
CREF - Newhouse, M.L. and H. Thompson. 1965. Mesothelioma of the pleura and peritoneum following exposure to asbestos in the London area. Br. J. Ind. Med. 22: 261-269.
CREF - Newhouse, M.L., G. Berry, J.C. Wagner and M.E. Turok. 1972. A study of the mortility of female asbestos workers. Br. J. Ind. Med. 29: 134-141.
CREF - Nicholson, W.J., I.J. Selikoff, H. Seidman, R. Lilis and P. Formby. 1979. Long-term mortality experience of chrysotile miners and millers in Thetford Mines, Quebec. Ann. N.Y. Acad. Sci. 330: 11-21.
CREF - NTP (National Toxicology Program). 1983. Carcinogenesis lifetime studies of chrysotile asbestos (CAS No. 12001-29-5) in Syrian golden hamsters (feed studies). Technical report series No. 246. Department of Health and Human Services, Research Triangle Park, NC.
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(feed studies). Technical report series No. 295. Department of Health and Human Servies, Research Triangle Park, NC.
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CREF - Peto, J., R. Doll, S.V. Howard, L.J. Kinlen and H.C. Lewinsohn. 1977. A mortility study among workers in an English asbestos factory. Br. J. Ind. Med. 34: 169-172.
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CREF - Polissar, L., R.K. Severson and E.S. Boatman. 1984. A case-control study of asbestos in drinking water and cancer risk. Am. J. Epidemiol. 119(3): 456-471.
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CREF - Seidman, H., I.J. Selikoff and E.C. Hammond. 1979. Short-term asbestos work exposure and long-term observation. Ann. N.Y. Acad. Sci. 330: 61-89.
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CREF - U.S. EPA. 1985. Drinking Water Criteria Document for Asbestos. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.
CREF - U.S. EPA. 1986. Airborne Asbestos Health Assessment Update. Prepared by the Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-84/003F.
CREF - Wagner, J.C., G. Berry, J.W. Skidmore and V. Timbrell. 1974. The effects of the inhalation of asbestos in rats. Br. J. Cancer. 29: 252-269.
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CREF - Weill, H., J. Hughes and C. Waggenspack. 1979. Influence of dose and fiber type on respiratory malignancy risk in asbestos cement manufacturing. Am. Rev. Respir. Dis. 120: 345-354.
HAREF- None

IRSN - 629
DATE - 930701
UPDT - 07/01/93, 1 field
STAT - Oral RfD Assessment (RDO) no data
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 07/01/93
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) no data
IRH - 09/01/92 CAR Carcinogenicity assessment under review on 03/31/92
IRH - 09/01/92 CAR Carcinogenicity assessment on-line
IRH - 09/01/92 REFS Bibliography on-line
IRH - 10/01/92 CREF Minor corrections to references
IRH - 07/01/93 CARDR Other EPA Documentation heading removed
RLEN - 17266
NAME - Refractory ceramic fibers
RN - NO CAS RN
SY - Ceramic fibers
SY - Refractory ceramic fibers
CAREV-

o CLASSIFICATION : B2; probable human carcinogen

o BASIS FOR CLASSIFICATION : No human data and sufficient evidence from animal studies. Chronic inhalation studies showed that several types of RCFs induced mesotheliomas and lung tumors in rats and hamsters. Administration of RCFs by intraperitoneal/ intrapleural injection or intratracheal instillation also caused peritoneal/ pleural mesotheliomas or lung tumors in rats and hamsters.

o HUMAN CARCINOGENICITY DATA :

None.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. There are three chronic inhalation studies on RCFs in rats and two on hamsters.

Davis et al. (1984) studied the effects of long-term inhalation exposure to ceramic aluminum silicate glass in rats. In this study, a group of 48 SPF Wistar rats (AF/HAN strain; sex unspecified) was exposed to the test fibers at 8.4 mg/cu.m (95 fibers/mL; fibers were <3 um in diameter and >5 um in length) for 7 hours/day, 5 days/week, for 12 months. Interim sacrifices of four animals were made at 12 and 18 months. The remaining rats were killed at 32 months. The survival rates of the treated and control groups were similar. A total of eight exposed animals developed pulmonary neoplasms (1 adenoma, 3 carcinomas, 4 malignant histiocytomas) and one had peritoneal mesothelioma. No pulmonary tumors of any type were found in the 40 unexposed control rats.

In another chronic inhalation study (Carborundum, 1990; Manville, 1991a), groups of 124 male Fischer 344 rats were exposed, 6 hours/day, 5 days/week, for 24 months, to 30 mg/cu.m (approximately 250 fibers/mL) of four different types of RCF: 1) kaolin RCF (0.96 in diameter and 24.2 um in length); 2) zirconia RCF (1.07 um in diameter and 18.5 um in length); 3) high purity kaolin RCF (1.29 um in diameter and 30.98 um in length); or 4) "after service" RCF (>15 um in length, diameter unspecified; a kaolin-based ceramic fiber, containing 27% crystalline silica, that had previously been exposed to high temperatures). The positive controls received chrysotile asbestos at 10 mg/cu.m (fibers >5 um in length, diameter unspecified). A group of negative controls was exposed to filtered air only. The preliminary results of this study showed statistically significant increased incidences of lung neoplasms in all animal groups exposed to RCF. The incidences of total lung tumors (adenoma and carcinoma) in different animal groups were: negative control

(air): 2/124 (1.6%); positive control (chrysotile): 12/63 (19.0%); kaolin RCF: 18/124 (14.6%); zirconia RCF: 11/124 (8.8%); high purity kaolin RCF: 17/124 (13.7%); "after service" RCF: 4/124 (3.2%). Increased incidences of pleural mesotheliomas were also observed in 3 out of 4 types of RCF [kaolin RCF: 2/124 (1.6%); zirconia RCF: 3/124 (2.4%); high purity kaolin RCF: 2/124 (1.6%)]. Although the incidences of these mesotheliomas are not statistically significantly different from that of the negative controls (0/124), they are considered biologically significant since mesotheliomas are not known to occur in experimental animals spontaneously.

Carborundum (1990) also conducted a single-dose chronic inhalation study with kaolin RCF in hamsters. A group of 140 male Syrian hamsters were exposed to airborne kaolin RCF at 30 mg/cu.m (approximately 200 fibers/mL; fibers were 0.96 um in diameter and 24.2 um in length) 6 hours/day, 5 days/week, for 18 months. A positive control group consisting of 80 male hamsters were administered chrysotile asbestos at 10 mg/cu.m (approximately 5000 fibers/mL; fibers >5 um in length, diameter unspecified). Preliminary results showed a 35% (36/102) incidence of malignant mesothelioma with moderate lung and pleural fibrosis in hamsters exposed to kaolin RCF. Nonmalignant pleural mesothelial growth with lung fibrosis was found in one of the chrysotile asbestos-exposed hamsters. No such neoplasms occurred in 73 negative control hamsters inhaling filtered air only.

Smith et al. (1987) studied the long-term health effects of refractory ceramic fibers in rats and hamsters. Female Osborne-Mendel rats and male Syrian hamsters were exposed to RCF (type unspecified, presumably kaolin RCF) at 12 mg/cu.m (approximately 200 fibers/mL) by inhalation ("nose-only") for 6 hours/day, 5 days/week, for 24 months. Approximately 83% of the fibers were >10 um in length and 86% were <2 um in diameter (the mean diameter of the fibers was 1.8 um). No pulmonary neoplasms were observed in the exposed rats (0/55) in this study. None of the exposed hamsters developed any lung tumors (0/70), but malignant mesothelioma was found in one hamster (1/70). With the exception of one bronchoalveolar tumor in a sham control hamster (exposed to filtered air) (1/58), none of the other sham controls or unmanipulated cage controls developed pulmonary or pleural tumors. [It should be noted that in this study, UICC crocidolite asbestos (positive control) only produced a low tumor incidence in rats (3/57; 1 mesothelioma, 2 bronchoalveolar tumors) and no tumors in hamsters.]

The carcinogenicity of RCFs has also been demonstrated in rats and hamsters by intraperitoneal/intrapleural injection or intratracheal instillation that are widely used for the study of the carcinogenic effects of asbestos and alternative fibers.

Pott et al. (1989, 1991) showed that ceramic aluminum silicate fibers are carcinogenic in rats via the intraperitoneal route. In one study (Pott et al., 1989), suspensions of either Ceramic "Fiberfrax" dust (50% <0.89 um in diameter; 50% <13 um in length) or ceramic "MAN" (50% <1.4 um in diameter; 50% <16 um in length) were injected into the abdominal cavity of female Wistar rats at five weekly doses of 9 mg of "Fiberfrax" (a total dose of 45 mg) or 15 mg of "MAN" (a total dose of 75 mg). High incidences of peritoneal tumors (mesothelioma or sarcoma) were observed 130 weeks after the first treatment in animal groups treated with ceramic "Fiberfrax" (33/47 or 70.2%) and with ceramic "MAN" (12/54 or 22.2%). Under similar experimental conditions, UICC chrysotile asbestos induced comparable incidences of peritoneal tumors in a dose-related manner but at considerably lower doses (12/36, 23/34 and 30/36 at 0.05, 0.25 and 1.0 mg, respectively). Only 2/102 rats in the saline control group had a peritoneal tumor.

In another study by Pott et al. (1991), four RCF samples were tested. Groups of 36 female Wistar rats received intraperitoneal injections of either: 1) a single dose (12 mg) of "Fiberfrax" I (median diameter: 0.47 um; median length: 5.5 um); 2) a single dose (12 mg) of "Fiberfrax" II (median diameter:

0.84 um; median length: 13.1 um); 3) 2 weekly doses (20 mg each) of "Fiberfrax" II (median diameter: 0.84 um; median length: 13.1 um); or 4) 2 weekly doses (20 mg each) of "Manville" (median diameter: 1.35 um; median length: 16.4 um). The incidences of peritoneal tumors (mesothelioma or sarcoma) observed in the respective animal groups after 131 weeks were: 1) 15/35 (42.9%); 2) 17/36 (47.2%); 3) 29/36 (80.6%); and 4) 6/36 (16.7%). None of the 34 control rats, which received i.p injections (50 doses, 1 mL each) of saline, had such neoplasms.

A group of 32 SPF Wistar rats of the AF/HAN strain (sex unspecified) received a single intraperitoneal injection of 25 mg of fibrous ceramic aluminum silicate glass (Davis et al., 1984). The injected fibers were predominately short and thin (90% <0.3 um in diameter and <3 um long). Three of the 32 treated rats developed peritoneal tumors (1 mesothelioma, 2 fibrosarcoma) approximately 850 days after injection. No negative controls were used in this study. The authors indicated that the low incidence of tumors observed in this study is probably because of the use of short fibers (90% <0.3 um in length).

Smith et al. (1987) reported that an RCF (type unspecified, presumably kaolin RCF) was carcinogenic in female Osborne-Mendel rats and male Syrian hamsters when intraperitoneally injected at a single dose (25 mg in 0.5 mL saline) into these animals at 100 days of age. The animals were then maintained for the duration of their lives. Approximately 86% of the fibers used were <2.0 um in diameter and 83% were >10 um in length. The mean diameter of the fibers was 1.8 um. Rats injected with RCF had significantly reduced mean lifespans resulting from the induction of abdominal mesotheliomas. At necropsy about 15 months after i.p. injections, 19/23 (83%) rats had developed peritoneal mesothelioma. The incidences of peritoneal mesothelioma in the hamsters were 13% (2/15) in one treated group and 24% (5/21) in a second treated group. Eighty-three percent (19/23) of the rats and 40% (8/25) of the hamsters injected with crocidolite asbestos (positive control) had abdominal mesotheliomas at their deaths. Negative saline controls and unmanipulated control animals had no tumors.

When the RCF (same type and dimension used in the above experiments) was administered to the rats and hamsters by intratracheal instillation (2 mg in 0.2 mL saline, once a week for 5 weeks), only pulmonary lesions and fibrosis but no tumors were induced (Smith et al., 1987).

In a study by Manville (1991b), groups of 107-109 Fischer 344 rats were intratracheally instilled with 2.0 mg of four different types of RCF: 1) kaolin RCF, 2) zirconia RCF, 3) high purity kaolin RCF, or 4) "after service" RCF (a kaolin-based ceramic fiber, containing 27% crystalline silica, which had previously been exposed to high temperatures). The dimensions of these fibers are assumed to be the same as those used in the inhalation study (Manville, 1991a). Positive controls were instilled with 0.66 mg suspension of chrysotile asbestos. Negative controls were instilled with vehicle (saline) alone. Preliminary results of this study show the induction of lung tumors (adenoma/carcinoma) by all four types of RCFs in the treated rats. The tumor incidences were: kaolin RCF: 6/109 (5.5%); zirconia RCF: 4/107 (3.7%); high purity kaolin: 4/109 (3.7%); and "after service" RCF: 7/108 (6.5%). In addition, pleural mesothelioma was present in 1 of 107 rats (0.9%) exposed to zirconia RCFs. The incidence of lung tumors in the positive control group (chrysotile asbestos) was 8/55 (14.5%). None of 118 negative control rats had any lung tumors.

Wagner et al. (1973) administered a single dose of 20 mg ceramic aluminum silicate fibers (0.5-1.0 um in diameter, length unspecified) or Canadian SFA chrysotile fibers (two samples) to groups of 31-36 SPF Wistar rats (about twice as many males as females) via intrapleural injection. Animals were held until natural death. Pleural mesotheliomas were observed in 3/31 (9.7%) rats treated with ceramic aluminum silicate fibers. Mean survival time for this

group was 736 days. The incidence of mesothelioma in the groups treated with the two samples of chrysotile fibers were: 21/32 (64%) and 23/36 (67%). Mean survival times for these groups were 639 and 568 days, respectively. In earlier experiments reported in the same study, no mesotheliomas were reported in negative (saline) controls: 0/48 rats had mesotheliomas in an earlier experiment in which the mean survival was 728 days and 0/32 rats had mesotheliomas in a second experiment in which the mean survival was 818 days.

---

o SUPPORTING DATA :

There is ample evidence from epidemiologic and animal studies that exposure to asbestos causes, in addition to lung cancer and mesothelioma, excess rates of lung fibrosis (asbestosis) and pleural changes. Many of these non-neoplastic pulmonary and pleural changes (e.g., pleural plaques) have been useful markers and most diagnostic for asbestos exposure. Refractory ceramic fibers (RCFs) are similar to asbestos in fiber sizes and many of their physical properties (e.g., durability), which are critical factors for their pathogenicity. Although no human data are available regarding cancer from exposure to RCFs, a pulmonary morbidity study conducted on workers manufacturing RCFs and RCF products at five U.S. manufacturing facilities has shown an increased rate of pleural plaques among workers in the RCF industry (Lockey et al., 1991). Inhalation studies in rats (Davis et al., 1984) and hamsters (Carborundum, 1990) also showed that aluminum silicate RCFs caused pulmonary and pleural fibrosis (in addition to lung tumors and mesothelioma).

CARO -

o CLASSIFICATION	: B2; probable human carcinogen
o BASIS FOR CLASSIFICATION	: No human data and sufficient evidence from animal studies. Chronic inhalation studies showed that several types of RCFs induced mesotheliomas and lung tumors in rats and hamsters. Administration of RCFs by intraperitoneal/ intrapleural injection or intratracheal instillation also caused peritoneal/ pleural mesotheliomas or lung tumors in rats and hamsters.

o ORAL DOSE-RESPONSE DATA :

The available data are not appropriate for oral quantitation.

CARI -

o CLASSIFICATION	: B2; probable human carcinogen
o BASIS FOR CLASSIFICATION	: No human data and sufficient evidence from animal studies. Chronic inhalation studies showed that several types of RCFs induced mesotheliomas and lung tumors in rats and hamsters. Administration of RCFs by intraperitoneal/ intrapleural injection or intratracheal instillation also caused peritoneal/ pleural mesotheliomas or lung tumors in rats and hamsters.

o INHALATION DOSE-RESPONSE DATA :

The available inhalation data (single dose) are not appropriate for quantitation.

CARDR-
o CARCINOGENICITY SOURCE :

Source Document -- U.S. EPA, 1988

The 1988 Health Hazard Assessment Document for Nonasbestos Fibers has received Agency and external review.
DOCUMENT

---

o REVIEW DATES : 03/31/92
o VERIFICATION DATE : 03/31/92
o EPA CONTACTS :

David Lai / OPPT -- (202)260-4302

Vanessa Vu / OPPT -- (202)260-1256

OREF - None
IREF - None

CREF - Carborundum. 1990. Two year inhalation bioassay of refractory ceramic fiber (RCF) in the rat and hamster. 8EHQ-0890-0553 Suppl. Document from W. Kelly, Vice President and General Manager, Fiber Division, the Carborundum Company, August 21, 1990. Office of Toxic Substances, U.S. EPA, Washington, DC.
CREF - Davis, J.M.G., J. Addison, R.E. Bolton, K. Donaldson, A.D. Jones and A. Wright. 1984. The pathogenic effects of fibrous ceramic aluminum silicate glass administered to rats by inhalation and peritoneal injection. In: Biological Effects of Man-made Mineral Fibers. Proceedings of a WHO/IRAC Conference, Volume 2, Copenhagen, Denmark, April 20-22, 1982. p. 303-322.
CREF - IARC (International Agency for Research on Cancer). 1988. IARC Monographs on the evaluation of carcinogenic risks to humans. Man-made mineral fibers and radon. Vol. 43, Lyon, France. p. 39-171.
CREF - Lockey, J., G. Lemasters, C. Rice, et al. 1991. An industry-wide pulmonary morbidity study of current and former workers manufacturing refractory ceramic fibers and RCF products. Presented in: Seventh International Symposium on Inhaled Particles. British Occupational Hygiene Society, Edinburg, U.K. Sept. 16-20, 1991. Abstract No. S8.7.
CREF - Manville. 1991a. Two year inhalation bioassay of refractory ceramic fiber (RCF) in the rat. 8EHQ-0691-0553 Suppl. Document from W.B. Bunn, Senior Director, Health Safety and Environment, Manville Sales Corporation, February 18, 1991. Office of Toxic Substances, U.S. EPA, Washington, DC.
CREF - Manville. 1991b. Intratracheal study of four different ceramic fibers in Fischer 344 rats. 8EHQ-0691-0553 Suppl. Document from W.B. Bunn, Senior Director, Health Safety and Environment, Manville Sales Corporation, June 10, 1991. Office of Toxic Substances, U.S. EPA, Washington, DC.
CREF - Pott F., M. Roller, U. Ziem et al. 1989. Carcinogenicity studies on natural and man-made fibers with the intraperitoneal test in rats. In: Non-occupational Exposure to Mineral Fibers, J. Bignon, J. Peto, R. Saracci, Ed. IARC Sci. Publ. No. 90. IARC, Lyon, France. p. 173-179.
CREF - Pott F., M. Roller, R.M. Rippe, P.-G. Germann and B. Bellmann. 1991. Tumors by intreperitoneal and intrapleural routes and their significance for the classification of mineral fibres. In: Mechanisms in Fibre Carcinogenesis, R.C. Brown, J.A. Hoskins and N.F. John, Ed. NATO ASI Series. Plenum Press, New York, London. p. 1-22.
CREF - Smith, D.M., L.W. Ortiz, R.F. Archuleta and N.F. Johnson. 1987. Long-term health effects in hamsters and rats exposed chronically to man-made vitreous fibres. Ann. Occup. Hyg. 31(4b): 731-752.
CREF - U.S. EPA. 1988. Health Hazard Assessment of Nonasbestos Fibers. Office

of Toxic Substances, Washington, DC. (Final draft)
CREF - Wagner, J.C., G. Berry and V. Timbrell. 1973. Mesotheliomata in rats after inoculation with asbestos and other minerals. Br. J. Cancer. 28: 173-185.
HREF- None

[IRIS] SS 2 /cf?
USER:
stop

DONE? (YES/NO)

USER:
yes

TIME 0:05:25 NLM TIME 15:38:22
...

GOOD-BYE!
THE ESTIMATED TOTAL COST FOR THIS 5 MINUTE TERMINAL SESSION IS $ 4.18.

*** END OF SESSION ***
TOXNET: call cleared (c 0,d 0): dte originated

please log in:

1 - IRIS
NAME - Barium
RN - 7440-39-3
IRSN - 9
DATE - 920120
UPDT - 01/20/92, 52 fields
STAT - Oral RfD Assessment (RDO) on-line 08/01/90
STAT - Inhalation RfC Assessment (RDI) pending 12/01/91
STAT - Carcinogenicity Assessment (CAR) no data
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 09/30/87 EXSR Regulatory Action section added
IRH - 03/01/88 RDO Dose conversion clarified
IRH - 03/01/88 RDO Text changed
IRH - 03/01/88 RDO Secondary contact changed
IRH - 06/30/88 RDO Contacts switched
IRH - 08/01/89 REFS Bibliography on-line
IRH - 06/01/90 RCRA EPA contact changed
CONTINUE PRINTING? (YES/NO/CONT)
USER:
cont

IRH - 07/01/90 RDO Withdrawn; new RfD verified (in preparation)
IRH - 07/01/90 REFS Bibliography withdrawn
IRH - 08/01/90 RDO Oral RfD summary replaced; RfD changed
IRH - 08/01/90 REFS Bibliography replaced
IRH - 12/01/91 RDI Inhalation RfC now under review
IRH - 01/01/92 EXSR Regulatory actions updated
RLEN - 14502
SY - Barium
SY - UN 1399
SY - UN 1400
SY - UN 1854

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased blood pressure	NOAEL: 10 mg/L (0.21 mg/kg/day)	3	1	7E-2 mg/kg/day
Subchronic to Chronic Human Drinking Water Studies	LOAEL: None			
Wones et al., 1990; Brenniman and Levy, 1984				

*Conversion Factors: 10 mg/L x 1.5 L/day/70 kg = 0.21 mg/kg/day

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o ORAL RFD STUDIES :

Wones, R.G., B.L. Stadler and L.A. Frohman. 1990. Lack of effect of drinking water barium on cardiovascular risk factor. Environ. Health Perspect. 85: 1-13.

Brenniman, G.R. and P.S. Levy. 1984. High barium levels in public drinking water and its association with elevated blood pressure. In: Advances in Modern Toxicology IX, E.J. Calabrese, Ed. Princeton Scientific Publications, Princeton NJ. p. 231-249.

No single study considered alone is appropriate to calculate a lifetime RfD for barium. The RfD must be based rather on a weight of evidence approach

which takes into account recent findings of the Wones et al. (1990) and Brenniman and Levy (1984) epidemiologic studies as well as the various rodent studies that have been conducted (Perry et al., 1983; McCauley et al., 1985; Schroeder and Mitchener, 1975a,b; Tardiff et al., 1980). Because of the number of studies involved, the complete reference citations are given in the Section VI.

Wones et al. (1990) administered barium (as barium chloride) in the drinking water of 11 healthy male volunteers. Subjects ranged in age from 27 to 61 years and had no previous history of diabetes, hypertension, or cardiovascular disease. Diets were strictly controlled throughout the 10-week study. Subjects were given 1.5 L/day of distilled and charcoal-filtered water containing 0 mg/L barium for weeks 0 to 2; 5 mg/L for weeks 3 to 6, and 10 mg/L for weeks 7 to 10. Blood and urine samples, as well as morning and evening blood pressures, were taken. Electrocardiograms and 24-hour continuous electrocardiographic monitoring were also performed.

There were no changes in systolic or diastolic blood pressures, or serum chemistry, especially total cholesterol, HDL, LDL, triglycerides, potassium or glucose levels. There was an increase in serum calcium levels that was attributed to a decrease in serum albumin levels. This increase, although statistically significant, was considered borderline and not clinically significant. There were also no changes in cardiac cycle as noted by electrocardiograms and no significant arrhythmias. A NOAEL of 10 mg/L was identified in this study which corresponds to 0.21 mg/kg/day, based on an actual consumption rate of 1.5 L/day and a 70-kg body weight.

Brenniman and Levy (1984) conducted a retrospective epidemiology study which compared human mortality and morbidity rates in populations ingesting elevated barium levels (2 to 10 mg/L) in their drinking water to populations ingesting very little or no barium (less than or equal to 0.2 mg/L). Mortality rates for cardiovascular diseases were determined for the years 1971-1975 and were age-adjusted. For the morbidity study, 1175 adult males and 1203 adult females were selected from communities in which the average drinking water concentration was 7.3 mg/L. Differences in mortality rates from all cardiovascular diseases were significantly higher ($p<0.05$) in the communities with elevated barium. However, these differences were largely in the 65 and over age group and did not account for confounding variables such as population mobility, or use of water softeners or medication.

Differences in blood pressure, prevalance of hypertension, stroke, and heart and renal disease were also measured between the individuals in the two communities. Data were analyzed using signed ranked test for age-specific rates, the weighted Z test for prevalence rates, and analysis of variance for blood pressures. No significant differences were found in mean systolic and diastolic pressures between the two communities. No significant differences were found when the total populations were broken down by duration (10 years or more), medication, or use of water softeners. Also, the prevalence rates for hypertension, stroke, and heart and kidney disease were not significantly different between the communities.

A concentration of 7.3 mg/L corresponds to a dose of 0.20 mg/kg/day (assuming a 70-kg adult drinks 2 L/day).

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o ORAL RFD UNCERTAINTY :

UF = 3. According to U.S. EPA guidelines, an uncertainty factor of 10 is applied when a NOAEL from a subchronic human study is employed. However, data are available from chronic human studies which support this NOAEL, as well as several oral chronic animal studies. Therefore, this UF is not considered necessary. In addition, another factor of 10 is used with a human study to protect sensitive individuals. However, the data base supports the finding that the critical effect is hypertension which results from long exposure durations, and that the population most at risk is the adult male.

Furthermore, the chosen study is a careful observation of this critical effect in adult males. Because of both the critical study's unique focus and the supporting studies, a 3-fold UF, instead of a 10-fold UF, was chosen as most appropriate to protect for sensitive individuals within that population.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

Occupational studies of workers exposed to barium dust have shown that workers develop "baritosis." Affected workers showed no symptoms, no abnormal physical signs, no loss of vital capacity or interference with function, although they had a significantly higher incidence of hypertension.

McCauley et al. (1985) studied the histologic and cardiovascular effects of drinking water containing 0, 10, 100, or 250 mg/L barium for 36 weeks; 0, 1, 10, 100, or 1000 mg/L barium for 16 weeks, or 0, 10, 100, or 250 mg/L (0, 1.4, 14, 35, or 140 mg/kg Ba) barium for 68 weeks on male Sprague-Dawley rats (6/group). Females were exposed to 0 or 250 mg/L for 46 weeks. No significant histologic, carcinogenic, or cardiovascular (including hypertension) effects were observed. No changes were reported in body weight, or food and water consumption in any of the treated animals. Animals treated at the highest dose (1000 mg/L) did exhibit ultrastructural changes in the kidney glomeruli and the presence of myelin figures. No other effects were reported at any dose level for males or females.

Perry et al. (1983) exposed weanling rats to barium at 1, 10, or 100 ppm in drinking water for up to 16 months (average daily barium doses of 0.051, 0.51, and 5.1 mg/kg, respectively). There were no signs of toxicity at any barium dose level. Systolic blood pressure measurements revealed no increase in animals exposed to 1 ppm for 16 months, an increase of 4 mm Hg ($p<0.01$) in animals exposed to 10 ppm barium for 16 months, and an increase of 16 mm Hg ($p<0.001$) in animals exposed to 100 ppm barium for 16 months. The animals in this study were maintained in a special contaminant-free environment and fed a diet designed to reduce exposure to trace metals. It is possible that the restricted intake of certain beneficial metals (e.g., calcium and potassium) may have predisposed the test animals to the hypertensive effects of barium (U.S. EPA, 1985).

Schroeder and Mitchener (1975a,b) exposed rats and mice to 5 mg/L barium in drinking water for a lifetime (approximately 0.25 mg/kg/day for rats and 0.825 mg/kg/day for mice). No adverse effects were observed; however, blood pressure was not measured.

Tardiff et al. (1980) exposed rats to barium at 0, 10, 50, or 250 ppm in drinking water for 4, 8, and 13 weeks. The barium concentrations were approximately 0, 2.75, 13.7, and 66.25 mg/kg/day at the beginning of the study and 0, 1.7, 6.6, and 31.5 mg/kg/day at the end of the study. Although the barium body burden increased with increasing barium dosage, no conclusive signs of barium toxicity were observed in these animals. Blood pressure was not measured.

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o ORAL RFD CONFIDENCE :

Study: Medium
Data Base: Medium
RfD: Medium

As previously stated, EPA does not believe that any single study, considered alone, is adequate to calculate an RfD for barium. However, EPA believes that medium confidence can be placed in the total data base used to determine the RfD.

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o ORAL RFD SOURCE DOCUMENT :

Source Document -- U.S. EPA. 1985. Draft Drinking Water Health Effects Criteria Document on Barium. Office of Drinking Water, Washington, DC. NTIS PB 86-118031/AS.

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o REVIEW DATES : 07/08/85, 07/22/85, 12/15/87, 05/17/90, 06/21/90
o VERIFICATION DATE : 06/21/90
o EPA CONTACTS :

Kenneth L. Bailey / ODW -- (202)260-5535 / FTS 260-5535

Linda R. Papa / ODW -- (513)569-7587 / FTS 684-7587

RDI -
o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption: 1E+3 ug/L

Fish Consumption Only: None

Considers technological or economic feasibility? -- NO

Discussion -- The criteria is the same as the existing standard for drinking water (1 mg/L).

Reference -- Quality Criteria for Water (7/76) EPA 440/9-76-023 [NTIS No. PB-263943].

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute -- none
Chronic -- none

Marine:

Acute -- none
Chronic -- none

Considers technological or economic feasibility? -- NO

Discussion -- It is generally believed that the physical and chemical properties of barium will preclude the existence of toxic soluble forms under usual marine and fresh water conditions and thus a restrictive criterion for aquatic life is considered unwarranted.

Reference -- Quality Criteria for Water, July, 1976, PB-263943

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 2 mg/L (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- The MCLG of 2 mg/L for barium is based on potential adverse effects reported in humans and animal studies.

Reference -- 56 FR 3600 (01/30/91); 56 FR 30266 (07/01/91)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 2 mg/L (Final, 1991)

Considers technological or economic feasibility? -- YES

Discussion -- EPA has set the MCL equal to the MCLG of 2 mg/L.

Monitoring requirements -- Ground water systems monitored every three years; surface water systems monitored annually; systems out of compliance must begin monitoring quarterly until system is reliably and consistently below MCL.

Analytical methodology -- Atomic absorption/furnace technique (EPA 208.2; SM 304); atomic absorption/direct aspiration (EPA 208.1; SM 303C); inductively coupled plasma (EPA 200.7A): PQL= 0.15 mg/L.

Best available technology -- Ion exchange; lime softening; reverse osmosis; electrodialysis.

Reference -- 56 FR 3526 (01/30/91); 56 FR 3600 (01/30/91); 56 FR 30266 (07/01/91).

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC - NO DATA

SARA - NO DATA

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline (800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - Brenniman, G.R. and P.S. Levy. 1984. Epidemiological study of barium in Illinois drinking water supplies. In: Advances in Modern Environmental Toxicology IX, E.J. Calabrese, R.W. Tuthill and L. Condie, Ed. Princeton Scientific Publications, Princeton NJ. p. 231-240.
OREF - McCauley, P.T., B.H. Douglas, R.D. Laurie and R.J. Bull. 1985. Investigations into the effect of drinking water barium on rats. Environ. Health Perspect. Vol. IX, E.J. Calabrese, Ed. Princeton Scientific Publications, Princeton, NJ. p. 197-210.
OREF - Perry, H.M., S.J. Kopp, M.W. Erlanger and E.F. Perry. 1983.

Cardiovascular effects of chronic barium ingestion. In: Trace Substances in Environmental Health, XVII, D.D. Hemphill, Ed. Proc. Univ. Missouri's 17th Ann. Conf. on Trace Substances in Environmental Health. University of Missouri Press, Columbia, MO.

OREF - Schroeder, H.A. and M. Mitchener. 1975a. Life-term effects of mercury, methyl mercury and nine other trace metals on mice. J. Nutr. 105: 452-458.

OREF - Schroeder, H.A. and M. Mitchener. 1975b. Life-term studies in rats: Effects of aluminum, barium, beryllium and tungsten. J. Nutr. 105: 421-427.

OREF - Tardiff, R.G., M. Robinson and N.S. Ulmer. 1980. Subchronic oral toxicity of BaCl2 in rats. J. Environ. Pathol. Toxicol. 4: 267-275.

OREF - U.S. EPA. 1985. Draft Drinking Water Health Effects Criteria Document on Barium. Office of Drinking Water, Washington, DC. NTIS PB 86-118031/AS.

OREF - Wones, R.G., B.L. Stadler and L.A. Frohman. 1990. Lack of effect of drinking water barium on cardiovascular risk factor. Environ. Health Perspect. 85: 1- 13.

IREF - None

CREF - None

HAREF- None

[IRIS] SS 2 /cf?
USER:
find 7440-23-5

Search in progress

NP (7440-23-5 (IRIS))
*NONE-

[IRIS] SS 2 /cf?
USER:
find 7647-14-5

Search in progress

NP (7647-14-5 (IRIS))
*NONE-

[IRIS] SS 2 /cf?
USER:
find 7440-39-3

Search in progress

SS (2) PSTG (1)

[IRIS] SS 3 /cf?
USER:
find nitrate

Search in progress

NITRATE APPEARS IN THE FOLLOWING CATEGORIES IN IRIS:

#	CATEGORY	POSTINGS
1	ID **	2
2	NCAR **	9
3	CAR **	8
4	DWHA **	3
5	EXSR **	3
6	REFS **	6

SPECIFY NUMBERS, EXPAND, ALL OR NONE-
USER:

```
find nitriter[C[C[C[C[C[C[C

[C[C[C[C[C[C IS NOT A VALID CHOICE.  PLEASE REENTER.
USER:
find niti

    Search in progress

NP (NITI (IRIS))
*NONE-

[IRIS] SS 3 /cf?
USER:
find nitrite

    Search in progress

NITRITE APPEARS IN THE FOLLOWING CATEGORIES IN IRIS:
   #       CATEGORY      POSTINGS
   1       ID     **           1
   2       NCAR   **           4
   3       CAR    **           1
   4       DWHA   **           2
   5       EXSR   **           2
   6       REFS   **           2
SPECIFY NUMBERS, EXPAND, ALL OR NONE-
USER:
1

SS (3) PSTG (1)

[IRIS] SS 4 /cf?
USER:
```

1 - IRIS
NAME - Benzene
RN - 71-43-2
IRSN - 270
DATE - 920501
UPDT - 05/01/92, 52 fields
STAT - Oral RfD Assessment (RDO) pending
STAT - Inhalation RfC Assessment (RDI) pending
STAT - Carcinogenicity Assessment (CAR) on-line 04/01/92
STAT - Drinking Water Health Advisories (DWHA) on-line 08/01/90
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 12/01/88 CAREV Anderson and Richardson citation year corrected
IRH - 12/01/88 CAREV Kissling and Speck citation year corrected
IRH - 07/01/89 RDI Inhalation RfD now under review
IRH - 02/01/90 CAR Clarified citations
IRH - 02/01/90 CAREV Corrected Maltoni, 1979 to Maltoni and Scarnato, 1979
IRH - 02/01/90 CAREV Corrected Maltoni, 1983 to Maltoni et al., 1983
IRH - 02/01/90 CAREV Corrected Synder et al., 1980 to 1981
IRH - 02/01/90 REFS Bibliography on-line
IRH - 03/01/90 CREF Clarify Maltoni et al., 1983 and NTP, 1986 references
IRH - 08/01/90 HADR Primary contact changed
IRH - 08/01/90 RCRA EPA contact changed
IRH - 01/01/91 CAR Text edited
IRH - 01/01/91 CARI Inhalation slope factor removed (global change)
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 04/01/92 CARO Text revised
RLEN - 26547
SY - Benzene
SY - benzol
SY - coal naphtha
SY - cyclohexatriene
SY - phene
SY - phenyl hydride
SY - polystream
SY - pyrobenzol
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA
VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

RDO -
o ORAL RFD SUMMARY :

A risk assessment for this substance/agent will be reviewed by an EPA work group.

RDI -

o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

CAREV-

o CLASSIFICATION	: A; human carcinogen
o BASIS FOR CLASSIFICATION	: Several studies of increased incidence of nonlymphocytic leukemia from occupational exposure, increased incidence of neoplasia in rats and mice exposed by inhalation and gavage, and some supporting data form the basis for this classification.

o HUMAN CARCINOGENICITY DATA :

Aksoy et al. (1974) reported effects of benzene exposure among 28,500 Turkish workers employed in the shoe industry. Mean duration of employment was 9.7 years (1-15 year range) and mean age was 34.2 years. Peak exposure was reported to be 210-650 ppm. Twenty-six cases of leukemia and a total of 34 leukemias or preleukemias were observed, corresponding to an incidence of 13/100,000 (by comparison to 6/100,000 for the general population). A follow-up paper (Aksoy, 1980) reported eight additional cases of leukemia as well as evidence suggestive of increases in other malignancies.

In a retrospective cohort mortality study Infante et al. (1977a,b) examined leukemogenic effects of benzene exposure in 748 white males exposed while employed in the manufacturing of rubber products. Exposure occurred from 1940-1949, and vital statistics were obtained through 1975. A statistically significant increase (p less than or equal to 0.002) of leukemias was found by comparison to the general U.S. population. There was no evidence of solvent exposure other than benzene. Air concentrations were generally found to be below the recommended limits in effect during the study period.

In a subsequent retrospective cohort mortality study Rinsky et al. (1981) observed seven deaths from leukemia among 748 workers exposed to benzene and followed for at least 24 years (17,020 person-years). This increased incidence was statistically significant; standard mortality ratio (SMR) was 560. For the five leukemia deaths that occurred among workers with more than 5 years exposure, the SMR was 2100. Exposures (which ranged from 10-100 ppm 8-hour TWA) were described as less than the recommended standards for the time period of 1941-1969.

In an updated version of the Rinsky et al. (1981) study, the authors followed the same cohort to 12/31/81 (Rinsky et al., 1987). An in his earlier study, cumulative exposure was derived from historic air-sampling data or interpolated estimates based on exisitng data. Standardized mortality rates ranged from 109 at cumulative benzene exposures under 40 ppm-years and increased montonically to 6637 (6 cases) at 400 ppm-years or more. The authors found significantly elevated risks of leukemia at cumulative exposures less than the equivalent current standard for occupational exposure which is 10 ppm over a 40-year working lifetime.

Ott et al. (1978) observed three deaths from leukemia among 594 workers followed for at least 23 years in a retrospective cohort mortality study, but the increase was not statistically significant. Exposures ranged from <2 to >25 ppm 8-hour TWA.

Wong et al. (1983) reported on the mortality of male chemical workers who had been exposed to benzene for at least 6 months during the years 1946-1975. The study population of 4062 persons was drawn from seven chemical plants, and jobs were categorized as to peak exposure. Those with at least 3 days/week exposure (3036 subjects) were further categorizeed on the basis of an 8-hour TWA. The control subjects held jobs at the same plants for at least 6 months

but were never subject to benzene exposure. Dose-dependent increases were seen in leukemia and lymphatic and hematopoietic cancer. The incidence of leukemia was responsible for the majority of the increase. It was noted that the significance of the increase is due largely to a less than expected incidence of neoplasia in the unexposed subjects.

Numerous other epidemiologic and case studies have reported an increased incidence or a causal relationship between leukemia and exposure to benzene (IARC, 1982).

---

o ANIMAL CARCINOGENICITY DATA :

Both gavage and inhalation exposure of rodents to benzene have resulted in development of neoplasia. Maltoni and Scarnato (1979) and Maltoni et al. (1983) administered benzene by gavage at dose levels of 0, 50, 250, and 500 mg/kg bw to 30-40 Sprague-Dawley rats/sex for life. Dose-related increased incidences of mammary tumors were seen in females and of Zymbal gland carcinomas, oral cavity carcinomas and leukemias/lymphomas in both sexes.

In an NTP (1986) study, benzene was administered by gavage doses of 0, 50, 100, or 200 mg/kg bw to 50 F344/N rats/sex or 0, 25, 50, or 100 mg/kg bw to 50 B6C3F1 mice/sex. Treatment was 5 times/week for 103 weeks. Significantly increased incidences ($p<0.05$) of various neoplasic growths were seen in both sexes of both species. Both male and female rats and mice had increased incidence of carcinomas of the Zymbal gland. Male and female rats had oral cavity tumors, and males showed increased incidences of skin tumors. Mice of both sexes had increased incidence of lymphomas and lung tumors. Males were observed to have harderian and preputial gland tumors and females had tumors of mammary gland and ovary. In general, the increased incidence was dose-related.

Slightly increased incidences of hematopoietic neoplasms were reported for male C57Bl mice exposed by inhalation to 300 ppm benzene 6 hours/day, 5 days/week for 488 days. There was no increase in tumor incidence in male AKR or CD-1 mice similarly exposed to 100 ppm or 100 or 300 ppm benzene, respectively. Likewise male Sprague-Dawley rats exposed by inhalation to 300 ppm benzene were not observed to have increased incidence of neoplasia (Snyder et al., 1981).

Maltoni et al. (1983) treated male and female Sprague-Dawley rats in the following manner. Starting at 13 weeks of age rats were exposed to 200 ppm benzene 4 hours/day, 5 days/week for 7 weeks; 200 ppm 7 hours/day, 5 days/week for 12 weeks; 300 ppm 7 hours/day, 5 days/week for 85 weeks. An 8-hour/day TWA for 5 days/week was calculated to be 241 ppm. A statistically significant increase was noted in hepatomas and carcinomas of the Zymbal gland.

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o SUPPORTING DATA :

Numerous investigators have found significant increases in chromosomal aberrations of bone marrow cells and peripheral lymphocytes from workers with exposure to benzene (IARC, 1982). Benzene also induced chromosomal aberrations in bone marrow cells from rabbits (Kissling and Speck, 1973), mice (Meyne and Legator, 1980) and rats (Anderson and Richardson, 1979). Several investigators have reported positive results for benzene in mouse micronucleus assays (Meyne and Legator, 1980). Benzene was not mutagenic in several bacterial and yeast systems, in the sex-linked recessive lethal mutation assay with Drosophila melanogaster or in mouse lymphoma cell forward mutation assay.

CARO -

o CLASSIFICATION : A; human carcinogen

o BASIS FOR CLASSIFICATION : Several studies of increased incidence of

nonlymphocytic leukemia from occupational exposure, increased incidence of neoplasia in rats and mice exposed by inhalation and gavage, and some supporting data form the basis for this classification.

o ORAL SLOPE FACTOR : 2.9E-2 per (mg/kg)/day
o DRINKING WATER UNIT RISK : 8.3E-7 per (ug/L)
o DOSE EXTRAPOLATION METHOD : One-hit (pooled data)
o RISK/WATER CONCENTRATIONS :

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+2 ug/L
E-5 (1 in 100,000)	1E+1 ug/L
E-6 (1 in 1,000,000)	1E+0 ug/L

---

o ORAL DOSE-RESPONSE DATA :

Tumor Type -- leukemia
Test Animals -- human
Route -- inhalation, occupational exposure
Reference -- Rinsky et al., 1981; Ott et al., 1978; Wong et al., 1983

The slope factor was derived from human data for inhalation exposure (see dose-response data for inhalation quantitative estimate). The human respiratory rate was assumed to be 20 cu.m/day and the human drinking water intake was assumed to be 2 L/day. The fraction of the administered dose absorbed systemically via inhalation and via drinking water were assumed to be equal.

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o ADDITIONAL COMMENTS :

The unit risk estimate is the geometric mean of four ML point estimates using pooled data from the Rinsky et al. (1981) and Ott et al. (1978) studies, which was then adjusted for the results of the Wong et al. (1983) study as described in the additional comments section for inhalation data.

The unit risk should not be used if the water concentration exceeds 1E+4 ug/L, since above this concentration the unit risk may not be appropriate.

---

o DISCUSSION OF CONFIDENCE :

The pooled cohorts were sufficiently large and were followed for an adequate time period. The increases in leukemias were statistically significant and dose-related in one of the studies. Wong et al. (1983) disagrees that exposures reported in Rinsky et al. (1981) were within the recommended standards. For the five leukemia deaths in persons with 5 or more years exposure, the author notes that mean exposure levels (range 15-70 ppm) exceeded the recommended standard (25 ppm) in 75% of the work locations sampled. A total of 21 unit risk estimates were prepared using 6 models and various combinations of the epidemiologic data. These range over slightly more than one order of magnitude. A geometric mean of these estimates is 2.7E-2. Regression models give an estimate similar to the geometric mean.

The risk estimate above based on reconsideration of the Rinsky et al. (1981) and Ott et al. (1978) studies is very similar to that of 2.4E-2/ppm (cited in U.S. EPA, 1980) based on Infante et al. (1977a,b), Ott et al. (1978) and Aksoy et al. (1974). It was felt by the authors of U.S. EPA (1985) that the exposure assessment provided by Aksoy was too imprecise to warrant inclusion in the current risk estimate.

Risk estimates based on animal gavage studies are about 5 times higher

than those derived from human data. Pharmacokinetic data which could impact the risk assessment are currently being evaluated.

CARI -

o CLASSIFICATION : A; human carcinogen

o BASIS FOR CLASSIFICATION : Several studies of increased incidence of nonlymphocytic leukemia from occupational exposure, increased incidence of neoplasia in rats and mice exposed by inhalation and gavage, and some supporting data form the basis for this classification.

o INHALATION UNIT RISK : 8.3E-6 per (ug/cu.m)

o DOSE EXTRAPOLATION METHOD : One-hit (pooled data)

o RISK/AIR CONCENTRATIONS :

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+1 ug/cu.m
E-5 (1 in 100,000)	1E+0 ug/cu.m
E-6 (1 in 1,000,000)	1E-1 ug/cu.m

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o INHALATION DOSE-RESPONSE DATA :

Tumor Type -- leukemia
Test Animals -- humans
Route -- inhalation, occupational exposure
Reference -- Rinsky et al., 1981; Ott et al., 1978; Wong et al., 1983

---

o ADDITIONAL COMMENTS :

The unit risk estimate is the geometric mean of four ML point estimates using pooled data from the Rinsky et al. (1981) and Ott et al. (1978) studies, which was then adjusted for the results of the Wong et al. (1983) study. The Rinsky data used were from an updated tape which reports one more case of leukemia than was published in 1981. Equal weight was given to cumulative dose and weighted cumulative dose exposure categories as well as to relative and absolute risk model forms. The results of the Wong et al. (1983) study were incorporated by assuming that the ratio of the Rinsky-Ott-Wong studies to the Rinsky-Ott studies for the relative risk cumulative dose model was the same as for other model-exposure category combinations and multiplying this ratio by the Rinsky-Ott geometric mean. The age-specific U.S. death rates for 1978 (the most current year available) were used for background leukemia and total death rates. It should be noted that a recently published paper (Rinsky et al., 1987) reported yet another case of leukemia from the study population.

The unit risk should not be used if the air concentration exceeds 100 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

The pooled cohorts were sufficiently large and were followed for an ade quate time period. The increases in leukemias were statistically significant and dose-related in one of the studies. Wong et al. (1983) disagrees that exposures reported in Rinsky et al. (1981) were within the recommended standards. For the five leukemia deaths in persons with 5 or more years exposure, the author notes that mean exposure levels (range 15-70 ppm) exceeded the recommended standard (25 ppm) in 75% of the work locations sampled. The risk estimate above based on reconsideration of the Rinsky et

al. (1981) and Ott et al. (1978) studies is very similar to that of 2.4E-2/ppm (cited in U.S. EPA, 1980) based on Infante et al. (1977a,b), Ott et al. (1978) and Aksoy et al. (1974). It was felt by the authors of U.S. EPA (1985) that the exposure assessment provided by Aksoy was too imprecise to warrant inclusion in the current risk estimate. A total of 21 unit risk estimates were prepared using 6 models and various combinations of the epidemiologic data. These range over slightly more than one order of magnitude. A geometric mean of these estimates is 2.7E-2/ppm. Regression models give an estimate similar to the geometric mean.

CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Benzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office (Cincinnati, OH) and Carcinogen Assessment Group (Washington, DC), and the Environmental Research Labs (Corvalis, OR; Duluth, MN; Gulf Breeze, FL) for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-018.

U.S. EPA. 1985. Interim Quantitative Cancer Unit Risk Estimates Due to Inhalation of Benzene. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Air Quality Planning and Standards, Washington, DC.

U.S. EPA. 1987. Memorandum from J. Orme, HEB, CSD/ODW to C. Vogt, Criteria and Standards Division, ODW, June, 1987.

The 1985 Interim Evaluation was reviewed by the Carcinogen Assessment Group.

The 1987 memorandum is an internal document.
DOCUMENT

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o REVIEW DATES : 03/05/87, 10/09/87
o VERIFICATION DATE : 10/09/87
o EPA CONTACTS :

D.L. Bayliss / ORD -- (202)260-5726 / FTS 260-5726

R. McGaughy / ORD -- (202)260-5898 / FTS 260-5898

HAONE-

Appropriate data for calculating a One-day HA are not available. It is recommended that the Ten-day HA of 0.235 mg/L used as the One-day HA.

HATEN-

Ten-day HA -- 2.35E-1 mg/L

NOAEL -- 2.35 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Deichman et al., 1963

Rats were exposed to benzene for 6 hours/day, 4 days/week by inhalation and their hematology was monitored weekly. By the second week of treatment, hematological impairment was observed at the 2659 mg/cu.m exposure concentration and there was some indication, especially in females, that white blood cells were depressed at the 103 mg/cu.m exposure concentration. No effect was seen when animals were exposed to 96 mg/cu.m for up to 4 months. Based on the conditions of exposure and an assumed absorption factor of 50%, a NOAEL of 2.35 mg/kg/day can be calculated.

HALTC-

A Longer-term HA has not been calculated for benzene because of its potent carcinogenicity.

HALTA-

A Longer-term HA has not been calculated for benzene because of its potent carcinogenicity.

HALIF-

Drinking Water Equivalent Level (DWEL) -- None

Lifetime HA -- None

Benzene is classified in Group A: Human carcinogen. Neither a DWEL nor a Lifetime HA have been calculated for benzene. Refer to Section II of this file for information on the carcinogenicity of this substance.

OLEP -

Odor perception threshold (air) -- 4.9 mg/cu.m.

Odor perception threshold (water) -- 2.0 mg/L.

ALAB -

Analysis of benzene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile aromatic and unsaturated organic compounds in water.

TREAT-

Treatment technologies which will remove benzene from water include granular activated carbon adsorption and air stripping.

HADR -
o HEALTH ADVISORY SOURCE :

Deichman, W.B., W.E. MacDonald and E. Bernal. 1963. The hemopoietic toxicity of benzene vapors. Toxicol. Appl. Pharmacol. 5: 201-224.
DOCUMENT

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o HEALTH ADVISORY REVIEW :

U.S. EPA. 1985. Drinking Water Criteria Document for Benzene. Office of

Drinking Water, Washington, DC. (Final draft)

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

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o EPA DRINKING WATER CONTACT :

Jennifer Orme / ODW -- (202)260-7586 / FTS 260-7586

Edward V. Ohanian / ODW -- (202)260-7571 / FTS 260-7571

ACUTE- NO DATA
BCF - NO DATA

CAA -

Considers technological or economic feasibility? -- YES

Discussion -- Benzene has been listed as a hazardous air pollutant under Section 112 of the Clean Ai Ac. EPA promulgated NESHAP for benzene from equipment leaks on June 6, 1984 (49 FR 23498) and proposed regulations for coke oven by-product plants.

Reference -- 40 CFR Part 61, Subpart J

EPA Contact -- Emissions Standards Division, OAQPS
(917)541-5571 / FTS 629-5571

WQCHU-

Water and Fish Consumption -- 6.6E-1 ug/L

Fish Consumption Only -- 4.0E+1 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, zero may not be attainable at this time, so the recommended criteria represents a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute LEC -- 5.3E+3 ug/L

Chronic LEC -- None

Marine:

Acute LEC -- 5.1E+3 ug/L
Chronic LEC -- 7.0E+2 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 0 mg/L (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of zero mg/L for benzene is proposed based on carcinogenic effects. In humans, exposure to benzene is associated with myelocytic anemia, thrombocytopenia and leukemia (acute myelogenous and monocytic leukemia). In animals, an increase in tumors and leukemia have been reported. EPA has classified benzene in Group A: sufficient evidence from epidemiological studies.

Reference -- 50 FR 46880 (11/13/85)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value (status) -- 0.005 mg/L (Final, 1987)

Considers technological or economic feasibility? -- YES

Discussion -- EPA has set an MCL based on detection limits.

Monitoring requirements -- All systems to be monitored for four consecutive quarters; repeat monitoring dependent upon detection, vulnerability status and system size.

Analytical methodology -- Gas chromatography (EPA 502.1, 502.2, 503.1); gas chromatographic/mass spectrometry (EPA 524.1, 524.2).

Best available technology -- Packed tower aeration; granular activated carbon.

Reference -- 52 FR 25690 (07/08/87); 56 FR 30266 (07/01/91)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD-

No data available

FIREV-

Action -- Voluntary cancellations (1985)

Considers technological or economic feasibility? -- NO

Summary of regulatory action -- All products voluntarily canceled based on concern for oncogenicity, mutagenicity and blood disorders.

Reference -- FR or NTIS No. not available.

EPA Contact -- Special Review Branch / OPP
(703)557-7400 / FTS 557-7400

CERC -

Value (status) -- 10 pounds (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The RQ for benzene is 10 pounds, based on its potential carcinogenicity. The available data indicate a hazard ranking of medium based on a potency factor of 0.27/mg/kg/day and a weight-of-evidence group A, which corresponds to an RQ of 10 pounds.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - None
IREF - None
CREF - Aksoy, M., S. Erdem and G. Dincol. 1974. Leukemia in shoeworkers exposed chronically to benzene. Blood. 44(6): 837-841.
CREF - Aksoy, M. 1980. Different types of malignancies due to occupational exposure to benzene: A review of recent observations in Turkey. Environ. Res. 23: 181.
CREF - Anderson, D. and C.R. Richardson. 1979. Chromosome gaps are associated with chemical mutagenesis (abstract No. Ec-9). Environ. Mutat. 1: 179.
CREF - IARC (International Agency for Research on Cancer). 1982. Benzene. In: Some industrial chemicals and dyestuffs. IARC Monographs on the evaluation of carcinogenic risk of chemicals to humans. IARC, WHO, Lyon, France. 29: 93-148.
CREF - Infante, P.F., R.A. Rinsky, J.K. Wagoner and R.J. Young. 1977a. Benzene and Leukemia. The Lancet. 2(8043): 867-869.
CREF - Infante, P.F., R.A. Rinsky, J.K. Wagoner and R.J. Young. 1977b. Leukemia in benzene workers. Lancet. 19: 76-78.
CREF - Kissling, M. and B. Speck. 1973. Chromosome aberrations in experimental benzene intoxication. HELV. Med. Acta. 36: 59-66.
CREF - Maltoni, C. and C. Scarnato. 1979. First experimental demonstration of the carcinogenic effects of benzene. Long-term bioassays on Sprague-Dawley Rats by oral administration. Med. Lav. 70: 352-357.
CREF - Maltoni, C., B. Conti and G. Cotti. 1983. Benzene: A multipotential carcinogen. Results of long-term bioassays performed at the Bologna Institute of Oncology. Am. J. Ind. Med. 4: 589-630.
CREF - Meyne, J. and M.S. Legator. 1980. Sex-related differences in cytogenetic effects of benzene in the bone marrow of Swiss mice. Environ. Mutat. 2: 43-50.
CREF - NTP (National Toxicology Program). 1986. Toxicology and carcinogenesis studies of benzene (CAS No. 71-43-2) in F344/N rats and B6C3F mice (gavage studies). NTP Technical Report Series No. 289. NIH Publication No. 86-2545.
CREF - Ott, M.G., J.C. Townsend, W.A. Fishbeck and R.A. Langner. 1978. Mortality among individuals occupationally exposed to benzene. Arch. Environ. Health. 33: 3-10.
CREF - Rinsky. R.A., R.J. Young and A.B. Smith. 1981. Leukemia in benzene workers. Am. J. Ind. Med. 2: 217-245.
CREF - Rinsky, R.A., A.B. Smith, R. Hornung, et al. 1987. Benzene and Leukemia. New England J. Med. 316(17): 1044-1050.
CREF - Snyder, C.A., M.N. Erlichman, S. Laskin, B.D. Goldstein, and R.E. Albert. 1981. The pharmacokinetics of repetitive benzene exposure at 300 and 100 ppm in AKR mice and Sprague-Dawley rats. Toxicol. Appl. Pharmacol. 57: 164-171.
CREF - U.S. EPA. 1980. Ambient Water Quality Criteria Document for Benzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office (Cincinnati, OH) and Carcinogen Assessment Group (Washington, DC), and the Environmental Research Labs (Corvalis, OR; Duluth, MN; Gulf Breeze, FL) for the

Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-018.
CREF - U.S. EPA. 1985. Interim Quantitative Cancer Unit Risk Estimates Due to Inhalation of Benzene. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Air Quality Planning and Standards, Washington, DC.
CREF - U.S. EPA. 1987. Memorandum from J. Orme, HEB, CSD/ODW to C. Vogt, Criteria and Standards Division, ODW, June 1987.
CREF - Wong, O., R.W. Morgan and M.D. Whorton. 1983. Comments on the NIOSH study of leukemia in benzene workers. Technical report submitted to Gulf Canada, Ltd., by Environmental Health Associates.
HAREF- Deichman, W.B., W.E. MacDonald and E. Bernal. 1963. The hemopoietic toxicity of benzene vapors. Toxicol. Appl. Pharmacol. 5: 201-224.
HAREF- U.S. EPA. 1985. Drinking Water Criteria Document for Benzene. Office of Drinking Water, Washington, DC. (Final draft)

1 - IRIS
IRSN - 133
DATE - 931201
UPDT - 12/01/93, 1 field
STAT - Oral RfD Assessment (RDO) no data
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 09/01/93
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 08/01/89 REFS Bibliography on-line
IRH - 01/01/92 CAR Carcinogen assessment noted as pending change
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 04/01/92 CAR Summary revised; oral quantitative section added
IRH - 04/01/92 CREF Carcinogen assessment references revised
IRH - 05/01/92 CARDR Work group review and verification date corrected
IRH - 07/01/92 CAR Text revised in NOTE
IRH - 07/01/92 CARO Range of slope factors corrected
IRH - 07/01/92 CARO Slope factor and risks corrected
IRH - 07/01/92 CARO Data table heading corrected
IRH - 07/01/92 CARO Slope factor corrected; last paragraph
IRH - 07/01/92 CARDR Secondary contact changed
IRH - 09/01/93 CAR Carcinogenicity assessment noted as pending change
IRH - 09/01/93 CARDR Work group review date added
IRH - 12/01/93 CREF Reference revised - U.S. EPA, 1991b
RLEN - 25912
NAME - Benzo[a]pyrene (BaP)
RN - 50-32-8
SY - BaP
SY - Benzo[a]pyrene
SY - BENZO(d,e,f)CHRYSENE
SY - 3,4-BENZOPIRENE
SY - 3,4-BENZOPYRENE
SY - 6,7-BENZOPYRENE
SY - BENZO(a)PYRENE
SY - 3,4-BENZPYREN
SY - 3,4-BENZPYRENE
SY - 3,4-BENZ(a)PYRENE
SY - BENZ(a)PYRENE
SY - 3,4-BENZYPYRENE
SY - BP
SY - 3,4-BP
SY - B(a)P
SY - RCRA WASTE NUMBER U022
CAREV-
o CLASSIFICATION : B2; probable human carcinogen
o BASIS FOR CLASSIFICATION : Human data specifically linking benzo[a]pyrene (BAP) to a carcinogenic effect are lacking. There are, however, multiple animal studies in many species demonstrating BAP to be

carcinogenic following administration by numerous routes. BAP has produced positive results in numerous genotoxicity assays. NOTE: The carcinogenicity assessment for benzo[a]pyrenemay change in the near future pending the outcome of a further review now being conducted by the Carcinogen Risk Assessment Verification Endeavor Work Group. At the June 1992 CRAVE Work Group meeting, a revised risk estimate for benzo[a]pyrene was verified (see Additional Comments for Oral Exposure). This section provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is preseed as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000 or 1 in 1,000,000. The Carcinogenicity Background Document provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users

Reference Dose (RfD) (RfC) sections are referred to the Oral and Reference Concentration for information on long-term toxic effects other than carcinogenicity.

o HUMAN CARCINOGENICITY DATA :

Inadequate. Lung cancer has been shown to be induced in humans by various mixtures of polycyclic aromatic hydrocarbons known to contain BAP including cigarette smoke, roofing tar and coke oven emissions. It is not possible, however, to conclude from this information that BAP is the responsible agent.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. The animal data consist of dietary, gavage, inhalation, intratracheal instillation, dermal and subcutaneous studies in numerous strains of at least four species of rodents and several primates. Repeated BAP administration has been associated with increased incidences of total tumors and of tumors at the site of exposure. Distant site tumors have also been observed after BAP administration by various routes. BAP is frequently used as a positive control in carcinogenicity bioassays.

BAP administered in the diet or by gavage to mice, rats and hamsters has produced increased incidences of stomach tumors. Neal and Rigdon (1967) fed BAP (purity not reported) at concentrations of 0, 1, 10, 20, 30, 40, 45, 50, 100 and 250 ppm in the diets of male and female CFW-Swiss mice. The age of the mice ranged from 17-180 days old and the treatment time from 1-197 days; the size of the treated groups ranged from 9 to 73. There were 289 mice (number of mice/sex not stated) in the control group. No forestomach tumors were reported in the 0-, 1- and 10-ppm dose groups. The incidence of forestomach tumors in the 20-, 30-, 40-, 45-, 50-, 100- and

250-ppm dose groups were 1/23, 0/37, 1/40, 4/, 23/34, 19/23 and 66/73, respectively. The authors felt that the increasing tumor incidences were related to both the concentration and the number of doses administered. Historical control forestomach tumor data are not available for CFW-Swiss strain mice. In historical control data from a related mouse strain, SWR/J Swill, the forestomach tumor incidence rate was 2/268 and 1/402 for males and females, respectively (Rabstein et al., 1).

Brune et al., (1981) fed 0.15 mg/kg BAP (reported to be "highly pure") in the diet of 32 Sprague-Dawley rats/sex/group either every 9th day or 5 times/week. These treatments resulted in annual average doses of 6 or 39 mg/kg, respectively. An untreated group of 32 rats/sex served as the control. Rats were treated until moribund or dead; survival was similar in all groups. Histologic examinations were performed on each rat. The combined incidence of tumors of the forestomach, esophs and larynx was 3/64, 3/64 and 10/64 in the control group, the group fed BAP every 9th day and the group fed BAP 5 times/week, respectively. A trend analysis showed a statistically significant tendancy for the proportion of animals with tumors of the forestomach, esophagus or larynx to increase steadily with dose (Knauf and Rice, 1992).

As part of the same study, Brune et al. (1981) administered BAP ("highly pure") orally to Sprague-Dawley rats by caffeine gavage. The rats were treated until moribund or dead; all rats were subjected to terminal histopathologic examination. Gavaged rats were divided into 3 dose groups of 32 rats/sex/group; the groups received 0.15 mg/kg per gavage either every 9th day (Group A), every 3rd day (Group B) or 5 times per week (Group C); these treatments resulted in annual average doses of 6, 18 or 39 mg/kg, respectively. Untreated and gavage (5 times/week) controls (32 rats/sex/group) were included. The median survival times for the

untreated
crol group; the gavage control group; and groups A, B and C were 129, 102,
112, 113 and 87 weeks, respectively. The survival time of Group C was short
compared with controls and may have precluded tumor formation (Knauf and Rice,
1992). The combined tumor incidence in the forestomach, esophagus and larynx
was 3/64, 6/64, 13/64, 26/64 and 14/64 for the untreated control group, gavage
control group, group A, group B and group C, respectively. There was a
statisticallignificant association between the dose and the proportions of
rats with tumors of the forestomach, esophagus or larynx. This association is
not characterized by a linear trend. The linearity was affected by the
apparently reduced tumor incidence that is seen in the high-dose group (Knauf
and Rice, 1992).

Intratracheal instillation and inhalation studies in guinea pigs, hamsters
and rats have resulted in elevated incidences of respiratory tract and upper
digestive tract tumors (U.S. EPA, 1991a). Male Syrian golden hamsters
(24/group) were exposed by inhalation to 0, 2.2, 9.5 or 46.5 mg BAP/cu.m in a
sodium chloride aerosol (Thyssen et al., 1981). (Greater than 99% of the
particles had diameters between 0.2 and 0.5 um.) For the first 10 weeks of
the study, the hamsters were exposed to BAP daily for 4.5 hours/day;
thereafter, daily for 3 hours/day. Animals dying within the first year of the
study were replaced; the effective number of hamsters in the control, low-,
mid- and high-dose groups was 27, 27, 26 and 25, respectively. (The total
time of treatment, although over 60 weeks, was not stated.) During the first
10 weeks, animals in the 3 dose groups reportedly lost weight. After week 10,
however, the body weights in all groups were similar until week 60 when the
body weights of hamsters in the high-dose group decreased and the mortality
increased significantly. The incidence of respiratory tract tumors (including
tumors of the nasal cavity, larynx and trachea) in the control,

low-, mid- and high-dose groups was 0/27, 0/27, 9/26 and 13/25, respectively; the incidences of upper digestive tract tumors (including tumors of the pharynx, esophagus and forestomach) were 0/27, 0/27, 7/26 and 14/25, respectively. Trend analysis for incidences of both respiratory tract tumors and upper gastrointestinal tract tumors showed a statistically significant tendancy for the proportion of animals with either tumor type to increase steadily with increased dose (Knauf and Rice, 1992).

Intraperitoneal BAP injections have caused increases in the number of injection site tumors in mice and rats (reviewed in U.S. EPA, 1991a). Subcutaneous BAP injections have caused increases in the number of injection site tumors in mice, rats, guinea pigs, hamsters and some primates (IARC, 1983; U.S. EPA, 1991a). BAP is commonly used as a positive control in many dermal application bioassays and has been shown to cause skin tumors in mice, rats, rabbits and guinea pigs. BAP is both an initiator and a complete carcinogen in mouse skin (IARC, 1983). Increased incidences of distant site tumors have also been reported in animals as a consequence of dermal BAP exposure (reviewed in U.S. EPA, 1991a).

BAP has also been reported to be carcinogenic in animals when administered by the following routes: i.v.; transplacentally; implantation in the stomach wall, lung, renal parenchyma and brain; injection into the renal pelvis; and vaginal painting (U.S. EPA, 1991a).

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o SUPPORTING DATA :

Benzo[a]pyrene has been shown to cause genotoxic effects in a broad range of prokaryotic and mammalian cell assay systems (U.S. EPA, 1991a). In prokaryotes, BAP tested positive in DNA damage assays and in both reverse and forward mutation assays. In mammalian cell culture assays, BAP

tested
positive in DNA damage assays, forward mutation assays,
chromosomal effects
assays and cell transformation assays.

CARO -
o CLASSIFICATION : B2; probable human carcinogen
o BASIS FOR CLASSIFICATION : Human data specifically linking benzo[a]pyrene (BAP) to a

carcinogenic effect

are lacking. There are,

however, multiple

animal studies in many species

demonstrating

BAP to be carcinogenic

following

administration by numerous

routes. BAP has

produced positive results in

numerous

genotoxicity assays. NOTE: The carcinogenicity assessment for

benzo[a]pyrene

may change in the near future

pending the

outcome of a further review now

being

conducted by the Carcinogen

Risk Assessment

Verification Endeavor Work

Group. At the June

1992 CRAVE Work Group meeting,

a revised risk

estimate for benzo[a]pyrene was

verified (see

Additional Comments for Oral

Exposure). This

section provides information on

three aspects

of the carcinogenic risk

assessment for the

agent in question; the U.S. EPA classification, and

quantitative estimates of

risk from oral exposure and

from inhalation

exposure. The classification

reflects a

the likelihood weight-of-evidence judgment of
carcinogen. The that the agent is a human
presented in quantitative risk estimates are
the result of three ways. The slope factor is
extrapolation application of a low-dose
the risk per procedure and is presented as
the (mg/kg)/day. The unit risk is
of either risk quantitative estimate in terms
per ug/cu.m per ug/L drinking water or risk
which risk is air breathed. The third form in
or air presented is a drinking water
risks of 1 in concentration providing cancer
Carcinogenicity 10,000 or 1 in 1,000,000. The
details on the Background Document provides
derive the rationale and methods used to
IRIS. Users carcinogenicity values found in
Reference Dose (RfD) are referred to the Oral
(RfC) sections and Reference Concentration
toxic effects for information on long-term
other than carcinogenicity.

o ORAL SLOPE FACTOR : 7.3E+0 per (mg/kg)/day
o DRINKING WATER UNIT RISK : 2.1E-4 per (ug/L)
o DOSE EXTRAPOLATION METHOD : Risk estimate based on a
geometric mean of
four slope

o RISK/WATER CONCENTRATIONS :

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	5E-1 ug/L
E-5 (1 in 100,000)	5E-2 ug/L
E-6 (1 in 1,000,000)	5E-3 ug/L

---

o ORAL DOSE-RESPONSE DATA :

Tumor Type -- forestomach, squamous cell papillomas and carcinomas
Test Animals -- CFW mice, sex unknown
Route -- oral, diet
Reference -- Neal and Rigdon, 1967

a) Conditional upper bound two-stage model with terms for promotion
(modification of Moolgavkar-Venson-Knudson, generalized forms of two-stage
model)

Administered Dose (ppm)	Tumor Incidence
0	0/289
1	0/25
10	0/24
20	1/23
30	0/37
40	1/40
45	4/40
50	24/34
100	19/23
250	66/73

Tumor Type -- squamous cell carcinoma of the forestomach
Test Animals -- SWR/J Swill mice
Route -- oral, diet
Reference -- Rabstein et al., 1973

Administered Dose (ppm)	Tumor Incidence
0	2/268* male
0	1/402* female

*See additional comments concerning the use of control data from other studies
that utilized similar mouse strains.

b) Same data as above. Upper bound estimate by extrapolation from 10%
response point to background of empirically fitted dose-response curve.
(Procedure using two-stage model described in (a)).

c) Same data as above except the additional 2 control groups
(Rabstein et al.,

1973) were excluded. Generalized Weibull-type dose-response model.

d) Tumor Type -- forestomach, larynx and esophagus, papillomas and carcinomas
(combined). Linearized Multistage Model, Extra Risk.

Test Animals -- Sprague-Dawley rats, males and females
Route -- oral, diet
Reference -- Brune et al., 1981

Dose (mg/kg diet/year)	Tumor Incidence
0	3/64
6	3/64
39	10/64

---

o ADDITIONAL COMMENTS :

NOTE: The range of oral slope factors calculated was: 4.5E+0 to 11.7E+0 per
(mg/kg)/day.

At the June 1992 CRAVE Work Group meeting, it was noted that an error had
been made in the 1991 document "Dose-Response Analysis of Ingested
Benzo[a]pyrene" which is quoted in the Drinking Water Criteria Document for
PAH. In the calculation of the doses in the Brune et al. (1981) study it was
erroneously concluded that doses were given in units of mg/year, whereas it
was in fact mg/kg/year. When the doses are corrected the slope factor is
correctly calculated as 11.7 per (mg/kg)/day, as opposed to 4.7 per
(mg/kg)/day as reported in the Drinking Water Criteria Document. The correct
range of slope factors is 4.5 to 11.7 per (mg/kg)/day, with a geometric mean
of 7.3 per (mg/kg)/day. A drinking water unit risk based on the revised slope
factor is 2.1E-4 per (ug/L). Therefore, these values have been changed on
IRIS and an Erratum to the Drinking Water Criteria Document is being prepared.

Risk estimates were calculated from two different studies in t species
of outbred rodents (Neal and Rigdon, 1967; Brune et al., 1981).

These studies have several commonalities including mode of administration, tumor sites, tumor types and the presumed mechanisms of action. The data sets were not combined prior to modeling (the preferred approach) because they employed significantly dissimilar protocols.

The geometric mean from several slope factors, each considered to be of equal merit, was used to calculate a single unit risk. These four slope factor estimates span less than a factor of three and each is based on an acceptable, but less-than-optimal, data set. Each estimate is based on a low-dose extrapolation procedure which entails the use of multiple assumptions and default procedures.

Clement Associates (1990) fit the Neal and Rigdon (1967) data to a two-stage dose response model. In this model the transition rates and the growth rate of preneoplastic cells were both considered to be exposure-dependent. (The functional form for the dose-dependence of preneoplastic cell growth rate was simple saturation.) A term to permit the modeling of BAP as its own promoter was also included. Historical control stomach tumor data from a related, but not identical, mouse strain, SWR/J Swill (Rabstein et al., 1973) and the CFW Texas colony (Neal and Rigdon, 1967) were used in the modeling. In calculating the lifetime unit risk for humans several standard assumptions were made: mouse food consumption was 13% of its body weight/day; human body weight was assumed to be 70 kg and the assumed body weight of the mouse 0.034 kg. The standard assumption of surface area equivalence between mice and humans was the cube root of 70/0.034. A conditional upper bound estimate was calculated to be 5.9 per (mg/kg)/day (U.S. EPA, 1991a).

A U.S. EPA report (1991b) argued that the upper-bound estimate calculated in Clement Associates (1990) involved the use of unrealistic conditions placed on certain parameters of the equation. Other objections to this

slope factor were also raised. The authors of this report used the Neal and Rigdon (1967) data to generate an upper-bound estimate extrapolated linearly from the 10% response point to the background of an empirically fitted dose-response curve (Clement Associates, 1990). Other results, from similar concepts and approaches used for other compounds, suggest that the potency slopes calculated in this manner are comparable to those obtained from a linearized multistage procedure for the majority of the other compounds. The upper bound estimate calculated in U.S. EPA (1991b) is 9.0 per (mg/kg)/day.

The authors of U.S. EPA (1991b) selected a model to reflect the partial lifetime exposure pattern over different parts of the animals' lifetimes. The authors thought that this approach more closely reflected the Neal and Rigdon (1967) regimen. A Weibull-type dose-response model was selected to accommodate the partial lifetime exposure; the upper-bound slope factor calculated from this method was 4.5 per (mg/kg)/day.

Using the dietary portion of the Brune et al. (1981) rat data, a linearized multistage procedure was used to calculate an upper bound slope factor for humans. In the interspecies conversion the assumed human body weight was 70 kg and the rat 0.4 kg. The slope factor calculated by this method was 11.7 per (mg/kg)/day.

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o DISCUSSION OF CONFIDENCE :

The data are considered to be less than optimal, but acceptable. There are precedents for using multiple data sets from different studies using more than one sex, strain and species; the use of the geometric mean of four slope factors is preferred because it makes use of more of the available data. The use of the geometric means was based on arguments presented in a personal communication (Stiteler, 1991).

CARDR-
o CARCINOGENICITY SOURCE :

Source Document -- U.S. EPA, 1991a,b

The 1991 Drinking Water Criteria Document for the polycyclic aromatic
hydrocarbons has received agency review.
DOCUMENT

---

o REVIEW DATES : 01/07/87, 12/04/91, 06/03/92, 08/05/93
o VERIFICATION DATE : 12/04/91
o EPA CONTACTS :

Robert E. McGaughy / OHEA -- (202)260-5898

Rita Schoeny / OHEA -- (513)569-7544

WQCHU-

Water and Fish Consumption: 2.8E-3 ug/L

Fish Consumption Only: 3.11E-2 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic
properties of this chemical, the ambient water concentration should be zero.
However, zero may not be obtainable at this time, so the recommended criteria
represents a E-6 estimated incremental increase of cancer over a lifetime. The
values given represent polynuclear aromatic hydrocarbons as a class.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS

(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute LEC -- none
Chronic LEC -- none

Marine:

Acute LEC -- 3.0E+2 ug/L
Chronic LEC -- none

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but
are the lowest effect levels found in the literature. LEC's are given when
the minimum data required to derive water quality criteria are not available.
The values given represent polynuclear aromatic hydrocarbons as a class.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value -- 0 mg/L (Proposed,1990)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed MCLG for benzo(a)pyrene is zero based on the
evidence of carcinogenic potential (B2).

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Health and Ecological Criteria Division / OST / (202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 0.0002 mg/L (Proposed, 1990)

Considers technological or economic feasibility? -- YES

Discussion -- The proposed MCL is equal to the PQL and is associated with a maximum lifetime individual risk of 1 E-4.

Monitoring requirements -- Community and non-transient water system monitoring based on state vulnerability assessment; vulnerable systems to be monitored quarterly for one year; repeat monitoring dependent upon detection and size of system.

Analytical methodology -- High pressure liquid chromatography (EPA 550, 550.1); gas chromatographic/mass spectrometry (EPA 525): PQL= 0.0002 mg/L.

Best available technology -- Granular activated carbon

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMCONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

Status -- Listed (Proposed, 1991)

Discussion -- "Unregulated" contaminants are those contaminants

for which
EPA establishes a monitoring requirement but which do not have an associated
final MCLG, MCL, or treatment technique. EPA may regulate these contaminants
in the futur
Monitoring requirement -- All systems to be monitored unless a vulnerability
assessment determines the system is not vulnerable.

Analytical methodology -- Gas chromatography/mass spectrometry (EPA 525);
high pressure liquid chromatography (EPA 550, 550.1).

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline /
(800) 426-4791

CERC -

Value -- 1 pound (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The RQ for benzo(a)pyrene is based on potential carcinogenicity (group B2). This chemical is currently under assessment for
carcinogenicity and chronic toxicity and the RQ is subject to change in future
rulemaking.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800) 424-9346 / (202) 260-3000 / FTS 260-3000

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - None
IREF - None
CREF - Brune, H., R.P. Deutsch-Wenzel, M. Habs, S. Ivankovic and D. Schmahl.
1981. Investigation of the tumorigenic response to benzo[a]pyrene in
aqueous caffeine solution applied orally to Sprague-Dawley rats. J.
Cancer Res. Clin. Oncol. 102(2): 153-157.
CREF - Clement Associates. 1990. Ingestion dose-response model to
benzo(a)pyrene. EPA Control No. 68-02-4601.
CREF - IARC (International Agency for Research on Cancer). 1983. Certain
Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds. Monographs
on the Evaluation of Carcinogenic Risk of the Chemical to Man, Vol. 3.
Lyon, France.
CREF - Knauf, L. and G. Rice. 1992. Statistical Evaluation of Several
Benzo[a]pyrene Bioassays. Memorandum to R. Schoeny, U.S. EPA,
Cincinnati, OH. January 2.
CREF - Neal, J. and R.H. Rigdon. 1967. Gastric tumors in mice fed
benzo[a]pyrene -- A quantitative

Med. 25(4):
553-557.
CREF - Rabstein, L.S., R.L. Peters and G.J. Spahn. 1973.
Spontaneous tumors
and pathologic lesions in SWR/J mice. J. Natl. Cancer
Inst. 50:
751-758.

CREF - Stiteler, W. 1991. Syracuse Research Corporation, Syracuse, NY.
Personal communication with R. Schoeny, U.S. EPA, Cincinnati, OH.
CREF - Thyssen, J., J. Althoff, G. Kimmerle and U. Mohr. 1981. Inhalation
studies with benzo[a]pyrene in Syrian golden hamsters. J. Natl. Cancer
Inst. 66: 575-577.
CREF - U.S. EPA. 1991a. Drinking Water Criteria Document for PAH. Prepared by
the Office of Health and Environmental Assessment, Environmental
Criter and Assessment Office, Cincinnati, OH for the Office of Water
Regulations and Standards, Washington, DC.
CREF - U.S. EPA. 1991b. Dose-Response Analysis of Ingested Benzo[a]pyrene (CAS
No. 50-32-8). Human Health Assessment Group, Office of Health and
Environmental Assessment, Washington, DC.
EPA/600/R-92/045.
HAREF- None

[IRIS] SS 4 /cf?
USER:

FICHE # 2

```
1    - IRIS
NAME - Beryllium
RN   - 7440-41-7
DATE - 930201
RLEN - 27537

[IRIS] SS 3 /cf?
1    - IRIS
IRSN - 11
DATE - 930201
UPDT - 02/01/93, 1 field
STAT - Oral RfD Assessment (RDO) on-line 02/01/93
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 09/01/92
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH  - 03/01/88 RDO Reference dose table clarified
IRH  - 03/01/88 RDO Text added
IRH  - 09/07/88 CAR Carcinogen summary on-line
IRH  - 01/01/90 CAREV References clarified
IRH  - 01/01/90 CAREV Text revised
IRH  - 01/01/90 CARO Quantitative estimate for oral exposure
section added
IRH  - 01/01/90 CARI Text revised
IRH  - 01/01/90 CARDR Work group review dates and verification
date added
IRH  - 01/01/90 REFS Bibliography on-line
CONTINUE PRINTING? (YES/NO/CONT)
USER:
y

IRH  - 02/01/90 OREF Puzanova et al. 1978 citation corrected
IRH  - 02/01/90 CREF Wagner et al. 1969 citation corrected
IRH  - 09/01/90 RDO Morgareidge ref. now Cox (same study-authors
reversed)
IRH  - 09/01/90 RCRA EPA contact changed
IRH  - 09/01/90 OREF Morgareidge ref. now Cox (same study-authors
reversed)
IRH  - 01/01/91 CAR Text edited
IRH  - 01/01/91 CARI Inhalation slope factor removed (global
change)
IRH  - 01/01/92 EXSR Regulatory actions updated
IRH  - 09/01/92 CAREV U.S. EPA citation year corrected, paragraph
3
IRH  - 09/01/92 CARDR Source document year corrected
IRH  - 09/01/92 CARDR Review statement revised
IRH  - 09/01/92 CREF U.S. EPA reference year corrected
IRH  - 02/01/93 RDO Primary contact changed
RLEN - 27537
NAME - Beryllium
RN   - 7440-41-7
SY   - Beryllium
SY   - Beryllium-9
SY   - Glucinum
SY   - RCRA waste number P015
CONTINUE PRINTING? (YES/NO/CONT)
USER:
y

SY   - UN 1567
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RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
No adverse effects Rat, Chronic Oral Bioassay Schroeder and Mitchner, 1975	NOAEL: 5 ppm in drinking water (0.54 mg/kg bw/day) LOAEL: none	100	1	5E-3 mg/kg/day

*Conversion Factors: 5 ppm (5 mg/L) x 0.035 L/day / 0.325 kg bw = 0.54 mg/kg bw/day

---

o ORAL RFD STUDIES :

CONTINUE PRINTING? (YES/NO/CONT)
USER:
cont

Schroeder, H.A. and M. Mitchner. 1975. Life-term studies in rats: Effects of aluminum, barium, beryllium and tungsten. J. Nutr. 105: 421-427.

Fifty-two weanling Long-Evans rats of each sex received 0 or 5 ppm beryllium (as BeSO4, beryllium sulfate) in drinking water. Exposure was for the lifetime of the animals. At natural death the rats were dissected and gross and microscopic changes were noted in heart, kidney, liver, and spleen. There were no effects of treatment on these organs or on lifespan, urinalysis, serum glucose, cholesterol, and uric acid, or on numbers of tumors. Male rats experienced decreased growth rates from 2 to 6 months of age.

Similar studies were carried out on Swiss (CD strain) mice in groups of 54/sex at doses of approximately 0.95 mg/kg/day (Schroeder and Mitchner, 1975). Female animals showed decreased body weight compared with untreated mice at 6 of 8 intervals. Male mice exhibited slight increases in body weight. These effects were not considered adverse, therefore, 0.95 mg/kg/day is considered a NOAEL.

An unpublished investigation by Cox et al. (1975) indicates a much higher dose
level (approximately 25 mg/kg/day) in the diet may be a NOEL.

---

o ORAL RFD UNCERTAINTY :

UF -- The uncertainty factor of 100 reflects a factor of 10 each for
interspecies conversion and for the protection of sensitive human

subpopulations.

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o ORAL RFD MODIFYING FACTOR :

MF -- None

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o ORAL RFD COMMENTS :

This RfD is limited to soluble beryllium salts. Data on the terato- genicity
or reproductive effects of beryllium are limited. It has been reported to
produce embryolethality and terata in chick embryos (Puzanova et al., 1978).

---

o ORAL RFD CONFIDENCE :

Study -- Low
Data Base -- Low
RfD -- Low

Confidence in the study is rated as low because only one dose level was
administered. Although numerous inhalation investigations and a supporting
chronic oral bioassay in mice exist, along with the work by Cox et al. (1975)
which indicates that a higher dose level might be a NOEL, these studies are
considered as low to medium quality; thus, the data base is given a low
confidence rating. The overall confidence in the RfD is low, reflecting the
need for more toxicity data by the oral route.

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o ORAL RFD SOURCE DOCUMENT :

Source Document -- U.S. EPA, 1985

The 1985 Drinking Water Criteria Document for Beryllium is currently under-
going Agency review.

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o REVIEW DATES : 12/02/85
o VERIFICATION DATE : 12/02/85
o EPA CONTACTS :

Linda R. Papa / OHEA -- (513)569-7587

Krishan Khanna / OST -- (202)260-7588

CAREV-
o CLASSIFICATION : B2; probable human carcinogen.
o BASIS FOR CLASSIFICATION : Beryllium has been shown to induce lung cancer via inhalation in rats and monkeys and to induce osteosarcomas in rabbits via intravenous or intramedullary injection. Human epidemiology studies are considered to be inadequate.
o HUMAN CARCINOGENICITY DATA :

Inadequate. Reported increases, while apparently associated with exposure, did not take a variety of possible confounding factors into account. Wagoner et al. (1980) observed 47 deaths from cancer among 3055 white males employed in beryllium-processing with a median duion of employment of 7.2 months. Among the 2068 followed for 25 years or more, 20 lung cancer deaths were observed. These increased incidences were statistically significant. When lung cancer mortality data became available for 1968-1975, the number of expected deaths was recalculated and the increased incidence was statistically significant only among workers followed 25 years or more (Bayliss, 1980; MacMahon, 1977, 1978). When the number expected deaths was adjusted for smoking, the increased incidence was no longer significant (U.S. EPA, 1986).

An earlier study of workers from this same beryllium processing plant, and several studies of workers from this plant combined with workers from other beryllium plants, have reported a statistically significant increased incidence of lung cancer (Bayliss and Wagoner, 1977; Mancuso, 1970, 1979, 1980). No adjustment was made for smoking in these studies, and all were

limited in tir ability to detect a possible increased incidence of lung
cancer because of methodological constraints and deficiencies.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. Based on the evidence for induction of tumors by a variety of
beryllium compounds in male and female monkeys and in several strains of rats
of both sexes, via inhalation intratracheal instillation, and the
induction of osteosarcomas in rabbits by intravenous or intramedullary
injection in multiple studies.

Slight increases in cancer incidence (not statistically significant in
comparison with controls) were reported in Long-Evans rats (52/sex/group)
administered 5 ppm beryllium sulfate in the drinking water for a lifetime.
The authors reported a slight excess of grossly observed tumors in the 5 ppm
group (9/33) over controls (4/26) in the male rats. Thewer of this test to
detect a carcinogenic effect was reduced by high mortality (approximately 60%
survived a pneumonia epidemic at 20 months) (Schroeder and Mitchener, 1975a).
Schroeder and Mitchener (1975b) administered 5 ppm beryllium sulfate in
drinking water to Swiss mice (54/sex/group) over a lifetime. A non-
statistically significant increase in incidence of lymphoma leukemias were
reported in the females (9/52) relative to controls (3/47).

An increase in reticulum cell sarcomas of the lungs was seen in male, but
not female Wistar-derived rats administered beryllium sulfate in the diat 5
and 50 ppm, but not at 500 ppm (Morgareidge et al., 1977). The incidence in
males equaled 10/49, 17/35, 16/40 and 12/39 for the control, low, intermediate
and high dose groups, respectively. Since the results were published only as
an abstract, and since no response was seen at the highest dose, these results
are considered to be only suggestive for the induction of canceria this
route.

Osteogenic sarcomas were induced in rabbits by intravenous injection of
beryllium compounds in at least 12 different studies and by intramedullary
injection in at least four studies (U.S. EPA, 1991). Bone tumors were induced
by beryllium oxide, zinc beryllium silicate, beryllium phosphate, beryllium

silicate and beryllium metal. No bone tumors were reported to be induced by intravenous injection of beryllium oxide or zinc beryllium silicate in rats or guinea pigs (Gardner and Heslington, 1946). Positive results, however, were reported in mice injected with zinc beryllium silicate, although the numbers were not listed (Cloudman et al., 1949). The sarcomas were generally reported to be quite malignant and metastasized to other organs.

Lung tumors, primarily adenomas and adenocarcinomas, have been induced via the inhalation route in both male and female Sprague-Dawley rats during exposure periods of up to 72 weeks by beryllium sulfate (Reeves et al., 1967), in both male and female Sherman and Wistar rats by beryllium phosphate, beryllium fluoride and zinc beryllium silicate (Schepers, 1961), in male Charles River CR-CD rats by beryl ore (Wagner et al., 1969) and in both male and female rhesus monkeys by beryllium sulfate (Vorwald, 1968). Positive results were seen in rats exposed to beryllium sulfate at concentrations as low as 2 ug/cu.m (Vorwald, 1968).

Tumors were also induced by intratracheal instillation of metallic beryllium, beryllium-aluminum alloys and beryllium oxide in both Wistar rats and rhesus monkeys. Adenomas, adenocarcinomas and malignant lymphomas were seen in the lungs, with lymphosarcomas and fibrosarcomas present at extrapulmonary sites (Groth et al., 1980; Ishinishi et al., 1980).

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o SUPPORTING DATA :

Beryllium sufate and beryllium chloride have been shown to be nonmutagenic in bacterial and yeast gene mutation assays (Simmon et al., 1979). In contrast, gene mutation studies in Chinese hamster V79 and CHO cells were positive (Miyaki et al., 1979; Hsie et al., 1979). Chromosomal aberrations and sister chromatid exchange were also induced by beryllium in cultured human lymphocytes and Syrain hamster embryo cells (Larramendy et al., 1981).

CARO -

o CLASSIFICATION : B2; probable human carcinogen.
o BASIS FOR CLASSIFICATION : Beryllium has been shown to induce lung cancer via inhalation in rats and monkeys and to induce osteosarcomas in rabbits via intravenous or intramedullary injection. Human epidemiology studies are considered to be inadequate.
o ORAL SLOPE FACTOR : 4.3 per(mg/kg)/day
o DRINKING WATER UNIT RISK : 1.2E-4 per(ug/L)
o DOSE EXTRAPOLATION METHOD : Linearized multistage procedure, extra risk
o RISK/WATER CONCENTRATIONS :

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	8.3E-1 ug/L
E-5 (1 in 100,000)	8.3E-2 ug/L
E-6 (1 in 1,000,000)	8.3E-3 ug/L

o ORAL DOSE-RESPONSE DATA :

Tumor Type -- gross tumors, all sites combined
Test Animals -- rat/Long-Evans, male
Route -- drinking water
Reference -- Schroeder and Mitchener, 1975a

Administered Dose ppm	Administered Dose (mg/kg)/day	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0	0	4/26
5	0.54	0.09	9/33

o ADDITIONAL COMMENTS :

The solubility and speciation of beryllium in air and water media vary, with ambient air characterized by relatively insoluble beryllium compounds such as beryllium oxide and metallic beryllium, and water characterized by moroluble forms. Carcinogenic potency varies according to the form of beryllium present.

Human equivalent doses were calculated using a human body weight of 70 kg, an animal weight of 0.325 kg and length of exposure, experiment and lifespan of 1126 days for treated and control animals.

The unit risk should not be used if the water concentration exceeds 8.3E+1 ug/L, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

The estimate is derived from a study which did not show a significant increase in tumorigenic response. While this study is limited by use of only one non-zero dose group, the occurrence of high mortality and unspecified type and site of the tumors, it was used as the basis of the quantitative estimate because exposure occurred via the most relevant ute. Oral risk estimates derived by extrapolation from studies in other species/strains for the intravenous and inhalation routes (also highly uncertain) are within an order of magnitude.

CARI -

o CLASSIFICATION	: B2; probable human carcinogen.
o BASIS FOR CLASSIFICATION	: Beryllium has been shown to induce lung cancer via inhalation in rats and monkeys and to induce osteosarcomas in rabbits via intravenous or intramedullary injection. Human epidemiology studies are considered to be inadequate.
o INHALATION UNIT RISK	: 2.4E-3 per (ug/cu.m)
o DOSE EXTRAPOLATION METHOD	: Relative risk
o RISK/AIR CONCENTRATIONS :	

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	4E-2 ug/cu.m
E-5 (1 in 100,000)	4E-3 ug/cu.m
E-6 (1 in 1,000,000)	4E-4 ug/cu.m

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o INHALATION DOSE-RESPONSE DATA :

Tumor Type --
Test Animals -- humans

Route -- inhalation, occupational exposure
Reference --

Beryllium Concentration in Workplace (ug/cu.m)	Unit Risk /ug/cu.m	Fraction of Lifetime	Effective dose (ug/cu.m)	95 percent Upper-bound Estimate of Relative Risk
100	1.61E-3	1.00	21.92	1.98
	1.79E-3			2.09
	6.44E-3	0.25	5.48	1.98
	7.16E-3			2.09
1000	1.61E-4	1.00	219.18	1.98
	1.79E-4			2.09
	6.44E-4	0.25	54.79	1.98
	7.16E-4			2.09

o ADDITIONAL COMMENTS :

Human data were used for the inhalation exposure quantitation despite limitations in the study. Humans are most likely to be exposed by inhalation to beryllium oxide, rather than other beryllium salts. Animal studies by inhalation of beryllium oxide have utilized intratracheal instillation, rather than general inhalation exposure.

Effective dose was determined by adjusting for duration of daily (8/24 hours) and annual (240/365 days) exposure, and the fraction of the lifetime at risk (i.e., time from onset of employment to termination of follow-up). The risk estimates were based on the data of Wagoner et al. (1980) in which the smoking adjusted, expected lung cancer deaths were found to range from 13.91 to 14.67, in comparison to 20 observed. Relative risk estimates of 1.36 and 1.44 were derived and the 95% confidence limits of these estimates, 1.98 and 2.09, respectively, were used to estimate the lifetime cancer risk. Note that all of the above estimates are based on one data set using a range of estimated exposure and exposure times. Because of uncertainties regarding workplace beryllium concentration and

exposure
duration, unit risks were derived using two estimates each of concentration,
fraction of lifetime exposed and relative risk. The recommended value is the
arithmetic mean of the 8 derived unit risks.

The unit risk should not be used if the air concentration exceeds 4
ug/cu.m, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

The estimate of risk for inhalation exposure was based upon an
epidemiologic study having several confounding variables. The estimates of
exposure levels and duration were also somewhat uncertain. While a
quantitative assessment based on several animal studies resulted in a similar
estimate of risk (which increases the confidence somewhat), the quality of the
available studies was poor (that is, they were conducted at single dose levels
or lacked control groups).

CARDR-
o CARCINOGENICITY SOURCE :

Source Document -- U.S. EPA, 1986, 1991

Source Document Review -- The values in 1986 Health Assessment Document for
Beryllium and the 1991 Drinking Water Criteria Document for Beryllium received
Agency and external review.

Other EPA Documentation -- None
DOCUMENT

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o REVIEW DATES : 05/04/88, 02/01/89, 12/07/89
o VERIFICATION DATE : 05/04/88 (inhalation); 02/01/89 (oral)
o EPA CONTACTS :

William Pepelko / OHEA -- (202)260-5904

David Bayliss / OHEA -- (202)260-5726

CAA -

Considers technological or economic feasibility? -- YES

Discussion -- Beryllium was listed as a hazardous air pollutant under section 112 of the CAA in 1971 on the basis that it can cause the chronic lung disease berylliosis. Emission standards promulgated for extraction, ceramic, and propellant plants, foundries, incinerators, and machine shops are 10 g/24 hr or attainment of an ambient concentration near the source of 0.01 ug/cu.m, 30 day average. This ambient concentration was judged adequate to protect the public health with an ample margin of safety. More complex standards were also promulgated for beryllium rocket motor firing. The NESHAPs are now under review, and will consider new health evidence that beryllium may be a carcinogen. Reporting of releases of massive forms of this hazardous substance is not required if the diameter of the pieces released exceeds 100 micrometers (0.004 inches).

Reference -- 40 CFR Part 61, Subparts C & D

EPA Contact -- Emissions Standards Division, OAQPS (917)541-5571 / FTS 629-5571

WQCHU-

Water and Fish Consumption: 6.8E-3 ug/L

Fish Consumption Only: 1.17E-1 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, zero may not be attainable at this time, so the recommended criterion represent a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80); Quality Criteria for Water, EPA 440/5-86-001 (5/87).

EPA Contact -- Criteria and Standards Division / OWRS

(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute LEC -- 1.3E+2 ug/L
Chronic LEC -- 5.3E+0 ug/L

Marine: None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but
are the lowest effect levels found in the literature. LECs are given when the
minimum data required to derive water quality criteria are not available.
Hardness has a substantial effect on acute toxicity.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value -- 0 mg/L (Proposed, 1990)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed MCLG for beryllium is zero based on the evidence
of carcinogenic potential (B2).

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline /
(800) 426-4791

MCL -

Value -- 0.001 mg/L (Proposed, 1990)

Considers technological or economic feasibility? -- YES

Discussion -- The MCL is based on 5x the MDL, which is associated with a maximum lifetime individual risk of 1 E-4.

Monitoring requirements -- Ground water systems every 3 years; surface water systems annually; will allow monitoring at up to 10-year intervals after the system completes 3 rounds of sampling at <50% of the MCL.

Analytical methodology -- Atomic absorption/furnace technique (EPA 210.2; ASTM D-3645; SM 304); inductively-coupled plasma (EPA 200.7; SM 305); ICP mass spectrometry (EPA 200.8): PQL= 0.001 mg/L.

Best available technology -- Activated alumina;ion exchange; reverse osmosis; lime softening; coagulation/filtration.

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

Status -- Listed (Final, 1991)

Discussion -- "Unregulated" contaminants are those contaminants for which EPA establishes a monitoring requirement but which do not have an associated final MCLG, MCL, or treatment technique. EPA may regulate these contaminants in the future.

Monitoring requirement -- All systems to be monitored unless a vulnerability assessment determines the system is not vulnerable.

Analytical methodology -- Atomic absorption/furnace technique (EPA 210.2; SM 304; ASTM D-3645); inductively coupled plasma (EPA 200.7; SM 305); spectrophotometric (EPA 200.8).

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

CERC -

Value (status) -- 10 pounds (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The RQ for beryllium is based on potential carcinogenicity.
Available data indicate a hazard ranking of medium based on a potency factor
of 79.70/mg/kg/day and a weight-of-evidence group B2, which correspond to
an RQ of 10 pounds. Reporting of releases of massive forms of this hazardous
substance is not required if the diameter of the pieces released exceeds 100
micrometers (0.004 inches).

Reference -- 54 FR 33418 (08/14/89)

EPA Contac- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - Cox, G.E., D.E. Bailey and K. Morgareidge. 1975. Chronic feeding
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the Food and Drug Research Laboratories, Inc., to the Aluminum Company
of America, Pittsburgh, PA.
OREF - Puzanova, L., M. Doskocil and A. Doubkova. 1978. Disturbances of the
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chloride at early stages of embryogenesis. Folia. Morphologica. 26(3):
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OREF - Schroeder, H.A. and M. Mitchener. 1975. Life-term studies in rats:
Effects of aluminum, barium, beryllium and tungsten. J. Nutr. 105:
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OREF - U.S. EPA. 1985. Drinking Water Criteria Document for Beryllium.
Prepared by the Office of Health and Environmental Assessment,
Environmental Criteria and Assessment Office, Cincinnati, OH for the
Office of Drinking Water, Washington, DC.
IREF - None
CREF - Bayliss, D.L. 1980. U.S. EPA, Washington, DC. Letter to William H.
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CREF - Bayliss, D.L. and J.K. Wagoner. 1977. Bronchogenic cancer and cardio-
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production facility. OSHA Beryllium Hearing, 1977, Exhibit 13.F.
CREF - Cloudman, A.M., D. Vining, S. Barkulis and J.J. Nickson. 1949. Bone
changes following intravenous injections of beryllium. Am. J. Pathol.
25: 810-811.
CREF - Gardner, L.U. and H.F. Heslington. 1946. Osteo-sarcoma from intravenous
beryllium compounds in rabbits. Fed. Proc. 5: 221. (Cited in U.S. EPA,
1987)
CREF - Groth, D.H., C. Kommineni and G.R. Mackay. 1980. Carcinogenicity of
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mammalian cell genetic toxicology: Study of the cytotoxicity and
mutagenicity of seventy individual environmental agents related to
energy technologies and three subfractions of crude synthetic oil in
the CHO/HGPRT system. Environ. Sci. Res. 15: 219-315.
CREF - Ishinishi, N., M. Mizunoe, T. Inamasu and A. Hisanga. 1980.
Experimental study on carcinogenicity of beryllium oxide and arsenic
trioxide to the lung of rats by an intratracheal instillation. Fukuoka
Igaku Zasshi. 71(1): 19-26. (Jap. with Eng. abstract)

CREF - Larramendy, M.L., N.C. Popescu and J.A. DiPaola. 1981. Induction by
inorganic metal salts of sister chromatid exchanges and chromosome
aberrations in human and Syrian hamster cell strains. Environ. Mutagen.
3: 597-606.
CREF - MacMahon, B. 1977. Evaluation of epidemiological materials. January 10,
1978. Brush Wellman, Cleveland, OH. OSHA Beryllium Hearings: 5.
CREF - MacMahon, B. 1978. OSHA Beryllium Hearings, comment on recent
post-hearing submissions. Docket No. H005, February 9, 1979.
CREF - Mancuso, T.F. 1970. Relation of duration of employment and prior
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Environ. Res. 3: 251-275.
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dusts and disease. In: Proc. Conference on Occupational Exposure to
Fibrous and Particulate Dust and Their Extension into the Environment,
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CREF - Schepers, G.W.H. 1961. Neoplasia experimentally induced by beryllium
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CREF - Schroeder, H.A. and M. Mitchener. 1975a. Life-term studies in rats:
Effects of aluminum, barium, beryllium and tungsten. J. Nutr. 105:
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CREF - Schroeder, H.A. and M. Mitchener. 1975b. Life-term effects of mercury,
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Mutagenic activity of chemical carcinogens and related compounds in the
intraperitoneal host-mediated assay. J. Natl. Cancer Inst. 62(4):
911-918.

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Assessment Office, Research Triangle Park, NC. EPA 600/8-84-026F.
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Office of Drinking Water, Washington, DC.
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monkeys. In: Use of Nonhuman Primates in Drug Evaluation, H. Vagtborg,
Ed. University of Texas Press, Austin, TX. p. 222-228.
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bertrandite and beryl, with production of pulmonary tumors by beryl.
Toxicol. Appl. Pharmacol. 15: 10-29.
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etiologic agent in the induction of lung cancer, nonneoplastic
respiratory disease, and heart disease among industrially exposed
workers. Environ. Res. 21: 15-34.
HAREF- None

[IRIS] SS 3 /cf?
USER:
benzo(a)pyrene

Search in progress

SS (3) PSTG (1)

[IRIS] SS 4 /cf?
USER:
print dl

2 - IRIS
NAME - 1,3-Butadiene
RN - 106-99-0
IRSN - 136
DATE - 920501
UPDT - 05/01/92, 52 fields
STAT - Oral RfD Assessment (RDO) no data
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 02/01/91
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) withdrawn 04/01/92
IRH - 03/01/88 CAREV Text revised
IRH - 03/01/88 CARI Confidence statement revised
IRH - 06/01/89 CARDR Primary contact changed
IRH - 07/01/89 CAREV Correct Meinhardt citation
IRH - 07/01/89 CAREV Correct citations
IRH - 07/01/89 REFS Bibliography on-line
IRH - 06/01/90 CAA Area code for EPA contact corrected
IRH - 01/01/91 CAR Text edited
IRH - 01/01/91 CARI Inhalation slope factor removed (global change)
IRH - 01/01/91 CREF Bond et al., 1986 and Cote and Bayard, 1990 refs added
IRH - 02/01/91 CARI Information on extrapolation process included
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 04/01/92 REFS Regulatory action section withdrawn
RLEN - 14419
SY - BIETHYLENE
SY - BIVINYL
SY - BUTADIEEN
SY - BUTA-1,3-DIEEN
SY - BUTADIEN
SY - BUTA-1,3-DIEN
SY - BUTADIENE
SY - 1,3-Butadiene
SY - Butadiene, 1,3-
SY - alphá,gamma-BUTADIENE
SY - DIVINYL
SY - ERYTHRENE
SY - NCI-C50602
SY - PYRROLYLENE
SY - VINYLETHYLENE
MF - C4H6
USE - This material is used primarily as a monomer and comonomer for synthetic rubbers and resins; it is also a chemical intermediate for several compounds (SRI, 1983).
COFO - Colorless gas (Merck, 1983) or liquefied compressed gas (inhibited) (CHRIS, 1978) with a mild aromatic (ACGIH, 1980) or gasoline-like (CHRIS, 1978) odor.
ODOR - Colorless gas (Merck, 1983) or liquefied compressed gas (inhibited) (CHRIS, 1978) with a mild aromatic (ACGIH, 1980) or gasoline-like (CHRIS, 1978) odor.
BP - 24F, -4.5C (Merck, 1983)
MP - -164F, -109C (Weast, 1979)
MW - 54.09
DEN - 0.6211 at 20C/4C (Weast, 1979)
VAP - 910 at 20C (ACGIH, 1980)
VAPD - 1.87 (Sax, 1979)
EVAP - Not Found
SOLW - Insoluble (Weast, 1979); 0.05% (NIOSH/OSHA, 1978)
FLPT - -105F (method not given) (Sax, 1979)
FLMT - Flammable Limits: LEL -- 2.0% (Patty, 1963) UEL -- 11.5% (Patty, 1963)
AVOI - Heat, air, phenol, chlorine dioxide, and crotonaldehyde (Sax, 1979), mixing with air (Clayton and Clayton, 1981-82). Elevated temperatures may cause polymerization, which can cause violent rupture of containers (NFPA, 1978, p. 49-22).

DCMP - May form explosive peroxides upon exposure to air (Sax, 1979). Formaldehyde and acrolein are produced when material is exposed to photooxidation with ozone and nitrogen dioxide, as in smog formation (Grant, 1974).

RDO - NO DATA

RDI - NO DATA

CAREV-

o CLASSIFICATION : B2; probable human carcinogen

o BASIS FOR CLASSIFICATION : Inadequate human data and sufficient rodent (mouse and rat) studies in which exposure to airborne concentrations of 1,3-butadiene caused multiple tumors and tumor types form the basis for this classification. Related compounds are carcinogenic and mutagenic.

o HUMAN CARCINOGENICITY DATA :

Inadequate. Of the three studies on workers specifically identified as being exposed to 1,3-butadiene, two were cohort studies while one was a cross-sectional study designed to look at certain hematologic parameters. One of the cohort studies was a mortality study of 14,000 workers at eight plants, and it found none of the Standard Mortality Ratios (SMR) for cancer to be significantly elevated (Matanoski et al., 1982). The second cohort study found an increase of borderline significance in the SMR for lymphatic and hematopoietic cancer in a subpopulation (Meinhardt et al., 1982). The cross-sectional study found no evidence of hematologic effects (Checkoway and Williams, 1982). Two studies found an association between employment in the synthetic rubber industry and an elevated risk of cancer. Synthetic rubber is manufactured from styrene and butadiene. In one case-control study, synthetic rubber plant workers were found to have an increased risk ratio for deaths from lymphatic and hematopoietic cancer (McMichael et al., 1976). The second, a cohort mortality study, found excess lung cancer deaths among workers in a synthetic rubber area of a plant. This latter finding was based on three deaths with no control for smoking (Andjelkovich et al., 1977). Given the inconsistency of results, the methodological limitations of the different studies, and the confounding effects of exposure to various solvents, styrene, and possibly other chemicals, the epidemiologic evidence is considered inadequate.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. Two lifetime inhalation studies of 1,3-butadiene in rodents were initiated. B6C3F1 mice (50/sex/group) were exposed to 625 or 1250 ppm for 6 hours/day, 5 days/week. Exposure began at 8-9 weeks of age, and all mice were killed after weeks 60-61 because of excessive deaths among treated mice. Increases were observed in the number of mice with primary tumors and in the number of mice with multiple primary tumors. Tumors occurring throughout the body included hemangiosarcomas of the heart, lymphomas and alveolar/bronchiolar adenomas/carcinomas (NTP, 1984).

Charles River CD rats (110/sex/group) were exposed to 1000 or 8000 ppm 1,3-butadiene for 6 hours/day, 5 days/week for 111 weeks (males) or 105 weeks (females). There was a treatment-related increase in mortality, some of which

was attributed to nephropathies in males. Significant increases occurred in incidence in both common and uncommon tumors including mammary gland tumors, thyroid follicular adenomas and carcinomas, and Leydig cell adenomas and carcinomas (Hazleton Laboratories Ltd, 1981). Because of problems with reporting of this study and because pharmacokinetic analysis indicated that the effective doses were the same for both treatment groups, this study was not considered adequate for the estimation of risk.

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o SUPPORTING DATA :

Three studies have shown 1,3-butadiene to be mutagenic for Salmonella typhimurium upon addition of mammalian hepatic homogenates for metabolism (de Meester et al., 1978, 1980; Poncelet et al., 1980). Pharmacokinetic and various types of toxicity studies indicate that the carcinogenic effect of 1,3-butadiene can be attributed to the metabolites 3,4-epoxybutane and/or 1,2,3,4-diepoxybutane. These metabolites, which are potent alkylating agents, have been shown to be mutagenic and carcinogenic (Lawley and Brookes, 1967; de Meester et al., 1978; Dean and Hodson-Walker, 1979; Perry and Evans, 1975; Wade et al., 1979; Voogd et al., 1981; Ehrenberg and Hussain, 1981; Conner et al., 1983; U.S. EPA, 1985). 1,3-Butadiene is structurally related to known carcinogens.

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CARO - NO DATA

CARI -

o CLASSIFICATION : B2; probable human carcinogen

o BASIS FOR CLASSIFICATION : Inadequate human data and sufficient rodent (mouse and rat) studies in which exposure to airborne concentrations of 1,3-butadiene caused multiple tumors and tumor types form the basis for this classification. Related compounds are carcinogenic and mutagenic.

o INHALATION UNIT RISK : 2.8E-4 per (ug/cu.m)

o DOSE EXTRAPOLATION METHOD : Linearized multistage procedure, extra risk

o RISK/AIR CONCENTRATIONS :

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	4E-1 ug/cu.m
E-5 (1 in 100,000)	4E-2 ug/cu.m
E-6 (1 in 1,000,000)	4E-3 ug/cu.m

-

o INHALATION DOSE-RESPONSE DATA :

Species/Strain Tumor Type	Dose Administered	Dose Internal Dose	Tumor Incidence		Reference
Mouse/B6C3F1; several tumor types	Route: Inhalation				NTP, 1984
	ppm	mg/kg/day	male	female	
	0	0	2/50	4/48	

625	18.4	43/49	31/48
1250	27.8	40/45	45/49

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o ADDITIONAL COMMENTS :

Animals dying before onset of first tumor (20 weeks) were eliminated. An adjustment was made for early sacrifice in the calculation. The concentration in ppm is assumed to be equivalent for the experimental animals and humans.

In determining the animal-to-equivalent-human dose, an adjustment was made to account for the lack of proportionality to external concentration at high levels. The function for the incremental cancer risk to the animals was based on a calculated internal dose (in mg/kg) and converted back to risk for low-dose ppm equivalents in the animal.

Animal upper-limit slope factors of 6.1E-1 per (mg/kg)/day for males, and 3.0E-1 per (mg/kg)/day for females were reconverted to air concentration units of 9.2E-1 per ppm and 4.5E-1 per ppm by assuming a 20% absorption rate at low exposures. Data from Bond et al. (1986) support the assumption that in mice and rats exposed to 13 ug 1,3-butadiene/L air or less, absorption will be 20%. The quantitative estimates of 1.8E+0 per (mg/kg)/day or 6.4E-1 per ppm is a geometric mean of slope factors derived from the male and female mouse data sets. This is a correction from U.S. EPA (1985) in which preliminary data was used to calculate the unit risk (Cote and Bayard, 1990).

The unit risk should not be used if the air concentration exceeds 16 ug/cu.m, since above this concentration the unit risk may not be appropriate.

---

o DISCUSSION OF CONFIDENCE :

Unit risks of 3.4E-1 and 1.9E-1 per (ppm) were calculated from male and female rat data, which were highly limited from a modeling standpoint, having only one effective dose, confusion over animal accounting, and other drawbacks.

Adequate numbers of mice were treated. Risk estimates derived from data on mice and rats differ by a factor of 3 for females (1.9E-1 per (ppm) vs. 5.6E-2 per (ppm) and 80 for males (3.4E-1 per (ppm) vs. 4.2E-3 per (ppm). The relatively close agreement of quantitative estimates across species for females supports the confidence in the unit risk. An alternate analysis using life-table adjustment for both genders of mice shows results within a factor of 2. Confidence is rated low. Estimates of human risk based on sketchy epidemiologic data indicate that the unit risk extrapolation from animal to human is consistent.

CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1985. Mutagenicity and Carcinogenicity Assessment Document for 1,3-Butadiene. Office of Health and Environmental Assessment, Washington, DC. EPA 600/8/85-004F.

The 1985 Mutagenicity and Carcinogenicity Document received both Agency and external review.

DOCUMENT

-

o REVIEW DATES : 01/07/87
o VERIFICATION DATE : 01/07/87
o EPA CONTACTS :

Dharm V. Singh / ORD -- (202)260-5958 / FTS 260-5958

Steven P. Bayard / ORD -- (202)260-5722 / FTS 260-5722

-

-

HAONE- NO DATA

-

HATEN- NO DATA

-

HALTC- NO DATA

-

HALTA- NO DATA

-

HALIF- NO DATA

-

OLEP - NO DATA

-

ALAB - NO DATA

-

TREAT- NO DATA

-

HADR - NO DATA

-

ACUTE-
o ACUTE TOXICITY :

Death can result 23 minutes after inhaling air containing 25% butadiene (Lefaux, 1968). It is a central nervous system depressant in high concentrations. It may be irritating to skin and mucous membranes (Merck, 1983). Contact with the liquid may cause frostbite. It can asphyxiate by the displacement of air (Student, 1981, p. 78). If inhaled, may be harmful;

contact may cause burns to skin and eyes. Vapors may cause dizziness or suffocation.

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o SIGNS AND SYMPTOMS :

Initial signs and symptoms include blurred vision, nausea, prickling and dryness of the mouth, throat, and nose, followed by fatigue, headache, vertigo, decreased blood pressure and pulse rate, unconsciousness, and respiratory paralysis (Clayton and Clayton, 1981-82).

BCF - NO DATA

CAA - NO DATA

WQCHU- NO DATA

WQCAQ- NO DATA

MCLG - NO DATA

MCL - NO DATA

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC - NO DATA

SARA - NO DATA

RCRA - NO DATA

TSCA - NO DATA
OREF - None
IREF - None
CREF - Andjelkovich, D., J. Taulbee, M. Symons and T. Williams. 1977. Mortality of rubber workers with reference to work experience. J. Occup. Med. 18: 387-394.
CREF - Bond, J.A., A.R. Dahl, R.F. Henderson, G.S. Dutcher, J.L. Mauderly and L.S. Birnbaum. 1986. Species differences in the disposition of inhaled butadiene. Toxicol. Appl. Pharmacol. 84: 617-627.
CREF - Checkoway, H. and T.M. Williams. 1982. A hematology survey of workers at a styrene-butadiene synthetic rubber manufacturing plant. Am. Ind. Hyg. Assoc. J. 43: 164-169.
CREF - Conner, M., J. Lou and O. Gutierrez de Gotera. 1983. Induction and rapid repair of sister-chromatid exchanges in multiple murine tissues in vitro by diepoxybutane. Mutat. Res. 108: 251-263.

CREF - Cote, I.L. and S.P. Bayard. 1990. Cancer risk assessment of 1,3-butadiene. Environ. Health Perspect. 86: 149-153.
CREF - Dean, B.J. and G. Hodson-Walker. 1979. An in vitro chromosome assay using cultured rat-liver cells. Mutat. Res. 64: 329-337.
CREF - de Meester, C., F. Poncelet, F. Roberfroid and M. Mercier. 1978. Mutagenicity of butadiene and butadiene monoxide. Biochem. Biophys. Res. Commun. 80: 298-305.
CREF - de Meester, C., F. Poncelet, F. Roberfroid and M. Mercier. 1980. The mutagenicity of butadiene towards Salmonella typhimurium. Toxicol. Lett. 6: 125-130.
CREF - Ehrenberg, L. and S. Hussain. 1981. Genotoxicity of some important epoxides. Mutat. Res. 86: 1-113.
CREF - Hazelton Laboratories Europe, Ltd. 1981. The toxicity and carcinogenicity of butadiene gas administered to rats by inhalation for approximately 24 months. Prepared for the International Institute of Synthetic Rubber Producers, New York, NY. Unpublished.
CREF - Lawley, P.D. and P. Brookes. 1967. Interstrand cross-linking of DNA by difunctional alkylating agents. J. Mol. Biol. 25: 143-160.
CREF - Matanoski, G.M., L. Schwartz, J. Sperrazza and J. Tonascia. 1982. Mortality of workers in the styrene-butadiene rubber polymer manufacturing industry. Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD. Unpublished.
CREF - McMichael, A.J., R. Spirtas, J.F. Gamble and P.M. Tousey. 1976. Mortality among rubber workers: Relationship to specific jobs. J. Occup. Med. 18: 178-185.
CREF - Meinhardt, T.J., R.A. Lemen, M.S. Crandall and R.J. Young. 1982. Environmental epidemiologic investigation of the styrene-butadiene rubber industry. Scand. J. Work Environ. Health. 8: 250-259.
CREF - National Toxicology Program (NTP). 1984. Toxicology and carcinogenesis studies of 1,3-Butadiene (CAS 106-99-0) in B6C3F1 mice (inhalation studies). National Toxicology Program.
CREF - National Toxicology Program (NTP) 1985. Draft report on the toxicology and carcinogenesis studies of 4-vinylcyclohexane in F344/N rats and B6C3F1 mice. NIH Publication No. 85-2559.
CREF - Perry, P. and H.J. Evans. 1975. Cytological detection of mutagen-carcinogen exposure by sister chromatid exchange. Nature. 258: 121-125.
CREF - Poncelet, F., C. deMeester, M. Duverger-van Bogaert, M. Lambotte-Vandepaer, M. Roberfroid and M. Mercier. 1980. Influence of experimental factors on the mutagenicity of vinylic monomers. Arch. Toxicol. Suppl. 4: 63-66.
CREF - U.S. EPA. 1985. Mutagenicity and Carcinogenicity Assessment Document for 1,3-Butadiene. Office of Health and Environmental Assessment, Washington, DC. EPA 600/8/85-004F.
CREF - Voogd, C.E., J.J. van de Stel and J.A. Jacobs. 1981. The mutagenic action of aliphatic epoxides. Mutat. Res. 89:269-282.
CREF - Wade, M.J., J.W. Moyer and C.H. Hine. 1979. Mutagenic action of a series of epoxides. Mutat. Res. 66: 367-371.
HAREF- None

[IRIS] SS 3 /cf?
USER:
stop

DONE? (YES/NO)

USER:
no

[IRIS] SS 3 /cf?
USER:
butyl alcohol

Search in progress

SS (3) PSTG (1)

[IRIS] SS 4 /cf?
USER:
print

1 - IRIS
NAME - n-Butanol
RN - 71-36-3
DATE - 920122
RLEN - 8819

[IRIS] SS 4 /cf?
USER:
print dl

1 - IRIS
IRSN - 137
DATE - 920122
STAT - Oral RfD Assessment (RDO) on-line 09/01/90
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 03/01/91
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 03/01/88 RDO Confidence levels revised
IRH - 09/01/90 RDO Citation spelling corrected from Staner to Sterner
IRH - 09/01/90 REFS Bibliography on-line
IRH - 01/01/91 CAR Carcinogen assessment now under review
IRH - 03/01/91 CAR Carcinogenicity assessment on-line
IRH - 03/01/91 CREF Carcinogenicity references added
IRH - 01/01/92 RDO Primary contact changed
IRH - 01/01/92 EXSR Regulatory action updated
RLEN - 8819
NAME - n-Butanol
CONTINUE PRINTING? (YES/NO/CONT)
USER:
cont

RN - 71-36-3
SY - ALCOOL BUTYLIQUE
SY - BUTANOL

SY - 1-BUTANOL
SY - BUTANOLEN
SY - Butanol, n-
SY - BUTANOLO
SY - BUTYL ALCOHOL
SY - n-BUTYL ALCOHOL
SY - BUTYL HYDROXIDE
SY - BUTYLOWY ALKOHOL
SY - BUTYRIC ALCOHOL
SY - CCS 203
SY - 1-HYDROXYBUTANE
SY - METHYLOLPROPANE
SY - NA 1120
SY - PROPYLCARBINOL
SY - PROPYLMETHANOL
SY - RCRA WASTE NUMBER U031
SY - UN 1120

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Hypoactivity and ataxia	NOAEL: 125 mg/kg/day LOAEL: 500 mg/kg/day	1000	1	1E-1 mg/kg/day

Rat Oral Subchronic Study

U.S. EPA, 1986

Conversion Factors: none

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o ORAL RFD STUDIES :

U.S. EPA. 1986. Butanol: Rat oral subchronic toxicity study. Office of Solid Waste, Washington, DC.

Four groups of male and female rats (30/sex/group) were dosed daily by gavage with 0, 30, 125 and 500 mg/kg/day of butanol for 13 weeks. Six weeks after the initiation of dosing, an interim sacrifice of 10 rats/sex was performed to evaluate clinical, biochemical and gross morphological changes. The remaining animals continued in the experiment until the day of the final sacrifice (day 92 or 93). Data generated from this study on body and organ weight changes, food consumption, moribundity, mortality, and ophthalmological, gross, and histopathologic examinations did not show any dose-related differences between control and treated animals. Slight but significant reductions in some hematologic parameters were observed in the mid- and high-dosed females at the interim, but not at final sacrifice. This effect was considered to be transitory rather than adverse. Ataxia and hypoactivity were consistently observed in high-dosed (500 mg/kg/day) males and females during the final 6 weeks of the dosing period. Thus, the 125 mg/kg/day dose of butanol is considered a NOAEL for central nervous system effects in rats. By application of an uncertainty factor of 1000, an RfD of 0.1 mg/kg/day or 9 mg/day for a 70 kg-person is derived.

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o ORAL RFD UNCERTAINTY :

UF = 1000. An uncertainty factor of 1000 was applied: 10 for intraspecies variability, 10 for interspecies extrapolation, and 10 for expanding subchronic to long-term exposure.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

Sterner et al. (1949) reported that occupational exposure to 100 ppm (300 mg/cu.m) butanol had no impact on workers' health. This 10-year study included hematological evaluations, test of liver function, urine analysis, chest X-rays, ophthalmological examinations, and comparison of absenteeism among butanol-exposed men vs. all men in the plant. Details of the experimental protocol of this study were not available for risk analysis. Several other human inhalation studies have reported irritations to eyes, nose, and throat, and mild headaches, at concentrations of 50 ppm (150 mg/cu.m) or higher; however, these effects were transitory in nature. An abstract of a rat inhalation study (4-month exposure) suggested a NOAEL of 0.8 mg/cu.m for reversible blood cholinesterase activity and increased thyroid activity.

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o ORAL RFD CONFIDENCE :

Study: High
Data Base: Low
RfD: Low

The oral subchronic study provided more than adequate toxicologic endpoints based on a very well-designed experimental protocol; therefore, a high confidence is recommended. The data base does not provide pertinent information on oral chronic or reproductive studies; therefore, a low confidence is recommended. A low to medium confidence is recommended for the RfD.

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o ORAL RFD SOURCE DOCUMENT :

The only U.S. EPA documentation at present is on IRIS.

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o REVIEW DATES : 05/14/86
o VERIFICATION DATE : 05/14/86
o EPA CONTACTS :

Harlar Choudhury / ORD -- (513)569-7553 / FTS 684-7553

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

CAREV-
o CLASSIFICATION : D; not classifiable as to human carcinogenicity
o BASIS FOR CLASSIFICATION : Based on no human and no animal cancer data.
o HUMAN CARCINOGENICITY DATA :

None.

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o ANIMAL CARCINOGENICITY DATA :

None.

SUPPORTING DATA :

1-Butanol was negative in reverse mutation and DNA damage tests in Salmonella typhimurium (McCann et al., 1975; Connor et al., 1985; Nakamura et al., 1987), but weakly positive for inhibition of DNA synthesis in Escherichia coli (Yoshiyama et al., 1973). Negative results were reported for sister

chromatid exchanges in chick embryo and Chinese hamster cells and for micronucleus formation in Chinese hamster cells (Bloom, 1982; Obe and Ristowe, 1977; Lasne et al., 1984). 1-Butanol induced spindle disturbances in Chinese hamster V79 lung cells (Onfelt, 1987).

CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1989. Health and Environmental Effects Document for 1-Butanol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

The 1989 Health and Environmental Effects Document for 1-Butanol has received Agency and external peer review.
DOCUMENT

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o REVIEW DATES : 12/06/90
o VERIFICATION DATE : 12/06/90
o EPA CONTACTS :

Charles Ris / ORD -- (202)260-5898 / FTS 260-5898

CERC -

Value (status) -- 5000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final adjusted RQ for n-butanol is 5000 pounds, based on application of the secondary criterion of biodegradation to the primary criterion RQ of 1000 pounds determined by ignitability. Available data indicate a flash point of 84F and a boiling point of 283F, which correspond to an RQ of 1000 pounds. However, since n-butanol biodegrades [BOD5: 96% theoretical (active sludge)], the 1000-pound RQ based on ignitability has been adjusted upward one level to 5000 pounds.

Reference -- 50 FR 13456 (04/04/85); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

REF - Sterner, J.H., H.C. Crouch, H.F. Brockmyre and M. Cusak. 1949. A ten-year study of butyl alcohol exposure. Am. Ind. Hyg. Assoc. 10(3): 53-59.
OREF - U.S. EPA. 1986. Butanol: Rat oral subchronic toxicity study. Office of Solid Waste, Washington, DC.
IREF - None

CREF - Bloom, S.E. 1982. 6. Detection of sister chromatid exchanges in vivo using avian embryos. In: Cytogen. Assays Environ. Mutagens. p. 137-159.
CREF - Connor, T.H., J.C. Theiss, H.A. Hanna et al. 1985. Genotoxicity of organic chemicals frequently found in the air of mobile homes. Toxicol. Lett. 25(1): 33-40.
REF - Lasne, C., Z.W. Gu, W. Venegas and I. Chouroulinkov. 1984. The in vitro micronucleus assay for detection of cytogenetic effects induced by mutagen- carcinogens: Comparison with the in vitro sister-chromatid exchange assay. Mutat. Res. 130(4): 273-282.
CREF - McCann, J., E. Choi, E. Yamasaki and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. USA. 72(12): 5135-5139.
CREF - Nakamura, S., Y. Oda, T. Shimada et al. 1987. SOS-inducing activity of chemical carcinogens and mutagens in Salmonella typhimurium TA1535/pSK1002: Examination with 151 chemicals. Mutat. Res. 192(4): 239-246.
CREF - Obe, G. and H. Ristow. 1977. Acetaldehyde, but not ethanol, induces sister chromatid exchanges in Chinese hamster cells in vitro. Mutat. Res. 56(2): 211-213.
CREF - Onfelt, A. 1987. Spindle disturbances in mammalian cells. III. Toxicity, c- mitosis and aneuploidy with 22 different compounds. Specific and unspecific mechanisms. Mutat. Res. 182(3): 135-154.
CREF - U.S. EPA. 1989. Health and Environmental Effects Document for 1-Butanol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.
CREF - Yoshiyama, Y., K. Nagai, H. Some and G. Tamura. 1973. Selective inhibition by pantoyl lactone and butyl alcohol of the initiation of DNA replication in E. coli. Agric. Biol. Chem. 37(6): 1317-1320.
"AREF- None

[IRIS] SS 4 /cf?
USER:

PRINT DL

1 - IRIS
IRSN - 213
DATE - 920122
STAT - Oral RfD Assessment (RDO) on-line 09/01/90
STAT - Inhalation RfC Assessment (RDI) pending 09/01/91
STAT - Carcinogenicity Assessment (CAR) no data
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 02/01/89 RDO Oral RfD summary noted as pending change
IRH - 09/01/90 RDO Price et al., 1984 corrected to Jones-Price et al., 84
IRH - 09/01/90 RCRA EPA contact changed
IRH - 09/01/90 REFS Bibliography on-line
IRH - 09/01/91 RDI Inhalation RfC now under review
IRH - 01/01/92 RDO Secondary contact changed
IRH - 01/01/92 EXSR Regulatory actions updated
RLEN - 12389
NAME - Carbon disulfide
RN - 75-15-0
SY - CARBON BISULFIDE
SY - CARBON BISULPHIDE
SY - Carbon Disulfide
SY - CARBON DISULPHIDE
SY - CARBONE (SUFURE DE)
SY - CARBONIO (SOLFURO DI)
SY - CARBON SULFIDE
SY - CARBON SULPHIDE
SY - DITHIOCARBONIC ANHYDRIDE
SY - KOHLENDISULFID (SCHWEFELKOHLENSTOFF)
SY - KOOLSTOFDISULFIDE (ZWAVELKOOLSTOF)
SY - NCI-C04591
SY - RCRA WASTE NUMBER P022
SY - SCHWEFELKOHLENSTOFF
SY - SOLFURO di CARBONIO
SY - SULPHOCARBONIC ANHYDRIDE
SY - UN 1131
SY - WEEVILTOX
SY - WEGLA DWUSIARCZEK
MF - CS2
USE - Carbon disulfide is used in the manufacture of soil disinfectants and vacuum tubes and is used as a solvent for cleaning and extractions, especially in metal treatment and plating. It is a fumigant for commodities, a corrosion inhibitor, and a polymerization inhibitor for vinyl chloride (SRI, 1983).
COFO - Mobile, clear, or faintly yellow liquid; reagent and commercial grades are foul-smelling. Pure distillates have sweet, pleasing ethereal odor (Merck, 1983)
ODOR - Mobile, clear, or faintly yellow liquid; reagent and commercial grades are foul-smelling. Pure distillates have sweet, pleasing ethereal odor (Merck, 1983)
BP - 116F, 46.5C (Merck, 1983)
MP - -167F, -110.8C (Weast, 1979)
MW - 76.13
DEN - 1.2632 at 20C/4C (Merck, 1983)
VAP - 360 at 25C (Sunshine, 1969)
VAPD - 2.67 (Merck, 1983)
EVAP - Not Found
SOLW - 0.294% at 20C (Merck, 1983)
FLPT - -22F, -30C (CC) (Merck, 1983, p. 251)
FLMT - Flammable Limits: LEL -- 1.3% (Merck, 1983); 1% (Sunshine, 1969) UEL -- 50% (Merck, 1983); 44% (Sunshine, 1969)

AVOI - Carbon disulfide decomposes on standing for a long time (Merck, 1983, p. 251). Avoid air, rust, halogens, metal azides, metals, oxidants; when exposed to heat or flame reacts violently with aluminum, chlorine, azides, hypochlorite, ethylamine diamine, ethylene imine, fluorine, metallic azides of lithium, potassium, cesium, rubidium, and sodium, nitrogen oxides, potassium, zinc and (sulfuric acid plus permanganate) (Sax, 1984, p. 641).

DCMP - When heated to decomposition, carbon disulfide emits highly toxic fumes of sulfur oxides and can react vigorously with oxidizing materials (Sax, 1984, p. 642).

RDO -

o ORAL RFD SUMMARY :

NOTE: The Oral RfD for carbon disulfide may change in the near future pending the outcome of a further review now being conducted by the Oral RfD Work Group.

Critical Effect	Experimental Doses*	UF	MF	RfD
Fetal toxicity/ malformations Rabbit Inhalation Teratogenic Study Hardin et al., 1981	NOEL: 20 ppm (62.3 mg/cu.m) converted to 11.0 mg/kg/day LOAEL: None	100	1	1E-1 mg/kg/day

*Conversion Factors: x 6 hour/24 hour x 1.6 cu.m/day breathing rate x 0.5 absorption rate / 1.13 kg bw

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o ORAL RFD STUDIES :

Hardin, B.D., G.P. Bond, M.R. Sikor, F.D. Andrew, R.P. Beliles and R.W. Niemeir. 1981. Testing of selected work place chemicals for teratogenic potential. Scand. J. Work Environ. Health. 7(Suppl. 4): 66-75.

The data reported in this study were generated at Litton Bionetics, Maryland (under contract to NIOSH). Rats and rabbits were exposed to 20 ppm or 62.3 mg/cu.m (recommended occupational exposure limit) and 40 ppm or 124.6 mg/cu.m of carbon disulfide (CS2) during the entire length of the pregnancy period and also 34 weeks before breeding to simulate occupational exposure.

Hardin et al. (1981) observed no effects on fetal development in rats or rabbits following inhalation exposure to 62.3 or 124.6 mg/cu.m, which corresponds to estimated equivalent oral dosages of 5 and 10 mg/kg for rats, and 11 and 22 mg/kg for rabbits. The highest NOEL from this study, 22 mg/kg for the rabbit, should not be used for an RfD estimate because adverse effects were seen in rabbit fetuses following oral exposure of pregnant does to 25 mg/kg (Jones-Price et al., 1984a,b). Therefore, the highest NOAEL that is below an effect level is the estimated low dose from the Hardin et al. (1981) inhalation study using rabbits. This dose level, 11 mg/kg, is the most appropriate basis for RfD derivation.

A NCTR-NTP oral study (Jones-Price et al., 1984a,b) observed 25 mg/kg/day in rabbits as an FEL (fetal resorption). Fetotoxicity band fetal malformations in this study were not observed in rats at the lowest level (100

mg/kg/day) of CS2 exposure. The data from this study also suggest that the rabbit fetus is more sensitive than the rat fetus to CS2-induced toxicity. Johnson et al. (1983) reported an epidemiologic study that employed a wide range of exposure with CS2, such as 0.04-5 ppm (mean: 1.2 ppm, low, exposure), 0.04-33.9 ppm (mean: 5.1 ppm, medium exposure) and 0.04-216 ppm (mn: 12.6 ppm, high exposure). In this study the entire population was exposed to a combined exposure of 7.3 ppm over a period of 12 or more years. Of the several clinical findings, the exposed population showed significant alterations in sensory conduction velocity and peroneal motor conduction velocity. However, the data indicated, in the opinion of the authors, that minimal neurotoxicity w evident, since the reduction in nerve conduction velocity was still within a range of clinically normal values and thus not associated with specific health consequences. Additionally, the exposed population had blood lead levels <40 mg/dL and the exposed air alone contained

H2S, H2SO4 and tin oxide. Therefore the 7.3 ppm CS2 can be considered as a NOAEL for neurotoxicity. This dose, when extrapolated to an oral dose of 10 mg/kg/day, lends support to the animal NOAEL of 11 mg/kg/day.

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o ORAL RFD UNCERTAINTY :

UF = 100. The uncertainty factor of 100 includes 10 for interspecies and 10 for intraspecies variability to the toxicity of this chemical in lieu of specific data.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

A Bulgarian study (Tabatcova et al., 1983) reported significant fetal malformations in rats exposed to a low CS2 dose of 0.03 mg/cu.m over three generations. Based on these data, an RfD can be drastically lower than the RfDs that could be derived from existing guidelines, epidemlogic data or other experimental data. However, the Bulgarian study did not present information on mode control exposure, animal diet, procedure for selection of F1 and F2 breeding pairs and purity of CS2 (hydrogen sulfide, a teratogenic compound, is often found as a contaminant). In a multigeneration study, toxic

effects of a compound can be confounded by the above factors.

---

o ORAL RFD CONFIDENCE :

Study: Medium
Data Base: Medium
RfD: Medium

The principal study was a well-designed multispecies study that provided adequate toxicologic endpoints; a medium confidence is assigned. The data base contains supportive reproductive and epidemiologic studies; therefore, a medium confidence is assigned. The RfD was supported by adequate oral reproductive and epidemiologic studies; however, additional oral chronic toxicity and reproductive studies are needed to support a higher than medium confidence level.

---

o ORAL RFD SOURCE DOCUMENT :

U.S. EPA. 1986. Health and Environmental Effects Profile on Carbon Disulfide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of

Solid Waste, Washington, DC.

ECAO-Cincinnati-Internal Review, 1986.

Extensive Agency wide review, 1986.

-

o REVIEW DATES : 06/24/85, 07/08/85, 07/22/85, 08/05/85
o VERIFICATION DATE : 08/05/85
o EPA CONTACTS :

Harlal Choudhury / ORD -- (513)569-7534 / FTS 684-7534

Robert Bruce / ORD -- (513)569-7553 / FTS 684-7553

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-

RDI -
o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

-

-

ACUTE-
o ACUTE TOXICITY :

Carbon disulfide affects the central nervous system, cardiovascular system, eyes, kidneys, liver, and skin. It may be absorbed through the skin as a vapor or liquid, inhaled, or ingested. The probable oral lethal dose for a human is between 0.5 and 5 g/kg or between 1 ounce and 1 pint (or 1 pound) for a 70-kg (150-lb.) person (Gosselin et al., 1976). Lowest lethal dose for humans has been reported at 14 mg/kg or 0.98 g for a 70-kg person (NIOSH/RTECS, 1985).

-

o SIGNS AND SYMPTOMS :

In acute poisoning, early excitation of the central nervous system occurs, followed by depression with stupor, restlessness, and unconsciousness. If recovery occurs, the patient usually passes through the after-stage of narcosis, with nausea, vomiting, headache, etc. (Sax, 1984 p. 642). Also possible are motor disturbances of the bowel, anemia, disturbances of cardiac rhythm, loss of weight, polyuria, and menstrual disorders.

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-
WQCHU-

No data available

-

-
WQCAQ-

Freshwater:

Acute -- none
Chronic -- 2.0E+0 ug/L (undissociated H25)

Marine:

Acute -- none
Chronic -- 2.0E+0 ug/L (undissociated H25)

Considers technological or economic feasibility? -- NO

Discussion -- Criteria were derived from a minimum data base consisting of acute and chronic tests on a variety of species. Requirements and methods are covered in the reference to the federal register.

Reference -- Quality Criteria for Water, EPA 440/9-76--023 (7/76), PB-263943

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

-

-
CERC -

Value (status) -- 100 pounds (Final, 1986)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on chronic toxicity. RQ assignments based on chronic toxicity reflect two primary attributes of the hazardous substance, the minimum effective dose (MED) levels for chronic exposure (mg/day for 70-kg person) and the type of effect (liver necrosis, teratogenicity, etc). A composite score is determined from an evaluation of these two attributes. Carbon disulfide was determined to have a composite score between 21 and 40, corresponding to a chronic toxicity RQ of 100 pounds.

Reference -- 51 FR 34534 (09/29/86); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

-

-
RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles and R.W. Niemeir. 1981. Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health. 7(Suppl. 4): 66-75.
OREF - Johnson, B.L., J. Boyd, J.R. Burg, S.T. Lee, C. Xintaras and B.E. Albright. 1983. Effects on the peripheral nervous system of workers' exposure to carbon disulfide. Neurotoxicology. 4(1): 53-66.
OREF - Jones-Price, C., R.W. Tyl, M.C. Marr and C.A. Kimmel. 1984a. Teratologic Evaluation of Carbon Disulfide (CAS No. 75-15-0) Administered to CD Rats on Gestational Days 6 through 15. National Center for Toxicological Research, Jefferson AR. Govt. Reports Announcements and Index, Issue 15. NTIS PB 84- 192343.
OREF - Jones-Price, C., R.W. Tyl, M.C. Marr and C.A. Kimmel. 1984b. Teratologic Evaluation of Carbon Disulfide (CAS No. 75-15-0) Administered to New Zealand White Rabbits on Gestational Days 6 through 15. National Center for Toxicological Research, Jefferson AR. Govt. Reports Announcements and Index, Issue 15. NTIS PB 84-192350.
OREF - Tabacova, S., B. Nikiforov and L. Balabaeva. 1983. Carbon disulphide intrauterine sensitization. J. Appl. Toxicol. 3(5): 223-229.
OREF - U.S. EPA. 1986. Health and Environmental Effects Profile on Carbon Disulfide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.
IREF - None
CREF - None
HAREF- None

[IRIS] SS 8 /cf?
USER:
STOP

DONE? (YES/NO)

USER:
YES

TIME 1:16:49 NLM TIME 16:41:07
...

```
GOOD-BYE!
THE ESTIMATED TOTAL COST FOR THIS 76 MINUTE TERMINAL SESSION IS $ 58.17.

*** END OF SESSION ***

TOXNET: call cleared (c  0,d  0): dte originated

please log in:
```

1 - IRIS
NAME - Carbon tetrachloride
RN - 56-23-5
IRSN - 19
DATE - 921007
UPDT - 10/07/92, 6 fields
STAT - Oral RfD Assessment (RDO) on-line 06/01/91
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 06/01/91
STAT - Drinking Water Health Advisories (DWHA) on-line 08/01/90
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 04/01/92
IRH - 03/01/88 RDO Dose conversion clarified
IRH - 03/01/88 RDO Principal study corrected
IRH - 03/01/88 RDO Text added
IRH - 03/01/88 RDO Text revised
IRH - 03/01/88 RDO Verification and meeting dates changed
IRH - 03/01/88 CAREV Text corrected
IRH - 03/01/88 CARO Confidence statement revised
IRH - 03/01/88 CARI Confidence statement revised
IRH - 03/01/88 HADV Health Advisory added
IRH - 06/30/88 RDO Primary contact changed
IRH - 12/01/89 RDO Corrected citation year for Condie et al.
IRH - 12/01/89 REFS Bibliography on-line
IRH - 06/01/90 CAA Area code for EPA contact corrected
IRH - 06/01/90 RCRA EPA contact changed
IRH - 08/01/90 HATEN Uncertainty factor text corrected
IRH - 08/01/90 HADR Primary contact changed
IRH - 01/01/91 CAR Text edited
IRH - 01/01/91 CARI Inhalation slope factor removed (global change)
IRH - 03/01/91 RDO Primary contact changed
IRH - 06/01/91 RDO Text edited
IRH - 06/01/91 CAR Text edited
IRH - 06/01/91 MCLG EPA contact changed
IRH - 06/01/91 MCL EPA contact changed
IRH - 08/01/91 CREF Blair et al., 1979 and Milham, 1976 references added
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 04/01/92 CAA CAA regulatory action withdrawn
IRH - 10/01/92 CREF Missing reference added
RLEN - 28123
SY - Acritet
SY - Benzinoform
SY - Carbona
SY - Carbon chloride
SY - Carbon tet
SY - Carbon tetrachloride
SY - Carbo tetrachloride
SY - Czterochlorek wegla
SY - ENT 4,705
SY - Fasciolin
SY - Flukoids
SY - Freon 10
SY - Halon 104
SY - Mecatorina
SY - Methane tetrachloride
SY - Methane, tetrachloro-
SY - Necatorina
SY - Necatorine
SY - Perchloromethane
SY - R 10
SY - Tetrachloorkoolstof
SY - Tetrachloormetaan
SY - Tetrachlorkohlenstoff, tetra
SY - Tetrachlormethan
SY - Tetrachlorocarbon

SY - Tetrachloromethane
SY - Tetrachlorure de carbone
SY - Tetrachorkohlenstoff uvasol
SY - Tetraclorometano
SY - Tetracloruro di carbonio
SY - Tetrafinol
SY - Tetraform
SY - Tetrasol
SY - Univerm
SY - Ventox
SY - Vermoestricid
SY - WLN: GXGGG.
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA
VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver lesions Subchronic Rat Gavage Study Bruckner et al., 1986	NOAEL: 1 mg/kg/day (converted to 0.71 mg/kg/day) LOAEL: 10 mg/kg/day (converted to 7.1 mg/kg/day)	1000	1	7E-4 mg/kg/day

*Conversion Factors: 1 mg/kg/day (NOAEL) x 5/7 = 0.71 mg/kg/day (5 day/week dosing regimen)

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o ORAL RFD STUDIES :

Bruckner, J.V., W.F. MacKenzie, S. Muralidhara, R. Luthra, G.M. Kyle and D. Acosta. 1986. Oral toxicity of carbon tetrachloride: Acute, subacute and subchronic studies in rats. Fund. Appl. Toxicol. 6(1): 16-34.

Male Sprague-Dawley rats were given 1, 10, or 33 mg carbon tetrachloride/kg/day by corn oil gavage, 5 days/week for 12 weeks. Liver lesions, as evidenced by mild centrilobular vacuolization and statistically significant increases in serum sorbitol dehydrogenase activity, were observed at the 10 and 33 mg/kg/day dosesm in a dose-related manner. Therefore, the LOAEL was established at 10 mg/kg/day (converted to 7.1 mg/kg/day) and the NOAEL was 1 mg/kg/day (converted to 0.71 mg/kg/day).

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o ORAL RFD UNCERTAINTY :

UF -- UF allows for interspecies and intrahuman variability and extrapolation from subchronic to chronic duration of exposure.

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o ORAL RFD MODIFYING FACTOR :

MF = None

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o ORAL RFD COMMENTS :

A 1983 draft of the Bruckner et al. (1986) study was used as the basis for the RfD by the RfD Work Group at a 05/20/85 verification meeting. When this study was subsequently published (Bruckner et al., 1986), no change to the verified value was required.

Subchronic studies in mice gavaged with carbon tetrachloride in corn oil (Condie et al., 1986; Hayes et al., 1985) support the critical effect and the magnitude of the NOAEL and LOAEL found in the rat studies. Additional studies (Alumot et al., 1976; NCI, 1976) in rats lend moderate support to the choice of a NOAEL in the chosen rat study.

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o ORAL RFD CONFIDENCE :

Study -- High
Data Base -- Medium
RfD -- Medium

The principal study was well conducted and good dose-response was observed in the liver, which is the target organ for carbon tetrachloride toxicity; thus, high confidence was assigned. Four additional subchronic studies support the RfD, but reproductive and teratology endpoints are not well investigated; thus, the data base rates a medium confidence. Medium confidence in the RfD follows.

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o ORAL RFD SOURCE DOCUMENT :

U.S. EPA. 1985. Drinking Water Criteria Document for Carbon Tetrachloride. Office of Drinking Water, Washington, DC.

Public review of RfD following ODW proposal of RMCL in June 1984.

Science Advisory Board review of RfD on January 14, 1986.

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o REVIEW DATES : 05/20/85
o VERIFICATION DATE : 05/20/85
o EPA CONTACTS :

Krishan Khanna / OST -- (202)260-7588

Michael L. Dourson / OST -- (513)569-7544

RDI - NO DATA
CAREV-
o CLASSIFICATION : B2; probable human carcinogen
o BASIS FOR CLASSIFICATION : Carcinogenicity in rats, mice, and hamsters
o HUMAN CARCINOGENICITY DATA :

Inadequate. There have been three case reports of liver tumors developing after carbon tetrachloride exposure. Several studies of workers (Milham, 1976; Blair et al., 1979) who may have used carbon tetrachloride have suggested that these workers may have an excess risk of cancer.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. Carbon tetrachloride has produced hepatocellular carcinomas in rats, mice, and hamsters, the species evaluated to date.

Hepatocellular carcinomas developed in Osborne-Mendel, Japanese, and Wistar rats, but not Sprague-Dawley or Black rats, following s.c. injection of carbon tetrachloride. Hyperplastic nodules were noted in Buffalo rats treated s.c. (Reuber and Glover, 1967a,b, 1970). Sensitivity varied among strains, and trends in incidence appeared inversely related to severity of cirrhosis.

Fifty Osborne-Mendel rats/sex were administered carbon tetrachloride by corn oil gavage at 47 and 94 mg/kg/injection for males and 80 and 159 mg/kg for females 5 times/week for 78 weeks. At 110 weeks, only 7/50 high-dose males and 14/50 high-dose females survived; 14/50 low-dose males and 20/50 low-dose females survived. The incidence of hepatocellular carcinomas was increased in animals exposed to carbon tetrachloride as compared with pooled colony controls. The apparent decrease in the incidence of hepatocellular carcinomas in high-dose female rats compared with the low-dose females (1/14 vs. 4/20, respectively) was attributed by the authors to increased lethality before tumors could be expressed (NCI, 1976a,b, 1977).

In this same study, using the same dosing schedule, male and female B6C3F1 mice received 1250 or 2500 mg/kg carbon tetrachloride. The incidences of hepatocellular carcinomas in males were 5/77, 49/49, and 47/48 in the control, low- and high-dose groups, respectively, and 1/80, 40/40, and 43/45 in the control, low- and high-dose groups, respectively.

Carbon tetrachloride administered by gavage has also been shown to produce neoplastic changes in livers of five additional strains of mice (C3H, A, Y, C, and L) (Andervont, 1958; Edwards, 1941; Eschenbrenner and Miller 1943; Edwards and Dalton, 1942; Edwards et al., 1942). In the last study, 56 male and 19 female L mice, which have a low incidence of spontaneous hepatomas, were treated with 0.1 mL of 40% carbon tetrachloride 2 or 3 times/week over 4 months, for a total of 46 treatments. Animals were killed 3 to 3.5 months after the last treatment. The combined hepatoma incidence of treated male mice was 47% (7/15 vs. 2/71 in the untreated male controls); treated females showed and incidence of 38% (3/8 vs. 0/81 in the untreated female controls).

As part of a larger study of liver carcinogens, Della Porta et al. (1961) treated Syrian golden hamsters (10/sex/dose) with carbon tetrachloride by gavage, weekly for 30 weeks. For the first 7 weeks, 0.25 mL of 0.05% carbon tetrachloride in corn oil was administered; this dose was halved for the remainder of the exposure period. All animals were observed for an additional 25 weeks. All of the 10 hamsters that were killed or dying between weeks 43 and 55 had liver cell carcinomas, compared with 0 in controls.

---

o SUPPORTING DATA :

Carbon tetrachloride was not mutagenic to either S. typhimurium or E. coli (McCann et al., 1975; Simmon et al., 1977; Uehleke et al., 1976). At low concentrations, carbon tetrachloride did not produce chromatid or chromosomal aberrations in an epithelial cell line derived from rat liver (Dean and Hodson-Walker, 1979). In vivo unscheduled DNA synthesis assays have likewise been negative in male Fischer 344 rats (Mirsalis and Butterworth, 1980; Mirsalis et al., 1982). Carbon tetrachloride produced mitotic recombination and gene conversion in S. cerevisiae, but only at concentrations which reduced viability to 10% (Callen et al., 1980). Carbon tetrachloride may be metabolized to reactive intermediates capable of binding to cellular nucleophilic macromolecules. Negative responses in bacterial mutagenicity assays may have been due to inadequate metabolic activation in the test systems.

CARO -
o CLASSIFICATION : B2; probable human carcinogen
o BASIS FOR CLASSIFICATION : Carcinogenicity in rats, mice, and hamsters
o ORAL SLOPE FACTOR : 1.3E-1 per (mg/kg)/day
o DRINKING WATER UNIT RISK : 3.7E-6 per (ug/L)
o DOSE EXTRAPOLATION METHOD : Linearized multistage procedure, extra risk
o RISK/WATER CONCENTRATIONS :

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	3E+1 ug/L
E-5 (1 in 100,000)	3E+0 ug/L
E-6 (1 in 1,000,000)	3E-1 ug/L

o ORAL DOSE-RESPONSE DATA :

Tumor Type -- Hepatocellular carcinomas/hepatomas
Test Animals -- various, see table
Route -- gavage
Reference -- several, see table

Administered Dose (mg/day)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence	Unit Risk per (ug/L)	Reference
Hamster/Syrian, male and female				
0	0	0/80	3.4E-5	Della Porta et al., 1961
0.95	1.02	10/19		
Mouse/L, male and female				
0	0	2/152	9.4E-6	Edwards et al., 1942
15	2.3	34/73		
Mouse/B6C3F1, male and female				
0	0	6/157	1.8E-6	NCI, 1976a,b, 1977
21	55.4	89/89		
42	110.8	90/93		
Rat/Osborne-Mendel:				
M, F 0	0	0/37	3.1E-7	NCI, 1976a,b, 1977
M 11	4.5	2/45		
F 18	7.4	4/46		
M 21	8.7	2/47		
F 36	14.9	1/30		

o ADDITIONAL COMMENTS :

A geometric mean was calculated from the unit risks derived from the four data sets above. Della Porta et al. (1961) did not report controls in this study, but did give incidence rate for vehicle controls in an earlier study. Animal doses are TWA.

The unit risk should not be used if the water concentration exceeds 3E+3 ug/L, since above this concentration the unit risk may not be appropriate.

o DISCUSSION OF CONFIDENCE :

The studies used were all deficient in some respect, precluding the choice of any one study as most appropriate. For all studies, data from males and females were combined because of the small sample sizes. In the first and second studies (Della Porta et al., 1961; Edwards et al., 1942) one dose was tested. Della Porta et al. (1961) did not report concurrent control

incidence. In the NCI (1976a,b) studies, tumor incidence in the mice was virtually 100%, and goodness-of-fit criteria were not satisfied for the multistage model. Tumor incidence in rats in these studies was higher at low doses, presumably because early mortality at higher doses precluded tumor formation. The studies lacked pharmacokinetic data. However, a common biological mechanism, cell death and regeneration, leading to development of the same tumor type, was suggested by observations in all the studies. Since the risk estimates from these data (across 3-4 species and strains) only vary by 2 orders of magnitude, a geometric mean was derived as the risk estimate to accommodate the several study deficiencies.

CARI -
o CLASSIFICATION : B2; probable human carcinogen
o BASIS FOR CLASSIFICATION : Carcinogenicity in rats, mice, and hamsters
o INHALATION UNIT RISK : 1.5E-5 per (ug/cu.m)
o DOSE EXTRAPOLATION METHOD : Linearized multistage procedure, extra risk
o RISK/AIR CONCENTRATIONS :

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	7E+0 ug/cu.m
E-5 (1 in 100,000)	7E-1 ug/cu.m
E-6 (1 in 1,000,000)	7E-2 ug/cu.m

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o INHALATION DOSE-RESPONSE DATA :

The inhalation risk estimates were calculated from the oral exposure data in CARO.

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o ADDITIONAL COMMENTS :

Inhalation risk was calculated assuming an air intake of 20 cu.m/day and 40% absorption rate by humans (U.S. EPA, 1984). This absorption coefficient was based on 30% inhalation in monkeys, and 30% and 57-65% inhalation in humans. A range of estimates of unit risk for inhalation exposures for the four studies cited above was determined, with 1.5E-5 per (ug/cu.m) calculated as the geometric mean for the unit risk.

The unit risk should not be used if the air concentration exceeds 7E+2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

See CARO.

CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1984. Health Assessment Document for Carbon Tetrachloride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8/82-001F.

The 1984 Health Assessment Document for Carbon Tetrachloride received

Agency and external review.
DOCUMENT

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o REVIEW DATES : 11/12/86, 12/04/86
o VERIFICATION DATE : 12/04/86
o EPA CONTACTS :

Jean C. Parker / OHEA -- (202)260-5898

Arthur Chiu / OHEA -- (202)260-5898

HAONE-

One-day HA -- 4E+0 mg/L

NOAEL -- 40 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Bruckner et al., 1986

Rats were administered single oral doses of carbon tetrachloride. Doses of 80 mg/kg and higher caused changes in liver enzymes (BUN, GPT, SDH, OCT) and histopathologic liver and kidney changes. A dose of 40 mg/kg produced no effects and is identified as the NOAEL.

HATEN-

Ten-day HA -- 1.6E-1 mg/L

LOAEL -- 16 mg/kg/day
UF -- 1000 (allows for interspecies and intrahuman variability with the use of a LOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Bruckner et al., 1986

Rats were administered nine doses of carbon tetrachloride by gavage over an 11-day period. The lowest dose tested (20 mg/kg/day) produced significant changes in serum enzyme levels and hepatic midzonal vacuolation. Higher doses caused more extensive liver damage. A LOAEL of 16 mg/kg/day is established after adjustment for the treatment schedule.

HALTC-

LONGER-TERM HEALTH ADVISORY FOR A CHILD

Longer-term (Child) HA -- 7.1E-2 mg/L

NOAEL -- 0.71 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Bruckner et al., 1986

Rats were administered carbon tetrachloride by gavage, 5 times weekly for 12 weeks, at doses of 1, 10, or 33 mg/kg/day. Doses of 10 and 33 mg/kg/day

were hepatotoxic (changes in serum enzyme levels, centrilobular vacuolation, and necrosis). The NOAEL of 1 mg/kg/day, based on a 7 days/week dosing regimen, is equivalent to 0.71 mg/kg/day.

HALTA-

Longer-term (Adult) HA -- 2.5E-1 mg/L

NOAEL -- 0.71 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 2 L/day water consumption for a 70-kg adult

Principal Study -- Bruckner et al., 1986

This study is the same as that for the longer-term (child) HA.

HALIF-

Drinking Water Equivalent Level (DWEL) -- 2.5E-2 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date -- 07/08/85 (see Section I.A. in this file)

Lifetime HA -- None.

Principal Study (DWEL) -- Bruckner et al., 1986

This study was used in the derivation of the oral chronic RfD; see the RfD Section for a description. Carbon tetrachloride is considered to be a probable human carcinogen. Refer to the carcinogenicity assessment section for information on the carcinogenicity of this substance.

OLEP -

Odor perception threshold -- 0.52 mg/L.

ALAB -

Analysis of carbon tetrachloride is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water. Confirmatory analysis is by mass spectrometry.

TREAT-

Treatment techniques which will remove carbon tetrachloride from drinking water include granular activated carbon adsorption, boiling, and air stripping. Conventional treatment processes (coagulation, sedimentation, filtration), even when augmented by the addition of powdered activated carbon, provide little removal of carbon tetrachloride.

HADR -
o HEALTH ADVISORY SOURCE :

Bruckner, J.V., W.F. MacKenzie, S. Muralidhara, R. Luthra, G.M. Kyle and D. Acosta. 1986. Oral toxicity of carbon tetrachloride: Acute, subacute and subchronic studies in rats. Fund. Appl. Toxicol. 6(1): 16-34.

DOCUMENT

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o HEALTH ADVISORY REVIEW :

U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Carbon Tetrachloride. Office of Drinking Water, Washington, DC.

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

---

o EPA DRINKING WATER CONTACT :

Jennifer Orme / OST -- (202)260-7586

Edward V. Ohanian / OST -- (202)260-7571

ACUTE- NO DATA
BCF - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption: 4.0E-1 ug/L

Fish Consumption Only: 6.94E+0 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For maximum protection from the potential carcinogenic properties of this chemical, the ambient concentration should be zero. However, zero may not be attainable at this time so the recommended criteria represents a E-6 estimated incremental increase in cancer risk over a lifetime.

Reference -- 45 FR 791318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute LEC -- 3.52E+4 ug/L
Chronic -- None

Marine:

Acute LEC -- 5.0E+4 ug/L
Chronic -- None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the

minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 791318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 0 mg/L (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0 mg/L for carbon tetrachloride is proposed based on carcinogenic effects. Carbon tetrachloride has been shown to be carcinogenic in rats, mice, and hamsters through oral exposure. Hepatocellular carcinomas in several studies have been observed. EPA has classified carbon tetrachloride in Group B2: sufficient evidence in animals and inadequate evidence in humans.

Reference -- 50 FR 46880 (11/13/85)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value (status) -- 0.005 mg/L (Final, 1987)

Considers technological or economic feasibility? -- YES

Discussion -- EPA has set an MCL based on detection limits.

Monitoring requirements -- All systems to be monitored for four consecutive quarters; repeat monitoring dependent upon detection and vulnerability status and system size.

Analytical methodology -- Gas chromatography (EPA 502.1, 502.2, 503.1); gas chromatographic/mass spectrometry (EPA 524.1, 524.2).

Best available technology -- Packed tower aeration; granular activated carbon.

Reference -- 52 FR 25690 (07/08/87); 56 FR 30266 (07/01/91)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD-

No data available

FIREV-

Action -- Voluntary cancellation (1986)

Considers technological or economic feasibility? -- No

Summary of regulatory action -- Voluntary cancellations were made in 1985 also. For specific details on the Special Review process for this active ingredient please call the EPA Contact.

Reference -- 50 FR 42997 (10/23/85); 54 FR 41004 (11/12/86); 52 FR 38200 (10/14/87) Proposed exemption revocation; 54 FR 6126 (02/08/89) Tolerance exemption on grains

EPA Contact -- Special Review Branch / OPP -- (703)557-7400 / FTS 557-7400

CERC -

Value (status) --10 pounds (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for carbon tetrachloride is based on potential carcinogenicity. Available data indicate a hazard ranking of medium based upon a potency factor of 59.9 mg/kg/day and assignment to weight-of-evidence group B2. This corresponds to an RQ of 10 pounds.

Reference -- 52 FR 8140 (03/16//87); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

___IV.E.1. TSCA, SECTION 6

Status -- Advance Notice of Proposed Rulemaking (ANPR) (1985)

Discussion -- EPA is developing a comprehensive and integrated strategy for a regulatory investigation of six solvents, including carbon tetrachloride.

Reference: 50 FR 42005 (10/17/85); 40 CFR 754

EPA Contact -- Chemical Control Division / OTS (202)260-3749 / FTS 260-3749

OREF - Alumot E., E. Nachtomi, E. Mandel and P. Holstein. 1976. Tolerance and acceptable daily intake of chlorinated fumigants in the rat diet. Food Cosmet. Toxicol. 14: 105-110.

OREF - Bruckner, J.V., S. Muralidhara, R. Luthra, G.M. Kyle, W.F. MacKenzie and D. Acosta. 1983. Oral toxicity of carbon tetrachloride: Acute, subacute and subchronic studies in rats. University of Georgia, Athens, GA. (Draft)

OREF - Bruckner, J.V., W.F. MacKenzie, S. Muralidhara, R. Luthra, G.M. Kyle and D. Acosta. 1986. Oral toxicity of carbon tetrachloride: Acute, subacute and subchronic studies in rats. Fund. Appl. Toxicol. 6(1): 16-34.

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1 - IRIS
IRSN - 443
DATE - 940105
UPDT - 01/05/94, 1 field
STAT - Oral RfD Assessment (RDO) pending 01/01/94
STAT - Inhalation RfC Assessment (RDI) on-line 11/01/90
STAT - Carcinogenicity Assessment (CAR) pending 05/01/93
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 11/01/90 RDI Inhalation RfC summary on-line
IRH - 11/01/90 REFS Bibliography on-line
IRH - 01/01/92 EXSR Regulatory Action section on-line
IRH - 09/01/92 RDO Oral RfD now under review
IRH - 05/01/93 RDO Work group review date added
IRH - 05/01/93 CAR Carcinogenicity assessment now under review
IRH - 12/01/93 RDO Work group review date added
IRH - 01/01/94 RDO Work group review date added
RLEN - 23167

NAME - Chlorine dioxide
RN - 10049-04-4
SY - Chlorine oxide
SY - Alcide
SY - Anthium Dioxcide
SY - Caswell No. 179A
SY - Chlorine dioxide
SY - Chlorine peroxide
SY - CHLORINE(IV) OXIDE
SY - Chloroperoxyl
SY - CHLORYL RADICAL
SY - Dioxido de cloro [Spanish]
SY - Dioxyde de chlore [French]
SY - Doxcide 50
SY - EPA Pesticide Chemical Code 020503
SY - HSDB 517

RDO -
o ORAL RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work
group.

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o REVIEW DATES : 08/12/92, 03/31/93, 10/14/93, 12/15/93

RDI -
o INHALATION RFD SUMMARY :

Critical Effect	Exposures*	UF	MF	RfC
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Vascular congestion and peribronchiolar edema 60-Day Rat Inhalation Study Paulet and Desbrousses, 1972	NOAEL: None LOAEL: 2.76 mg/cu.m (1 ppm) LOAEL(ADJ): 0.41 mg/cu.m LOAEL(HEC): 0.64 mg/cu.m	3000 1 2E-4 mg/cu.m
Hemorrhagic alveoli and congested capillaries in the lungs 45-Day Rabbit Inhalation Study Paulet and Desbrousses, 1970	NOAEL: None LOAEL: 6.9 mg/cu.m (2.5 ppm) LOAEL(ADJ): 0.82 mg/cu.m LOAEL(HEC): 0.49 mg/cu.m	

*Conversion Factors: MW=67.46.
Paulet and Desbrousses, 1972: Assuming 25C and 760 mmHg, LOAEL (mg/cu.m) =
1.0 ppm x 67.46 / 24.45 = 2.76. LOAEL(ADJ) = 2.76 mg/cu.m x 5 hours/day x 5
days/week = 0.41. The LOAEL(HEC) was calculated for a gas:respiratory effect
in the THoracic region. MVa = 0.17 cu.m, MVh = 20 cu.m, Sa(TH) = 3461.6
sq.cm, Sh(TH) = 640581 sq.cm. RGDR(TH) = (MVa/Sa) / (MVh/Sh) = 1.57.
LOAEL(HEC) = LOAEL(ADJ) x RGDR = 0.64 mg/cu.m.

Paulet and Desbrousses, 1970: Assuming 25C and 760 mmHg, LOAEL(mg/cu.m) = 2.5
ppm x 67.46 / 24.45 = 6.9. LOAEL(ADJ) = 6.9 mg/cu.m x 4 hours/day x 5
days/week = 0.82. The LOAEL(HEC) was calculated for a gas:respiratory effect
in the THoracic region. MVa = 1.10 cu.m, Sa(TH) = 59,100 sq.cm. RGDR(TH) =
(MVa/Sa) / (MVh/Sh) = 0.596. LOAEL(HEC) = 0.49 mg/cu.m.

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o INHALATION RFD STUDIES :

Paulet, G. and S. Desbrousses. 1972. Toxicology of chlorine dioxide. Arch. Mal. Prof. Med. Trav. Secur. Soc. 33(1-2): 59-61.

Paulet, G. and S. Desbrousses. 1970. Effect of a weak concentration of chlorine dioxide on laboratory animals. Arch. Mal. Prof. Med. Trav. Secur. Soc. 31(3): 97-106.

The studies by Paulet and Desbrousses (1970, 1972) are selected as co-critical because they identify a LOAEL for respiratory effects. The 1972 study is 60 days long but uses only one exposure concentration. The 1970 study uses several exposure concentrations and exposures of 30 and 45 days. Since these durations are shorter than the typical subchronic duration, they are used as co-critical to provide additional support.

In a study aimed at establishing a threshold for the respiratory effects observed in their 1970 study, Paulet and Desbrousses (1972) exposed eight Wistar rats (sex not specified) to 1 ppm chlorine dioxide (2.76 mg/cu.m) 5 hours/day, 5 days/week (duration-adjusted concentration = 0.41 mg/cu.m) for 2 months. The number of controls was not specified). Body weight and blood counts were measured, and histopathological examination of the lungs and liver was conducted at study termination. The animals appeared normal throughout the experiment. The authors state that weight gain, RBC and WBC counts were not affected, but concurrent control data are not presented. Microscopic evaluation of the lungs revealed vascular congestion and peribronchiolar edema in all animals examined without alteration of the epithelium or parenchyma. This report identifies a LOAEL for respiratory effects in rats of 1 ppm (HEC = 0.64 mg/cu.m).

Rabbits and rats (strains not specified) were exposed to chlorine dioxide under four different regimens: in the first, 5 rats/sex were exposed to 10 ppm chlorine dioxide 2 hours/day for 30 days; in the second, 10

rats/sex and
4 rabbits were exposed to 5 ppm chlorine dioxide 2 hours/day for 30 days;
third, 10 rats/sex were exposed to 2.5 ppm chlorine dioxide 7 hours/day for
30 days; and fourth, 8 rabbits were exposed to 2.5 ppm chlorine dioxide 4
hours/day for 45 days. In each experiment, an equal number of animals exposed
to room air served as controls. The animals were presumably exposed 5
days/week, although this was not explicitly stated. Duration-adjusted
exposure concentrations were 1.6 mg/cu.m, 0.82 mg/cu.m, 1.4 mg/cu.m, and 0.82
mg/cu.m for groups 1, 2, 3 and 4, respectively. Body weight, blood cell
counts, and histopathological examination of the liver and lungs and other
tissues were conducted for each group. The most prominent effects observed at
10 ppm were clinical signs of respiratory irritation (nasal discharge) and
localized bronchopneumonia, with desquamation of the alveolar epithelium.
Both white and red blood cell counts were significantly increased. The
observed effects were similar in regimen 2 (5 ppm) for both the rats and the
rabbits (that is, clinical signs of respiratory irritation, with focal
bronchopneumonia and localized broncho-alveolar lesions), but much less severe
than those observed for regimen 1. No changes in weight gain or blood cell
counts were found. Regimens 3 and 4 (2.5 ppm) produced lymphocytic
infiltration of the alveolar spaces, alveolar vascular congestion, hemorrhagic
alveoli, and epithelial erosions and inflammatory infiltrations of the bronchi
in the rats; and hemorrhagic alveoli and congested capillaries in the lungs of
the rabbits. In rats, weight gain was stated to be "slightly slowed" (data
not presented), RBC counts were 85% of control, and WBC counts were 116% of
control (no statistical tests presented). In rabbits, there was no exposure-
related effect on weight gain, RBC counts were 80% of control, and WBC counts
were 116% of control (no statistical tests presented, authors state that cell
counts "changed very little"). In this experiment, another

groups of rats and rabbits were sacrificed 10 days after the termination of chlorine dioxide exposure, and recovery from the pulmonary lesions was evident. These results indicate that subchronic exposure to chlorine dioxide results in respiratory irritation and bronchiolar and alveolar lesions, the severity of which increases with concentration. The liver was not adversely affected at any tested concentration. This study identifies a LOAEL for thoracic respiratory effects in rabbits (assuming male New Zealand strain) exposed to 2.5 ppm (HEC = 0.49 mg/cu.m) and in rats (assuming female Wistar rats) at 2.5 ppm (HEC = 2.26 mg/cu.m). A LOAEL for blood effects was also identified for rats and rabbits at 2.5 ppm (HEC = 1.4 mg/cu.m for rat and 0.82 mg/cu.m for rabbit using the calculation for an extrarespiratory effect of a gas with periodicity attained and the default value for b:a lambda(A)/lambda(H) = 1).

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o INHALATION RFD UNCERTAINTY :

UF -- An uncertainty factor of 10 is used for protection of sensitive human subpopulations, 3 for interspecies extrapolation, 10 for use of a subchronic study, and 10 for use of a LOAEL for a mild effect and to account for the lack of developmental and reproductive studies.

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o INHALATION RFD MODIFYING :

MF -- None
FACTOR

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o INHALATION RFD COMMENTS :

Paulet and Desbrousses (1974) studied the effects of "discontinuous" exposure of rats (10 to 15/study) to chlorine dioxide at different concentrations and different frequencies of exposure for 1 month. The rats

were exposed to 5, 10, and 15 ppm, for 15 minute periods, 2 or 4 times/day for 1 month. Each study also utilized appropriate controls that were exposed to room air. At 15 ppm chlorine dioxide one animal died, and the remaining animals exhibited nasal discharge, congested lungs, and catarrhous lesions of the alveoli with peribronchiolar infiltrations that were more pronounced in animals exposed 4 times/day. These lesions were reversible, and were no longer apparent in animals sacrificed 15 days after the termination of exposure. No changes were observed in the livers of the 15-ppm animals. At 10-ppm, no deaths occurred, nor were clinical signs of toxicity noted, but body weight gain was significantly reduced in these animals. Necropsy revealed signs of alveolar irritation at 10-ppm that was less pronounced than was seen at 15 ppm. Animals exposed to 5 ppm chlorine dioxide did not exhibit any clearly exposure-related changes in either clinical signs, body weight gain, hematological parameters, or gross pathology of the lungs.

Dalhamn (1957) conducted a series of experiments in rats (strain not specified) that investigated the effects of acute high-level as well as subchronic high- and low-level inhalation exposure to chlorine dioxide. In the first series of experiments, a total of three rats were exposed to 800, 1100, and 3400 ppm 3 minutes/week, once a week for 3 weeks. An additional three rats served as controls. Animal behavior was observed during the exposure. Respiratory distress and copious nasal and ocular discharge was evident in all exposed rats, and body weight gain was depressed in these animals over the 3-week period. Histological examination revealed small areas of recent bronchopneumonia and hyperemia of the renal corticomedullary junction in two of the exposed rats. In the second experiment, four rats were exposed to 260 ppm of chlorine dioxide for 2 hours. One animal died during exposure, and all exhibited ocular discharge and epitaxis. Pulmonary edema

and circulatory engorgement were noted at necropsy. In the third experiment, five rats were exposed to 10 ppm of chlorine dioxide (27.59 mg/cu.m) 4 hours/day for up to 14 days (duration-adjusted concentration = 4.6 assuming exposures 7 days/week) while five rats served as controls. All exposed rats died within the 14-day period and exhibited marked respiratory distress (rhinorrhea and "embarrassed respiration") and body weight gain reduction. Respiratory infection and acute renal and hepatic congestion were seen in the exposed animals at necropsy. In the final set of experiments, five rats were exposed to 0.1 ppm of chlorine dioxide (0.27 mg/cu.m) 5 hours/day for 10 weeks (duration-adjusted concentration = 0.046 mg/cu.m assuming exposures 7 days/week) and an additional five rats served as controls. No effects on animal behavior were observed and no histopathological changes in liver, kidney, or lung were noted in the exposed animals. Respiratory infection was observed in control rats in several of the groups in this study. This study identifies a FEL in rats of 10 ppm for a 14-day exposure (HEC = 7.22 mg/cu.m for respiratory effects in the thoracic region; HEC = 4.6 mg/cu.m for extrarespiratory effects) and a NOAEL of 0.1 ppm for a 10-week exposure (HEC = 0.072 mg/cu.m for respiratory effect in the thoracic region) but the effect of concurrent pulmonary infection in these animals is unknown.

Very little information is available on the human health effects of inhaled chlorine dioxide. Two cases of chlorine dioxide poisoning, one fatal, have been reported following exposure to 19 ppm chlorine dioxide (duration of exposure not specified) in bleach tank workers (Elkins, 1959). Elkins (1959) also reported that 5 ppm of chlorine dioxide is definitely irritating to the respiratory tract based on the nonfatal case. An investigation of 12 workers in a sulfite-cellulose plant exposed to chlorine dioxide (in addition to chlorine and sulfur dioxide) for 5 years, generally at concentrations that did

not exceed 0.1 ppm, revealed that a majority of these workers (7/12) exhibited signs and symptoms of ocular and respiratory irritation leading to slight bronchitis (Gloemme and Lundgren, 1957). Although the levels of chlorine dioxide were not quantified, these effects were attributed to short-term exposure to levels well above 0.1 ppm as a result of leaks from faulty vacuum equipment. Ferris et al. (1967) compared the respiratory function of 147 pulp mill workers to that of 124 paper mill workers. The former group was exposed to chlorine and chlorine dioxide, or sulfur dioxide, and the latter group served as controls. Concentrations of chlorine dioxide varied from trace amounts to 0.25 ppm (levels of chlorine were somewhat higher). No difference was found among workers with regard to pulmonary function tests (e.g., forced vital capacity, maximal expiratory flow, forced expiratory flow, or forced expiratory volume). Significant differences in the incidence of subjective respiratory complaints (shortness of breath and excess phlegm) were observed between pulp mill workers exposed to chlorine and chlorine dioxide as compared with pulp mill workers exposed to sulfur dioxide. Concurrent exposure to chlorine gas confounds the interpretation of these results.

Exner-Freisfeld et al. (1986) reported a case of acute intoxication of a female gardener following exposure to chlorine dioxide while bleaching dried flowers. The woman experienced coughing, pharyngeal irritation and headache while mixing the bleaching solution. This lead to increasing cough and dyspnea 7 hours later that required hospitalization. She exhibited tachypnea, tachycardia, rales on auscultation, leukocytosis, and an initial reduction in vital capacity and forced expiratory volume upon admittance. Blood gas analysis showed that hypoxemia was evident despite alveolar hyperventilation. The woman's symptoms improved after the administration of corticosteroids.

The toxicity of chlorine dioxide in animals following oral

administration in drinking water has been extensively studied because of the chemical's use as a disinfectant in public drinking water supplies. Adverse effects on the hematopoietic system, including RBC fragility, count, and morphology, have been observed following oral administration of chlorine dioxide and its two principal metabolites, ClO2- and chlorate (ClO3-) (Abdel-Rahman et al., 1980, 1985; Moore and Calabrese, 1980; 1982). These effects appear to be mediated by the metabolite, ClO2- and are most likely due to the strong oxidizing activity of these compounds. Chlorine dioxide has also been shown to induce a hypothyroid effect in monkeys and developing rats (Bercz et al., 1982; Harrington et al., 1986; Orme et al., 1985; Taylor and Pfohl, 1985). This effect is unique to chlorine dioxide and is not seen following exposure to ClO2-or ClO3-. Chlorine dioxide apparently mediates these effects by decreasing the gastrointestinal bioavailability of dietary iodine by oxidizing it to its reactive elemental state and increasing its binding to organic substances in the GI tract.

Tuthill et al. (1982), conducted a retrospective epidemiologic study of morbidity and mortality records from a population in Massachusetts that used chlorine dioxide as a primary water disinfectant during the 1940s. This study revealed a statistically significant positive association between chlorine dioxide exposure of women during pregnancy and premature newborns as assessed by the attending physician. Birth weight also appeared lower in the infants born to exposed mothers, but this effect was no longer apparent after controlling for the age of the mother. No other measures of prematurity (jaundice, birth defects, discharge condition, death in the first year, maximum weight loss, weight loss at 6 days, or birth length) were affected by exposure to chlorine dioxide. There are several limitations associated with this study that render the results suggestive rather than

conclusive.

Suh et al. (1983) administered 0 to 100 ppm of chlorine dioxide to rats in their drinking water for 2.5 months prior to and throughout gestation. Separate groups of animals were treated with 1 and 10 ppm ClO2- or ClO3-. No evidence of maternal toxicity was seen in any of these animals. A decreased number of implants and live fetuses per dam and an increase in fetal weight were observed in the dams administered 100 ppm chlorine dioxide. The latter effect is presumably due to the fact that the high-dose dams carried fewer fetuses and that there were more male fetuses born to these animals. The increased incidences in several minor skeletal anomalies observed in the treated animals were not statistically significant and therefore were not considered treatment-related. Animals exposed to ClO2- and ClO3- exhibited increases in fetal length only. However, Moore and Calabrese (1982) found that ClO2- administration to A/J mice in drinking water from the time of breeding through weaning resulted in a decrease in the average weight of pups at weaning and in birth-to-weaning growth rate.

Administration of Alcide liquid and gel in the drinking water to rats and mice and Allay gel applied to the skin of rabbits generally failed to elicit any signs of maternal or developmental toxicity (Abdel-Rahman et al., 1987; Gerges et al., 1985; Skowronski et al., 1985). However, fetal weights and lengths in rabbits dermally exposed to Allay gel were significantly reduced.

The only information found regarding the reproductive effects of chlorine dioxide in animals indicated that administration of 5 daily doses of up to 0.4 mg chlorine dioxide, 1.0 mg ClO2-, or 1.0 mg ClO3- by gavage to B6C3F1 mice failed to induce any sperm-head abnormalities (Meier et al., 1985).

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o INHALATION RFD CONFIDENCE : Study -- Low Data Base -- Low

RfC -- Low

Desbrousses (1970, studies by Paulet and

rabbits and 1972) identify only a LOAEL in

in 60- and rats for adverse lung effects

lacking in 45-day studies, and was

no adequate experimental detail. There were

inhalation studies that subchronic or chronic

acceptable examined lung effects, and no

studies on developmental or reproductive

Therefore, the inhaled chlorine dioxide.

base, and RfC confidence in the study, data

is low.

o INHALATION RFD SOURCE :

Source Document -- This assessment is not presented in any existing U.S. EPA
document.

Other EPA Documentation -- None
DOCUMENT

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o REVIEW DATES : 06/21/90, 09/20/90
o VERIFICATION DATE : 09/20/90
o EPA CONTACTS :

Daniel J. Guth / OHEA -- (919)541-4930

Annie M. Jarabek / OHEA -- (919)541-4847

FISTD-

Status -- List "D" Pesticide (1989)

Reference -- 54 FR 43388 (10/24/89)

EPA Contact -- Registration Branch / OPP
(703)557-7760 / FTS 557-7760

FIREV-

No data available

TSCA -

No data available

OREF - None
IREF - Abdel-Rahman, M.S., D. Couri and R.J. Bull. 1980. Kinetics of CLO2 and
effects of CLO2, CLO2-, and CLO3- in drinking water on blood
glutathione and hemoloysis in rat and chicken. J. Environ. Pathol.
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105- 113.
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Appl. Toxicol. 7(3): 161-166.
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Abstract)
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of chemicals used for drinking water disinfection for production of
chromosomal damage and sperm-head abnormalities in mice. Environ.
Mutagen. 7(2): 201- 211.
IREF - Moore, G.S. and E.J. Calabrese. 1980. The effects of chlorine dioxide
and sodium chlorite on erythrocytes of A/J and C57L/J mice. J. Environ.
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IREF - Moore, G.S. and E.J. Calabrese. 1982. Toxicological effects of chlorite
in the mouse. Environ. Health Perspect. 46: 31-37.
IREF - Orme, J., D.H. Taylor, R.D. Laurie and R.J. Bull. 1985. Effects of
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Environ. Health. 15(2): 315-322.
IREF - Paulet, G. and S. Desbrousses. 1970. On the action of CLO2 at low
concentrations on laboratory animals. Arch. Mal. Prof. Med. Trav.
Secur. Soc. 31(3): 97-106.
IREF - Paulet, G. and S. Desbrousses. 1972. On the toxicology of

chlorine
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rats. J. Appl. Toxicol. 3(2): 75-79.
IREF - Taylor, D.H. and R.J. Pfohl. 1985. Effects of chlorine dioxide on
neurobehavioral development of rats. In: Water Chlorination, Vol 5.
Chemistry, Environmental Impact and Health Effects, R.L. Jolley et al.,
Ed. Fifth Conference on Water Chlorination: Environmental Impact and
Health Effects, Williamsburg, VA., USA. ISBN 0-87371-005-3; 0(0). p.
355-364.
IREF - Tuthill, R.W., R.A. Giusti, G.S. Moore and E.J. Calabrese. 1982. Health
effects among newborns after prenatal exposure to ClO2-disinfected
drinking water. Environ. Health Perspect. 46: 39-45.
CREF - None
HAREF- None

2 - IRIS
IRSN - 23
DATE - 920120
UPDT - 01/20/92, 52 fields
STAT - Oral RfD Assessment (RDO) on-line 03/01/88
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) no data
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 03/31/87 RDO Documentation corrected
IRH - 09/01/90 RCRA EPA contact changed
IRH - 09/01/90 REFS Bibliography on-line
IRH - 08/01/91 OREF Amo, 1973 & Hertting et al. 1960 references clarified
IRH - 01/01/92 RDO Primary contact changed
IRH - 01/01/92 EXSR Regulatory actions updated
RLEN - 10892

NAME - Chlorine cyanide
RN - 506-77-4
SY - CHLORCYAN
SY - Chlorine Cyanide
SY - CHLOROCYAN
SY - CHLOROCYANIDE
SY - CHLOROCYANOGEN
SY - CHLORURE DE CYANOGENE
SY - Cyanogen chloride
SY - RCRA WASTE NUMBER P033
SY - UN 1589

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Rat Chronic Oral Study Howard and Hanzal, 1955	NOAEL: 10.8 mg/kg/day cyanide converted to 25.3 mg/kg/day of chlorine cyanide	100	5	5E-2 mg/kg/day
Weight loss, thyroid effects and myelin degeneration Rat Subchronic to Chronic Oral Bioassay Philbrick et al., 1979	LOAEL: 30 mg/kg/day cyanide (70 mg/kg/day ClCN)			

*Conversion Factors: molecular weight conversion factor = 61/26 [MW ClCN = 61; MW CN = 26]

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o ORAL RFD STUDIES :

Howard, J.W. and R.F. Hanzal. 1955. Chronic toxicity for rats by food treated with hydrogen cyanide. Agric. Food Chem. 3: 325-329.

Since chloride is present in very high levels physiologically, an RfD of

3.5 mg/day is recommended based on the maximum number of molar equivalents (1) of cyanide (CN) released in aqueous solutions or dilute acids.

In this 2-year dietary study, rats (10/sex/group) were administered food fumigated with hydrogen cyanide. The average daily concentrations were 73 and 183 mg CN/kg diet. From the data reported on food consumption and body weight, daily estimated doses were 4.3 mg and 10.8 mg CN/kg bw. The average food CN concentrations were estimated based on the authors' data for concentration at the beginning and end of each food preparation period and by assuming a first-order rate of loss for the intervening period. There were no treatment-related effects on growth rate, no gross signs of toxicity, and no histopathological lesions.

Studies by Philbrick et al. (1979) showed decreased weight gain and thyroxin levels and myelin degeneration in rats at 30 mg/kg/day CN. Other chronic studies either gave higher effect levels or used the subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an RfD because effective dose levels of chronically ingested CN are not documented. Therefore, the study of Howard and Hanzel (1955) provides the highest NOAEL, 10.8 mg/kg/day for CN, and is chosen for the derivation of an RfD for CN of 1.5 mg/day or 0.02 mg/kg/day.

Cyanide is metabolized extensively in the liver, indicating that the only relevant route of administration for quantitative risk assessment in the derivation of an oral RfD is the oral route of administration.

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o ORAL RFD UNCERTAINTY :

UF = 100. According to the U.S. EPA (1985), an uncertainty factor of 100 is used to derive the RfD (10 for species extrapolation, 10 for

sensitive
population).

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o ORAL RFD MODIFYING FACTOR :

MF = 5. A modifying factor of 5 is used to account for the apparent tolerance to cyanide when it is ingested with food rather than when it is administered by gavage or by drinking water.

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o ORAL RFD COMMENTS :

Decreased protein efficiency ratio was produced by dietary cyanide treatment of rats during gestation, lactation, and postweaning growth phase in the Tewe and Maner (1981a) experiment: the dose level of cyanide (10.6 mg/kg/day) producing that effect is slightly lower than the currently accepted NOAEL of 10.8 mg/kg/day (U.S. EPA, 1985). Furthermore, Tewe and Maner (1981b) tested sows. Possible effects observed at about 9.45 mg/kg/day were proliferation of glomerular cells of the kidneys and reduced activity of the thyroid glands in the young sows. However, the number of animals in this experiment was very small. A Japanese study (Amo, 1973) indicated that 0.05 mg/kg/day of cyanide obtained from drinking water decreased the fertility rate and survival rate in the F1 generation and produced 100% mortality in the F2 generation in mice. However, these data are not consistent with the body of available literature.

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o ORAL RFD CONFIDENCE :

Study: Medium
Data Base: Medium
RfD: Medium

The confidence in the study is medium because adequate records of food consumption and body weight were maintained and animals of both

sexes were
tested at two doses for 2 years. The data base is rated medium because a
small but sufficient number of studies support the chosen study. Medium
confidence in the RfD follows. Additional chronic/reproductive studies are
needed to support a higher level of confidence in the RfD.

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o ORAL RFD SOURCE DOCUMENT :

The only U.S. EPA documentation at present is on IRIS.

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o REVIEW DATES : 08/05/85
o VERIFICATION DATE : 08/05/85
o EPA CONTACTS :

Moiz Mumtaz / ORD -- (513)569-7553 / FTS 684-7553

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

WQCHU-

Water and Fish Consumption: 2E+2 ug/L (cyanide)

Fish Consumption Only: None

Considers technological or economic feasibility? -- NO

Discussion -- This value is the same as the drinking water standard and
approximates a safe level assuming consumption of contaminated organisms and
water.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute -- 2.2E+1 ug/L (cyanide)
Chronic -- 5.2E+0 ug/L (cyanide)

Marine:

Acute -- 1E+0 ug/L (cyanide)
Chronic -- None

Considers technological or economic feasibility? -- NO

Discussion -- Criteria were derived from a minimum database consisting of
acute and chronic tests on a variety of species. Requirements and methods are
covered in the reference.

Reference -- 51 FR 8361 (03/11/86)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value -- 0.2 mg/L [cyanide] (Proposed, 1990)

Considers technological or economic feasibility? -- NO

Discussion -- EPA is proposing to regulate cyanide based on its potential
adverse effects reported in a two-year study in rats. The MCLG is based
upon a DWEL of 0.76 mg/L and an assumed drinking water contribution of
20 percent.

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline /
(800) 426-4791

MCL -

Value -- 0.2 mg/L [cyanide] (Proposed, 1990)

Considers technological or economic feasibility? -- YES

Discussion -- EPA is proposing an MCL equal to the proposed MCLG of 0.2 mg/L.

Monitoring requirements -- Ground water systems every 3 years; surface water systems annually; will allow monitoring at up to 10-year intervals after the system completes 3 rounds of sampling at <50% of the MCL.

Analytical methodology -- Distillation, titrimetric (EPA 335.2; ASTM D-2036-82A; SM 412C; USGS I-3300-84); distillation, automated spectrometric (EPA 335.3; ASTM D-2036-82A; SM 412D); PQL= 0.2 mg/L.

Best available technology -- Ion exchange; reverse osmosis; chlorine oxidation.

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

Status -- Listed [cyanide] (Final, 1991)

Discussion -- "Unregulated" contaminants are those contaminants for which EPA establishes a monitoring requirement but which do not have an associated final MCLG, MCL, or treatment technique. EPA may regulate these

contaminants
in the future.

Monitoring requirement -- All systems to be monitored unless a vulnerability
assessment determines the system is not vulnerable.

Analytical methodology -- Spectrophotometric (EPA 335.3; ASTM D-2036-82A;
SM 412D).

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

CERC -

Value (status) -- 10 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ was based on reactivity of the CN- ion and
aquatic toxicity, as established under CWA Section 311(b)(4). Available data
indicate that the aquatic 96-Hour Median Threshold Limit for chlorine cyanide
is between 0.1 and 1 ppm.

Reference -- 50 FR 13456 (04/04/85); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

RCRA -

Status -- Listed (total free cyanide)

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - Amo, H. 1973. Effects of oral administration of CN and heavy metals in
long term on breeding and chromosome analyses of mice. Nagoya shiritsu
Diagaku Igakkai Zasshi. 24(1): 48-66.
OREF - Crampton, R.F., I.F. Gaunt, R. Harris et al. 1979. Effects of low
cobalamin diet and chronic cyanide toxicity in baboons. Toxicology.
12(3): 221-234.
OREF - Hertting, G., O. Kraupp, E. Schnetz and St. Wuketich. 1960.
Untersuchungen uber die Folgen einer chronischen Verabreichung akut
toxischer Dosen von Naturimcyanid an Hunden. Octa Pharmacol. Toxicol.
17: 27-43.
OREF - Howard, J.W. and R.F. Hanzal. 1955. Chronic toxicity for rats of food
treated with hydrogen cyanide. Agric. Food Chem. 3(4): 325-329.
OREF - Lessell, S. 1971. Experimental cyanide optic neuropathy. Arch.
Opthalmol. 86(2): 194-204.
OREF - Philbrick, D.J., J.B. Hopkins, D.C. Hill, J.C. Alexander and R.G.
Thomson. 1979. Effects of prolonged cyanide and thiocyanate feeding in
rats. J. Toxicol. Environ. Health. 5: 579-592.
OREF - Tewe, O.O. and J.H. Maner. 1981a. Long-term and carry-over effect of
dietary inorganic cyanide (KNC) in the life cycle performance and
metabolism of rats. Toxicol. Appl. Pharmacol. 58: 1-7.

OREF - Tewe, O.O. and J.H. Maner. 1981b. Performance and pathophysiological
changes in pregnant pigs fed cassava diets containing different levels
of cyanide. Res. Veter. Sci. 30: 147-151.
IREF - None
CREF - None
HAREF- None

3 - IRIS
IRSN - 510
DATE - 931101
UPDT - 11/01/93, 1 field
STAT - Oral RfD Assessment (RDO) on-line 11/01/93
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) no data
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) no data
IRH - 08/01/91 RDO Oral RfD now under review
IRH - 08/01/92 RDO Work group review dates added
IRH - 10/01/92 RDO Work group review date added
IRH - 12/01/92 RDO Work group review dates added
IRH - 01/01/93 RDO Oral RfD assessment on-line
IRH - 01/01/93 OREF Oral RfD references on-line
IRH - 02/01/93 OREF Oral RfD references corrected
IRH - 03/01/93 RDO Work group review date added
IRH - 09/01/93 RDO Oral RfD noted as going to be externally peer reviewed
IRH - 11/01/93 RDO Note revised
RLEN - 40826
NAME - Aroclor 1016
RN - 12674-11-2
SY - AROCLOR 1016
SY - HSDB 6352

RDO -
o ORAL RFD SUMMARY :

NOTE: A peer review of the non-cancer oral reference dose for Aroclor 1016,
to determine the adequacy of the studies underlying the reference dose for use
in risk assessments or otherwise, has been tentatively scheduled for December
1993.

Critical Effect	Experimental Doses*	UF	MF	RfD
Reduced birth weights	NOAEL: 0.25 ppm in feed	100	1	7E-5

		(0.007 mg/kg-day)
mg/kg-day		
Monkey Reproductive Bioassay		LOAEL: 1 ppm in feed (0.028 mg/kg-day)
Barsotti and van Miller, 1984; Levin et al., 1988; Schantz et al., 1989, 1991		

*Conversion Factors: Dams received a total average intake of 4.52 mg/kg (0.25 ppm) or 18.41 mg/kg (1 ppm) throughout the 21.8-month (654 days) dosing period. These doses are equivalent to 0.007 mg/kg-day and 0.028 mg/kg-day for the identified NOAEL and LOAEL respectively.

o ORAL RFD STUDIES :

Barsotti, D.A. and J.P. van Miller. 1984. Accumulation of a commercial polychlorinated biphenyl mixture (Aroclor 1016) in adult rhesus monkeys and their nursing infants. Toxicology. 30: 31-44.

Levin, E.D., S.L. Schantz and R.E Bowman. 1988. Delayed spatial alternation deficits resulting from perinatal PCB exposure in monkeys. Arch. Toxicol. 62: 267-273.

Schantz, S.L., E.D. Levin, R.E. Bowman et al. 1989. Effects of perinatal PCB exposure on discrimination-reversal learning in monkeys. Neurotoxicol. Teratol. 11: 243-250.

Schantz, S.L., E.D. Levin and R.E. Bowman. 1991. Long-term neurobehavioral effects of perinatal polychlorinated biphenyl (PCB) exposure in monkeys. Environ. Toxicol. Chem. 10: 747-756.

These are a series of reports that evaluated perinatal toxicity and long-term neurobehavioral effects of Aroclor 1016 in the same groups of infant monkeys. Aroclor 1016 is a commercial mixture of polyclorinated biphenyls (PCBs) devoid of chlorinated dibenzofurans (Barsotti and van Miller, 1984).

Analysis of the commercial feed used for this study revealed contamination with congeners specific for Aroclor 1248, present in the parts per billion range. These congeners were present in the control as well as test diets.

Aroclor 1016 was administered to groups of 8 adult female rhesus monkeys via diet in concentrations of 0, 0.25 or 1.0 ppm for approximately 22 months. Based on a reported total Aroclor intake of 4.52 and 18.41 mg/kg over the 22-month exposure period (Schantz et al., 1989, 1991), the low- and high-doses are estimated to be 0.007 and 0.028 mg/kg-day, respectively. Exposure began 7 months prior to breeding and continued until offspring were weaned at age 4 months. No exposure-related effects on maternal food intake, general appearance, hematology, serum chemistry (SGPT, lipid, and cholesterol analyses) or number of breedings were observed (Barsotti and van Miller, 1984). All monkeys had uncomplicated pregnancies, carried their infants to term and delivered viable offspring. Teratologic examinations were not performed. Mean birth weights of the infants in the control, 0.007 and 0.028 mg/kg-day dose groups were 521 g, 491 g and 442 g, respectively (Barsotti and van Miller, 1984). The decrease in birth weight in the high-dose group was significantly ($p<0.01$) lower than in controls. Further statistical analysis of the infant birth weight data by the Agency indicated that gestation length did not significantly affect birth weight and the distribution of male and female infants in the various dose groups could not account for the difference in birth weights among the dose groups. Agency reanalysis of the data confirmed the significant decrease in body weight for the high-dose infants, although slightly different average values were obtained. Males that had sired some infants were exposed to Aroclor 1248, so the birth weight data were also analyzed excluding these infants. The results for this adjusted data indicated that control infants weighed 528 g, low-dose infants weighed 486 g,

and high-dose infants weighed 421 g. Even with this adjustment there was still a significant difference ($p<0.01$) in birth weight for the high-dose group when compared with controls. No significant differences between treatment and control groups were detected in neonatal head circumference or crown-to-rump measurements. Both exposure groups showed consistent weight gains, but infant weights in the high-dose group were still lower (864 g) at weaning, although not significantly different from the controls (896 g). Hyperpigmentation was present at birth in the low- and high-dose infants but did not persist once dosing was stopped. This clinical change was determined not to be a critical adverse effect. The concentration of Aroclor 1016 in breast milk was higher than the maternal dose. No exposure-related hematologic effects were observed in the infants during the nursing period (Barsotti and van Miller, 1984). One of the offspring in the high-dose group went into shock and died on the day following weaning for unknown reasons (Schantz et al., 1989, 1991).

Behavioral testing of the infant monkeys was first performed at age 14 months and no overt signs of PCB toxicity were observed (Schantz et al., 1989, 1991). Two-choice discrimination-reversal learning was assessed using simple left-right spatial position, color and shape discrimination problems, with and without irrelevant color and shape cues. One of the offspring in the low-dose group stopped responding early in testing for an unknown reason and could not be induced to resume; therefore, test results were obtained using 6, 7 and 6 infants in the control, low- and high-dose groups, respectively. The offspring in the high-dose (0.028 mg/kg-day) group were significantly ($p<0.05$) impaired in their ability to learn the spatial position discrimination problem (i.e., achieved 9 correct choices in 10 trials), requiring more than 2.5 times as many trials as their age-matched controls. There were no significant

learning differences between these groups on this problem during overtraining (ability to achieve greater than or equal to 90% correct choices in two consecutive daily sessions) or position reversals. The only other exposure-related effect was significantly facilitated learning ability ($p<0.05$) on the shape discrimination problem at 0.028 mg/kg-day.

Performance on delayed spatial alternation (a spatial learning and memory task) was assessed in the offspring monkeys at age 4-6 years (Levin et al., 1988; Schantz et al., 1991). The two Aroclor-exposed groups were not significantly different from controls ($p<0.05$) in test performance. However, the exposed groups did significantly ($p<0.05$) differ from each other. The difference between the two exposed groups was due to a combination of facilitated performance at the low-dose (0.007 mg/kg-day) and impaired performance at the high-dose (0.028 mg/kg-day). Although these data are insufficient for establishing an exposure-effect relation due to the lack of difference between exposed and control groups, the investigators suggested that the performance deficit at 0.028 mg/kg-day may have been exposure-related. The investigators noticed that a paradoxical biphasic effect occurred on the same test when comparing low-dose and high-dose infants. This same effect has been observed for lead-exposed monkeys.

To summarize the above, adult monkeys that ingested 0.007 or 0.028 mg/kg-day doses of Aroclor 1016 for approximately 22 months showed no evidence of overt toxicity. Effects occurring in the offspring of these monkeys consisted of hairline hyperpigmentation at greater than or equal to 0.007 mg/kg-day, and decreased birth weight and possible neurologic impairment at 0.028 mg/kg-day. Based on the reduced birth weights of prenatally-exposed monkeys, the 0.007 mg/kg-day dose is the NOAEL and the 0.028 mg/kg-day dose is a LOAEL in monkeys.

The results of the neurobehavioral tests in the monkey offspring at 14 months and 4-6 years of age indicate adverse learning deficits at the 0.028 mg/kg-day maternal dose. Evaluation of these data is complicated by possible inconsistencies in the outcome of both the discrimination-reversal learning tests (learning was impaired and facilitated on different problems) and the delayed spatial alternation test (performance significantly differed between the two exposed groups, but not between either test group and the control). However, there is evidence suggesting that deficits in discrimination-reversal learning and delayed spatial alternation are related to decreased brain dopamine (Schantz et al., 1991), which has been observed in monkeys orally exposed to Aroclor 1016 (Seegal et al., 1990, 1991). Behavioral dysfunctions, including deficits in visual recognition and short-term memory, also have been observed in infants of human mothers who consumed fish contaminated with PCB mixtures of unknown composition (Fein et al., 1984a,b; Jacobsen et al., 1985, 1990; Gladen et al., 1988).

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o ORAL RFD UNCERTAINTY :

UF -- A 3-fold factor is applied to account for sensitive individuals. The results of these studies, as well as data for human exposure to PCBs, indicate that infants exposed transplacentally represent a sensitive subpopulation. A factor of 3 is applied for extrapolation from rhesus monkeys to human. A full 10-fold factor for interspecies extrapolation is not considered necessary because of similarities in toxic responses and metabolism of PCBs between monkeys and humans and the general physiologic similarity between these species. In addition, the rhesus monkey data are predictive of other changes noted in human studies such as chloracne, hepatic changes, and effects on reproductive function. A factor of 3 is applied because of limitations in the

data base. Despite the extensive amount of animal laboratory data and human epidemiologic information regarding PCBs, the issue of male reproductive effects is not directly addressed and two-generation reproductive studies are not available. As the study duration was considered as somewhat greater than subchronic, but less than chronic, a partial factor of 3 is used to account for extrapolation from a subchronic exposure to a chronic RfD.

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o ORAL RFD MODIFYING FACTOR :

MF -- None

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o ORAL RFD COMMENTS :

Male pig-tailed macaques [Macaca nemistrina], (number not reported, age 3-7 years, 5-9 kg initial body weight) were administered Aroclor 1016 dissolved in corn oil on bread in doses of 0, 0.8, 1.6 or 3.2 mg/kg-day for 20 weeks (Seegal et al., 1991). There were no overt signs of intoxication or exposure-related effects on body weight gain. Neurochemical analyses of various regions of the brain were performed following termination of exposure. Dose-related decreased concentrations of dopamine were observed in the caudate nucleus, putamen, substantia nigra, and hypothalamus, but not in the globus pallidus or hippocampus. There were no exposure-related changes in concentrations of norepinephrine, epinephrine, or serotonin. Other neurologic endpoints were not evaluated.

Subchronic oral studies of Aroclor 1016 have been performed in species other than monkeys. These species were tested at doses higher than the 0.007 and 0.028 mg/kg-day doses fed to monkeys in the principal studies.

Groups of 10 female Sprague-Dawley rats (age not reported, body weight approximately 225-250 g at start) were fed 0, 1, 5 or 50 ppm

Aroclor 1016 in the diet for 5 months (Byrne et al., 1988). The Aroclor was dissolved in acetone that was evaporated from the diet prior to feeding. Using a rat food consumption factor of 0.05 kg food/kg bw (U.S. EPA, 1987), the doses are estimated to be 0, 0.05, 0.25 and 2.5 mg/kg-day. Serum levels of adrenal cortical hormones were evaluated four times throughout the treatment period. Adrenal dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHS) levels were significantly ($p<0.05$) reduced at all treatment levels after approximately 100 days of exposure. Serum corticosterone (the principal glucocorticoid in rats), adrenal weight, adrenal histology, and nonadrenal endpoints other than food consumption were not evaluated. Food consumption did not significantly differ between and among control and treatment groups. Because insufficient information is available to determine whether the decreases in circulating adrenal hormones were physiologically significant, it is uncertain whether the doses are NOAELs or LOAELs for Aroclor 1016 in rats.

Male Balb/c mice (18-20 g body weight) were fed Aroclor 1016 mixed in diet at concentrations of 0 or 5 ppm for 3 or 6 weeks (Loose et al., 1978). Using a mouse food consumption factor of 0.13 kg food/kg bw (U.S. EPA, 1987), the dose is estimated to be 0.65 mg/kg-day. Sensitivity to Salmonella typhosa endotoxin (15 mice per endotoxin dose) and resistance to infection by Plasmodium berghei (malaria parasitemia; number of mice not reported) were evaluated. Sensitivity to the endotoxin was significantly ($p<0.05$) increased after 3 weeks of exposure as indicated by endotoxin LD50 values of 152 and 844 ug in the Aroclor-exposed and control groups, respectively. Sensitivity to the endotoxin after 6 weeks of Aroclor exposure was not evaluated. There were no significant ($p<0.05$) effects of Aroclor exposure for 3 or 6 weeks on malaria lethality as indicated by post-inoculation survival time. No other

endpoints were evaluated in this study. When injected into neonates, splenic cells from C57Bl/6 male mice exposed to 167 ppm (21.71 mg/kg-day) dietary Aroclor 1016 for 3 weeks elicited a greater graft-versus-host reaction than controls (Silkworth and Loose, 1978). Based on the decreased resistance to infection leading to death, 0.65 mg Aroclor 1016/kg-day suggests a LOAEL for immunotoxicity for subchronic exposure in male mice.

Aulerich and Ringer (1977) performed a breeding study in which groups of 8 female and 2 male adult pastel mink were fed diets containing 0 or 2 ppm Aroclor 1016 for 39 weeks or until the kits were 4 weeks of age. The Aroclor was dissolved in acetone which was evaporated from the diet prior to feeding. Using assumed values of 150 g/day for food consumption and 0.8 kg for body weight for female mink (Bleavins et al., 1980), the estimated dose of Aroclor 1016 is 0.4 mg/kg-day. Monthly determinations showed no statistically significant differences ($p<0.05$) between the control and treated mink in body weight gain, hemoglobin, and hematocrit. Additionally, tabulated data showed no treatment-related effects on female survival, numbers of females mated, number of females that gave birth, number of kits born alive or dead, number of births per female, average birth weight or number of kits alive at 4 weeks. The evidence for lack of treatment-related effects on body weight, hematology, reproduction and survival suggests that 0.4 mg/kg-day is a NOAEL for Aroclor 1016 in mink.

Groups of adult Pastel mink were fed a diet containing 0 ppm (24 females and 6 males) or 20 ppm (12 females and 3 males) Aroclor 1016 during a 247-day breeding study (Bleavins et al., 1980). Aroclor was dissolved in acetone which was evaporated from the diet prior to feeding. Using assumed values of 150 g/day for food consumption and 0.8 kg for body weight for female mink reported by the investigators, the estimated dose of Aroclor 1016 is 3.8

mg/kg-day. There were no deaths in the exposed or control males. Mortality was higher in the exposed females [25% (3/12) compared with 12.5% (3/24) in controls], but no clear difference in survival time was observed. Necropsies for gross abnormalities were performed on all control and treated mink that died; these showed effects only in the treated mink consisting of emaciation characterized by an almost complete absence of body fat. Histologic examinations were not performed. The incidence of mated females giving birth was reduced in the exposed group [44.4% (4/9) compared with 76.2% (16/21) in controls], but average gestation length, live births and birth weight did not significantly differ ($p>0.05$) between exposed and control groups. Body weight at age 4 weeks, average number of infants per lactating female and infant biomass (average body weight gain through age four weeks x average number of infants raised per lactating female) were significantly ($p<0.05$) reduced in the exposed group. Mortality during the first 4 weeks of life was increased in the exposed group [56.0% (14/25) compared with 24.1% (19/79) in controls]. The investigators noted that the adverse effects on reproduction do not appear to be due to an effect on spermatogenesis, since PCB-treated male mink have had acceptable levels of reproduction when mated to untreated females in other studies. The evidence for impaired reproduction and increased maternal and postnatal mortality suggests that 3.8 mg Aroclor 1016/kg-day is an FEL in mink. Although the FEL from this study and NOEL of 0.4 mg/kg-day from Aulerich and Ringer (1977) suggest that the dose-severity slope for Aroclor 1016 in mink is steep, neither study tested sufficient numbers of animals or dose levels to allow definitive conclusions to be drawn.

Dermal lesions including skin irritation, chloracne and increased pigmentation of skin and nails have been observed in humans occupationally exposed to Aroclor 1016 and other Aroclor formulations by both inhalation and

dermal routes (Fischbein et al., 1979, 1982, 1985; Ouw et al., 1976; Smith et al., 1982). However, insufficient data are available to determine possible contributions of Aroclor 1016 alone, extent of direct skin exposure and possible contaminants in these occupational studies.

Decreased birth weight has also been reported in infants born to women who were occupationally exposed to Aroclor 1016 and other Aroclor formulations (Taylor et al., 1984, 1989), ingested PCB-contaminated fish (Fein et al., 1984a,b) and ingested heated Kanechlor PCBs during the Yusho and Yu-Cheng incidents (Rogan, 1989; Yamashita, 1977). Due to uncertainties regarding actual sources of PCB exposure, and other confounding factors and study limitations, the decreases in human birth weight cannot be solely attributed to PCBs, particularly specific PCB mixtures. However, due to the consistency with which the effect has been observed, the human data are consistent with the Aroclor 1016-induced decreased birth weight in monkeys reported in the principal studies.

The human data available for risk assessment of Aroclor 1016 are useful only in a qualitative manner. Studies of the general population exposed to PCBs by consumption of contaminated food, particularly neurobehavioral evaluations of infants exposed in utero and/or through lactation, have been reported, but the original PCB mixtures, exposure levels and other details of exposure are not known (Kreiss et al., 1981; Humphrey, 1983; Fein et al., 1984a,b; Jacobson et al., 1984a, 1985, 1990a,b; Rogan et al., 1986; Gladen et al., 1988). Most of the information on health effects of PCB mixtures in humans is available from studies of occupational exposure. Some of these studies examined workers who had some occupational exposure to Aroclor 1016, but in these studies concurrent exposure to other Aroclor mixtures nearly always occurred, exposure involved dermal as well as inhalation routes (the

relative contribution by each route was not known), and monitoring data were lacking or inadequate (Fischbein et al., 1979, 1982, 1985; Fischbein, 1985; Warshaw et al., 1979; Smith et al., 1982; Lawton et al., 1985).

Information specifically on the oral absorption of Aroclor 1016 is not available, but studies of individual congeners and PCB mixtures of higher chlorine content in animals indicate, in general, that PCBs are readily and extensively absorbed. These studies have found oral absorption efficiency on the order of 75 to >90% in rats, mice, monkeys and ferrets (Albro and Fishbein, 1972; Allen et al., 1974; Tanabe et al., 1981; Bleavins et al., 1984; Clevenger et al., 1989). A study of a PCB mixture containing 54% chlorine provides direct evidence of absorption of PCBs in humans after oral exposure (Buhler et al., 1988), and indirect evidence of oral absorption of PCBs by humans is available from studies of ingestion of contaminated fish by the general population (Schwartz et al., 1983; Kuwabara et al., 1979). There are no quantitative data regarding inhalation absorption of PCBs in humans but studies of exposed workers suggest that PCBs are well absorbed by the inhalation and dermal routes (Maroni et al., 1981a,b; Smith et al., 1982; Wolff, 1985). PCBs distribute preferentially to adipose tissue and concentrate in human breast milk due to its high fat content (Jacobson et al., 1984b; Ando et al., 1985).

The metabolism of PCBs following oral and parenteral administration in animals has been extensively studied and reviewed, but studies in animals following inhalation or dermal exposure are lacking (Sundstrom and Hutzinger, 1976; Safe, 1980; Sipes and Schnellmann, 1987). Information on metabolism of PCBs in humans is limited to occupationally exposed individuals whose intake is derived mainly from inhalation and dermal exposure (Jensen and Sundstrom, 1974; Wolff et al., 1982; Schnellmann et al., 1983; Safe et al., 1985; Fait et

al., 1989). In general, metabolism of PCBs depends on the number and position of the chlorine atoms on the phenyl rings of the constituent congeners (i.e., congener profile of the PCB mixture) and animal species. Although only limited data are available on metabolism of PCBs following inhalation exposure, there is no reason to suspect that PCBs are metabolized differently by this route.

Data exist on the in vitro hepatic metabolism and in vivo metabolic clearance of 2,2',3,3',6,6'-hexachlorobiphenyl and 4,4'-dichlorobiphenyl congeners in humans, monkeys, dogs, and rats (Schnellmann et al., 1985). Both of these congeners are present in Aroclor 1016, but the hexachlorobiphenyl is only a minor constituent. For each congener, the Vmax values for metabolism in the monkey, dog and rat are consistent with the respective metabolic clearance values found in vivo. Thus, the kinetic constants for PCB metabolism obtained from the dog, monkey, and rat hepatic microsomal preparations were good predictors of in vivo metabolism and clearance for these congeners. In investigations directed at determining which species most accurately predicts the metabolism and disposition of PCBs in humans, the in vitro metabolism of these congeners was also studied using human liver microsomes (Schnellmann et al., 1983, 1984). Available data suggest that metabolism of PCBs in humans most closely resembles that of the monkey and rat. For example, the in vitro apparent Km and Vmax for humans and monkeys are comparable. These studies show consistency between the in vitro and in vivo findings and collectively indicate that metabolism of the two congeners is similar in monkeys and humans.

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o ORAL RFD CONFIDENCE :

Study -- Medium
Data Base -- Medium

RfD -- Medium

Confidence in the critical studies is rated medium since essentially only one group of monkeys has been examined. The initial study was well conducted in a sensitive animal species (rhesus monkeys) that closely resembles humans for many biological functions. These studies evaluated many sensitive endpoints of PCB toxicity and the effects observed have also been documented for human exposure. Many sophisticated reproductive and neurologic tests were performed over 6 years and many clinical chemistry determinations were conducted on the dams during the exposure period. Very extensive analyses of feed samples and tissue samples from dosed monkeys were performed. Although contamination of the control laboratory primate diet with PCBs other than those found in Aroclor 1016 was detected, the level of contamination was at the level of parts per billion and dosing of Aroclor 1016 was in the parts per million range. Because the contamination was consistent across all treatment groups and controls, quantitative comparison of adverse effects can be made. The investigators carefully documented the levels of test material and contaminant throughout the exposure and post-exposure period in animal tissues. Because the system of placentation, hemothelial-chorial with bidiscoidal distribution, is similar for Rhesus monkeys and humans, it is felt that toxic events that are induced during gestation for Rhesus monkeys will be highly predictive of similar events in humans. Historically, developmental neurobehavioral effects observed in rhesus monkeys are predictive of similar effects in humans. Although these studies were performed in an academic setting prior to the era of Good Laboratory Practices- Quality Control-Quality Assurance, the study report provides ample documentation of the experimental protocol and quality of data collected. While the group sizes for this study are small (8 monkeys/group) when compared with the standards for rodent

studies they are within the acceptable range for studies of large mammalian species as determined by EPA.

The data base for PCBs in general is extensive. Studies examining Aroclor 1016 have been performed in rhesus monkeys, mice, rats and mink. However, despite the extensive amount of data available only medium confidence can be placed in the data base at this time. It is acknowledged that mixtures of PCBs found in the environment do not match the pattern of congeners found in Aroclor 1016, therefore the RfD is only given medium confidence. For those particular environmental applications where it is known that Aroclor 1016 is the only form of PCB contamination, use of this reference dose may rate high confidence. For all other applications only medium confidence can be given. The U.S. EPA recognizes that there is a diversity of opinion among scientists concerning the use of the monkey studies for determining PCB toxicity. However, all of the studies in the vast data base for this chemical mixture support the conclusions reached in this document.

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o ORAL RFD SOURCE DOCUMENT :

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1980, 1984, 1989, 1990

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o REVIEW DATES : 02/21/90, 03/25/92, 06/23/92, 09/24/92, 10/15/92, 11/04/92, 02/11/93

o VERIFICATION DATE : 11/04/92

o EPA CONTACTS :

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IREF - None
CREF - None
HAREF- None

2 - IRIS
NAME - Chloroform
RN - 67-66-3
IRSN - 24
DATE - 920904
UPDT - 09/04/92, 2 fields
STAT - Oral RfD Assessment (RDO) on-line 09/01/92
STAT - Inhalation RfC Assessment (RDI) pending
STAT - Carcinogenicity Assessment (CAR) on-line 03/01/91
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 04/01/92
IRH - 03/01/88 RDO Dose conversion clarified
IRH - 03/01/88 RDO LOAEL and RfD in text corrected
IRH - 03/01/88 RDO Text revised
IRH - 03/01/88 RDO Text revised
IRH - 06/30/88 CAR Carcinogen summary on-line
IRH - 06/30/88 RDO Primary contact changed
IRH - 10/01/89 RDI Inhalation RfD now under review
IRH - 06/01/90 CAA Area code for EPA contact corrected
IRH - 06/01/90 RCRA EPA contact changed
IRH - 01/01/91 CAR Text edited
IRH - 01/01/91 CARI Inhalation slope factor removed (global change)
IRH - 02/01/91 CARI Information on extrapolation process included
IRH - 02/01/91 CARI Text edited
IRH - 03/01/91 CARDR Primary contact changed
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 04/01/92 CAA CAA regulatory action withdrawn
IRH - 07/01/92 RDO Clarify Schwetz citation
IRH - 07/01/92 CREF Oral RfD references on-line
IRH - 07/01/92 CREF Carcinogenicity assessment references on-line
IRH - 09/01/92 RDO Primary contact changed
RLEN - 24262
SY - Chloroform
SY - Formyl Trichloride
SY - Freon 20
SY - Methane Trichloride
SY - Methane, Trichloro-
SY - Methenyl Chloride
SY - Methenyl Trichloride
SY - Methyl Trichloride
SY - NCI-C02686
SY - R-20
SY - TCM
SY - Trichloroform
SY - Trichloromethane
MF - CHCl3
USE - Chloroform is used as a grain fumigant; solvent for pesticides, adhesives (IARC, 1972-1985) fats, oils, rubbers, alkaloids, waxes (Merck, 1976); chemical intermediate for dyes and pesticides; and a component of cough syrups, toothpastes, and liniments (SRI, 1983). Not registered as a pesticide in the U.S. (USEPA/Pesticide Index, 1985).
COFO - Chloroform is a clear, colorless and mobile liquid with a characteristic odor.
ODOR - Chloroform is a clear, colorless and mobile liquid with a characteristic odor.
BP - 143F, 61.7C
MP - -82.3F, -63.5C
MW - 119.39
DEN - 1.4832 at 20C/4C
VAP - 100 at 10.4C
VAPD - 4.12
EVAP - (Carbon Tetrachloride = 1) 1.18
SOLW - 1 mL/200 mL at 25C
FLPT - None

FICHE # 3

FLMT - Not Found
AVOI - Chloroform develops acidity from prolonged exposure to air and light (General Electric Co., 1979, MSDS #315). Chloroform explodes when in contact with aluminum powder or magnesium powder or with alkali metals (e.g., lithium, sodium, and potassium) (NFPA, 1978) and dinitrogen tetroxide. Chloroform reacts vigorously with acetone in the presence of potassium hydroxide or calcium hydroxide (Bretherick, 1979). It is oxidized by strong oxidizers such as chromic acid, forming phosgene and chlorine (IARC, 1972-1985). Chloroform reacts vigorously with triisopropylphosphine (Bretherick, 1979).
DCMP - When heated, chloroform emits hydrogen chloride, chlorine, and toxic and corrosive oxides of carbon and chlorine (General Electric Co., 1979, MSDS #315) and phosgene (ITI, 1982).

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Fatty cyst formation in liver	NOEL: none	1000	1	1E-2 mg/kg/day
Dog, Chronic Oral Bioassay	LOAEL: 15 mg/kg/day (converted to 12.9 mg/kg/day)			

Heywood et al., 1979

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*Conversion Factors: 15 mg/kg/day x 6 days/7 days = 12.9 mg/kg/day

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o ORAL RFD STUDIES :

Heywood, R., R.J. Sortwell, P.R.B. Noel, et al. 1979. Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. J. Environ. Pathol. Toxicol. 2: 835-851.

In this study beagle dogs were administered chloroform in a toothpaste base (0.5 mL of toothpaste base/kg/day) in gelatin capsules. A control group composed of 16 males and 16 females received the vehicle, and additional control groups of eight animals/sex were administered an alternative toothpaste or were left untreated. Experimental groups of eight male and eight female dogs received 15 or 30 mg chloroform/kg/day for 6 days/week. Treatment was continued for 7.5 years. Fatty cysts, considered to be treatment-related, were observed in livers of some dogs in both treatment groups. Nodules of altered hepatocytes were considered treatment-related but not dose-dependent. A dose-related increase in SGPT levels was noted and a less marked increase in SGOT was noted in the high-dose animals. The LOAEL was determined to be 12.9 mg/kg/day, and an RfD was set at 0.01 mg/kg/day.

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o ORAL RFD UNCERTAINTY :

UF -- Uncertainty factors of 10 each were applied to the LOAEL of 12.9 mg/kg/day to account for the interspecies conversion, protection of sensitive human subpopulations, and concern that the effect seen was a LOAEL and not a NOEL.

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o ORAL RFD MODIFYING FACTOR :

MF -- None

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o ORAL RFD COMMENTS :

Chloroform is considered to be highly fetotoxic, but not teratogenic (Schwetz et al., 1974; Thompson et al., 1974).

A study in rats, using only one treatment dose (Palmer et al., 1979), identified 60 mg/kg/day by gavage as a LOAEL for decreased weight gain, plasma cholinesterase and relative liver weight. Other data in the literature (Jorgenson et al., 1982) also indicate changes in liver fat to be treatment-related.

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o ORAL RFD CONFIDENCE :

Study -- Medium
Data Base -- Medium
RfD -- Medium

The critical study (Heywood et al., 1979) was of chronic duration, used a fairly large number of dogs, and measured multiple endpoints; however, only two treatment doses were used and no NOEL was determined. Therefore, confidence in the study is rated medium. Confidence in the data base is considered medium to low; several studies support the choice of a LOAEL, but a NOEL was not found. Confidence in the RfD is also considered medium to low.

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o ORAL RFD SOURCE DOCUMENT :

U.S. EPA. 1985. Drinking Water Criteria Document for Trihalomethanes. Office of Drinking Water, Washington, DC. (External Review Draft)

The 1985 Drinking Water Criteria Document for Trihalomethanes is currently undergoing Agency review.

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o REVIEW DATES : 12/02/85, 05/15/86
o VERIFICATION DATE : 12/02/85
o EPA CONTACTS :

Nancy Chiu / OST -- (202)260-7587

Michael L. Dourson / OHEA -- (513)569-7533

RDI -
o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

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o REVIEW DATES : 09/20/89
CAREV-
o CLASSIFICATION : B2; probable human carcinogen
o BASIS FOR CLASSIFICATION : Based on increased incidence of several tumor types in rats and three strains of mice
o HUMAN CARCINOGENICITY DATA :

Inadequate. There are no epidemiologic studies of chloroform itself. Chloroform and other trihalomethanes are formed from the interaction of chlorine with organic material found in water. Several ecological and case-control studies of populations consuming chlorinated drinking water in which chloroform was the major chlorinated organic show small significant increases in the risk of rectal bladder or colon cancer on an intermittent basis. Many other suspected carcinogens were also present in these water supplies.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. Chloroform has been tested for carcinogenicity in eight strains of mice, two strains of rats and in beagle dogs.

In a gavage bioassay (NCI, 1976), Osborne-Mendel rats and B6C3F1 mice were treated with chloroform in corn oil 5 times/week for 78 weeks. Fifty male rats received 90 or 125 mg/kg/day; females initially were treated with 125 or 250 mg/kg/day for 22 weeks and 90 or 180 mg/kg/day thereafter. Male mice received 100 or 200, raised to 150 or 300 mg/kg/day at 18 weeks; females were dosed with 200 or 400, raised to 250 or 500 mg/kg/day. A significant increase in kidney epithelial tumors was observed in male rats and highly significant increases in hepatocellular carcinomas in mice of both sexes. Liver nodular hyperplasia was observed in low-dose male mice not developing hepatocellular carcinoma. Hepatomas have also developed in female strain A mice and NLC mice gavaged with chloroform (Eschenbrenner and Miller, 1945; Rudali, 1967).

Jorgenson et al. (1985) administered chloroform (pesticide quality and distilled) in drinking water to male Osborne-Mendel rats and female B6C3F1 mice at concentrations of 200, 400, 900, and 1800 mg/L for 104 weeks. These concentrations were reported by the author to correspond to 19, 38, 81, and 160 mg/kg/day for rats and 34, 65, 130, and 263 mg/kg/day for mice. A significant increase in renal tumors in rats was observed in the highest dose group. The increase was dose related. The liver tumor incidence in female mice was not significantly increased. This study was specifically designed to measure the effects of low doses of chloroform.

Chloroform administered in toothpaste was not carcinogenic to male C57B1, CBA, CF-1 or female ICI mice or to beagle dogs. Male ICI mice administered 60 mg/kg/day were found to have an increased incidence of kidney epithelial tumors (Roe et al., 1979; Heywood et al., 1979). A pulmonary tumor bioassay in strain A/St mice was negative as was one in which newborn C57X DBA2/F1 mice were treated s.c. on days 1 to 8 of life (Theiss et al., 1977; Roe et al., 1968).

---

o SUPPORTING DATA :

The majority of tests for genotoxicity of chloroform have been negative. These negative findings include covalent binding to DNA, mutation in Salmonella, a Drosophila sex-linked recessive, tests for DNA damage a micronucleus test, and transformation of BHK cells. By contrast one study demonstrated binding of radiolabeled chloroform to calf thymus DNA following metabolism by rat liver microsomes (DiRenzo, 1982). Chloroform caused mitotic recombination in Saccharomyces (Callen et al., 1980) and sister chromatid exchange in cultured human lymphocytes and in mouse bone marrow cells exposed in vivo (Morimoto and Koizumi, 1983).

The carcinogenicity of chloroform may be a function of its metabolism to phosgene, which is known to cross-link DNA. A host-mediated assay using mice indicated that chloroform was metabolized in vivo to a form mutagenic to Salmonella strain TA1537. Likewise urine extracts from chloroform-treated mice were mutagenic (Agustin and Lim-Sylianco, 1978).

Chloroform administered to mice in drinking water promoted growth and metastasis of Ehrlich ascites cells injected i.p. (Capel et al., 1979).

CARO -

o CLASSIFICATION	: B2; probable human carcinogen
o BASIS FOR CLASSIFICATION	: Based on increased incidence of several tumor types in rats and three strains of mice
o ORAL SLOPE FACTOR	: 6.1E-3 per (mg/kg)/day
o DRINKING WATER UNIT RISK	: 1.7E-7 per (ug/L)
o DOSE EXTRAPOLATION METHOD	: Linearized multistage procedure, extra risk
o RISK/WATER CONCENTRATIONS :	

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	6E+2 ug/L
E-5 (1 in 100,000)	6E+1 ug/L
E-6 (1 in 1,000,000)	6E+0 ug/L

---

o ORAL DOSE-RESPONSE DATA :

Tumor Type -- all kidney tumors
Test Animals -- rat/Osborne-Mendel, male
Route -- drinking water
Reference -- Jorgensen et al., 1985

Dose		
Administered (mg/L)	Human Equivalent (mg/kg/day)	Tumor Incidence
0	0	1/50
200	3.4	6/313
400	6.9	7/148
900	14.8	3/48
1800	28.9	7/50

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o ADDITIONAL COMMENTS :

Historical control kidney tumor incidence was 5/301.

The unit risk should not be used if the water concentration exceeds 6E+4 ug/L, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

This assay was designed for detection and quantitation of effects at low dose; thus, large numbers of animals were treated and observed for their lifetime. Exposure route and vehicle is relevant to the medium for which the risk estimate was developed.

CARI -
o CLASSIFICATION : B2; probable human carcinogen
o BASIS FOR CLASSIFICATION : Based on increased incidence of several tumor types in rats and three strains of mice
o INHALATION UNIT RISK : 2.3E-5 per (ug/cu.m)
o DOSE EXTRAPOLATION METHOD : Linearized multistage procedure, extra risk
o RISK/AIR CONCENTRATIONS :

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	4E+0 ug/cu.m
E-5 (1 in 100,000)	4E-1 ug/cu.m
E-6 (1 in 1,000,000)	4E-2 ug/cu.m

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o INHALATION DOSE-RESPONSE DATA :

Tumor Type -- hepatocellular carcinoma
Test Animals -- mouse, B6C3F1, female
Route -- oral, gavage

Reference -- NCI, 1976

Dose		Tumor Incidence
Administered (mg/kg/day)	Human Equivalent (mg/kg/day)	
Female		
0	0	0/20
238	9.9	36/45
477	19.9	39/41
Male		
0	0	1/18
138	6.2	18/50
277	12.5	44/45

---

o ADDITIONAL COMMENTS :

This inhalation quantitative risk estimate is based on data from a gavage study. Above doses are TWA; body weights at the end of the assay were 35 g, males and 28 g, females. Vehicle control animals were run concurrently and housed with test animals. All treated animals experienced decreased body weight gain. Survival was reduced in high-dose males and in all treated females.

Experimental data for this compound support complete absorption of orally administered chloroform under conditions of this assay. There are no apparent species differences in this regard. Extrapolation of metabolism-dependent carcinogenic responses from mice to humans on the basis of body surface area is supported by experimental data. The incidence data for both male and female mice were used to derive slope factors of 3.3E-2 and 2.0E-1 per (mg/kg)/day, respectively. The unit risk was prepared by taking a geometric mean of the slope factor and assuming 100% for low doses of chloroform in air.

The unit risk should not be used if the air concentration exceeds 400 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

Adequate numbers of animals were treated and observed.

Risk estimates derived from male rat kidney tumor data (2.4E-2) (NCI, 1976) and studies by Roe et al. (1979) (1.0E-1) are generally supportive of the risk estimate.

CARDR-

o CARCINOGENICITY SOURCE :

U.S. EPA. 1985. Health Assessment Document for Chloroform. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC for the Office of Air Quality Planning and Standards. EPA 600/8-84-004F.

U.S. EPA. 1987. Drinking Water Criteria Document for Trihalomethanes. Office of Drinking Water, Washington, DC. Draft.

NCI (National Cancer Institute). 1976. Report on Carcinogenesis Bioassay of Chloroform. National Cancer Institute, Washington, DC. NTIS PB 264018.

The Health Assessment Document for Chloroform received extensive Agency and external review.

The Draft Drinking Water Criteria Document for Trihalomethanes has received external peer review.

DOCUMENT

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o REVIEW DATES : 10/29/86, 08/26/87
o VERIFICATION DATE : 08/26/87
o EPA CONTACTS :

Nancy Chiu / OST -- (202)260-7587

David Bayliss / OHEA -- (202)260-5726

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE-
o ACUTE TOXICITY :

Chloroform is classified as moderately toxic. A probable oral lethal dose for humans is 0.5 to 5 g/kg (between 1 ounce and 1 pint) for a 150-lb. person. The mean lethal dose is probably near 1 fluid ounce (44 g) (Gosselin et al., 1976). Also, it is a central nervous system depressant and a gastrointestinal irritant (Challen et al., 1958). Chloroform has caused rapid death attributable to cardiac arrest.

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o SIGNS AND SYMPTOMS :

Symptoms of acute exposure include fainting sensation, vomiting, dizziness, salivation, nausea, fatigue, and headache (ACGIH, 1971-1979). Other symptoms are respiratory depression, coma, kidney damage, and liver damage (IARC, 1972-1985). Liquid in the eye causes tearing and conjunctivitis (Grant, 1974). Symptoms of chronic exposure include loss of appetite, hallucinations, moodiness, and physical and mental sluggishness (NIOSH, 1974).

BCF - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption: 1.9E-1 ug/L

Fish Consumption Only: 1.57E+1 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, zero may not be obtainable at this time, so the recommended criteria represents an E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute LEC -- 2.89E+4 ug/L
Chronic LEC -- 1.24E+3 ug/L

Marine: None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

No data available

MCL -

Value (status) -- 0.10 mg/L [total trihalomethanes*] (Interim, 1979)

Considers technological or economic feasibility? -- YES

Discussion -- An interim MCL of 0.10 mg/L for total trihalomethanes* is proposed based on chronic toxicity data for chloroform and existing technology and treatment methods. Chloroform produced central nervous system depression, hepatic, renal, teratogenic and carcinogenic effects at dose levels from 30 to 350 mg/kg.
*Chloroform (67-66-3), dibromochloromethane (124-48-1), bromodichloromethane (75-27-4) and bromoform (75-25-2).

Monitoring requirements -- This MCL applies only to community water systems which serve a population of 10,000 or more individuals and which add a

disinfectant (oxidant) to the water in any part of the drinking water treatment process. Monitoring frequency is dependent upon system size.

Analytical methodology -- Purge and trap gas chromatography (EPA 502.1).

Best available technology -- Granular activated carbon; powdered activated carbon; biological activated carbon; ion exchange.

Reference -- 44 FR 68624 (11/29/79)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

Status -- Listed (Final, 1987)

Discussion -- "Unregulated" contaminants are those contaminants for which EPA establishes a monitoring requirement but which do not have an associated final MCLG, MCL, or treatment technique. EPA may regulate these contaminants in the future.

Monitoring requirement -- Monitoring required for all water systems at a minimum frequency of once every 5 years.

Analytical methodology -- Gas chromatography (EPA 502.1, 502.2, 503.1); gas chromatographic/mass spectrometry (EPA 524.1, 524.2).

Reference -- 52 FR 25690 (07/08/87)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

SMCL - NO DATA

FISTD-

No data available

FIREV-

Action -- Final regulatory decision - PD4 (1983)

Considers technological or economic feasibility? -- YES

Summary of regulatory action -- The agency determined that applicator exposure had been reduced to a minimum as a result of label amendments. Registrants were required to submit data to establish tolerances of permissible residues on raw agricultural commodities. Compound returned to the registration process. Criterion of concern: oncogenicity.

Reference -- 48 FR 498 (01/05/83)

EPA Contact -- Special Review Branch / OPP
(703)557-7400 / FTS 557-7400

CERC -

Value (status) -- 10 pounds (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The RQ for chloroform is based on potential carcinogenicity. Available data indicate a hazard ranking of medium based on a potency factor of 1.97 mg/kg/day and assignment to weight-of-evidence group B2. These correspond to an RQ of 10 pounds.

Reference -- 52 FR 8140 (03/16/87); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - Heywood, R., R.J. Sortwell, P.R.B. Noel, et al. 1979. Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. J. Environ. Pathol. Toxicol. 2: 835-851.

OREF - Jorgenson, T.A., C.J. Rushbrook and D.C.L. Jones. 1982. Dose-response study of chloroform carcinogenesis in the mouse and rat: Status report. Environ. Health Perspect. 46: 141-149.

OREF - Palmer, A.K., A.E. Street, F.J.C. Roe, A.M. Worden and N.J. Van Abbe. 1979. Safety evaluation of toothpaste containing chloroform. II. Long-term studies in rats. J. Environ. Pathol. Toxicol. 2: 821-833.

OREF - Schwetz, B.A., B.J.K. Leong and P.J Gehring. 1974. Embryo- and fetotoxicity of inhaled chloroform in rats. Toxicol. Appl. Pharmacol. 28: 442-451.

OREF - Thompson, D.J., S. D. Warner and V.B. Robinson. 1974. Teratology studies on orally administered chloroform in the rat and rabbit. Toxicol. Appl. Pharmacol. 29: 348-357.

OREF - U.S. EPA. 1985. Drinking Water Criteria Document for Trihalomethanes.

Office of Drinking Water, Washington, DC. (External Review Draft)
IREF - None
CREF - Augstin, J.S. and C.Y. Lim-Syliano. 1978. Mutagenic and clastogenic effects of chloroform. Bull. Phil. Biochem. Soc. 1: 17-23.
CREF - Callen, D.F., C.R. Wolf and R.M. Philpot. 1980. Cytochrome P-450 mediated genetic activity and cytotoxicity of seven halogenated aliphatic hydrocarbons in saccharomyces cerevisiae. Mutat. Res. 77: 55-63.
CREF - Capel, I.D., H.M. Dorrell, M. Jenner, M.H. Pinnock and D.C. Williams. 1979. The effect of chloroform ingestion on the growth of some murine tumours. Eur. J. Cancer. 15: 1485-1490.
CREF - DiRenzo, A.B., A.J. Gandolf and I.G. Sipes. 1982. Microsomal bioactivation and covalent binding of aliphatic halides to DNA. Toxicol. Letters. 11: 243- 252.
CREF - Eschenbrenner, A.B. and E. Miller. 1945. Induction of hepatomas in mice by repeated oral administration of chloroform, with observations on sex differences. J. Natl. Cancer Inst. 5: 251-255.
CREF - Heywood, R., R.J. Sortwell, P.R.B. Noel, et al. 1979. Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. J. Environ. Pathol. Toxicol. 2: 835-851.
CREF - Jorgenson, T.A. E.F. Meierhenry, C.J. Rushbrook, R.J. Bull and M. Robinson. 1985. Carcinogenicity of chloroform in drinking water to male Osborne-Mendel rats and female B6C3F1 mice. Fund. Appl. Toxicol. 5: 760-769.
CREF - Morimoto, K. and A. Koizumi. 1983. Trihalomethanes induce sister chromatid exchanges in human lymphocytes in vitro and mouse bone marrow cells in vivo. Environ. Res. 32: 72-79.
CREF - NCI (National Cancer Institute). 1976. Report on carcinogenesis bioassay of chloroform. Report No. (NIH) 76-1279. PB-264 018. Bethesda, Maryland.
CREF - Roe, F.J.C., R.L. Carter and B.C.V. Mitchley. 1968. Test of chloroform and AS-hydroxyquinoline for carcinogenicity using newborn mice. Br. Emp. Campgn. 46: 13.
CREF - Roe, F.J.C., A.K. Palmer, A.N. Worden and N.J. Van Abbe. 1979. Safety evaluation of toothpaste containing chloroform. I. Long-term studies in mice. J. Environ. Pathol. Toxicol. 2: 799-819.
CREF - Rudali, G. 1967. A propos de l'activate oncogene de quelques hydrocarbures halogens utilises en therapeutique. Springer Verlag. 7: 138-143.
CREF - Theiss, J.C., G.D. Stoner, M.B. Shimkin and E.K. Weisberger. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res. 37: 2717-2720.
CREF - U.S. EPA. 1985. Health Assessment Document for Chloroform. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC for the Office of Air Quality Planning and Standards. EPA/600/8-84/004F.
CREF - U.S. EPA. 1987. Drinking Water Criteria Document for Trihalomethanes. Office of Drinking Water, Washington, DC.
HAREF- None

1 - IRIS
NAME - Chromium(III)
RN - 16065-83-1
IRSN - 27
DATE - 920604
UPDT - 06/04/92, 52 fields
STAT - Oral RfD Assessment (RDO) on-line 03/01/88
STAT - Inhalation RfC Assessment (RDI) pending
STAT - Carcinogenicity Assessment (CAR) pending 05/01/92
STAT - Drinking Water Health Advisories (DWHA) on-line 11/01/90
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 03/01/88 RDO Critical effect added
IRH - 03/01/88 HADV Health Advisory added
IRH - 08/01/89 REFS Bibliography on-line
IRH - 08/01/90 RCRA EPA contact changed
IRH - 10/01/90 RDI Inhalation RfC now under review
IRH - 11/01/90 HADV Full Health Advisory summary added
IRH - 01/01/92 RDO Secondary contact changed
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 05/01/92 CAR Carcinogenicity assessment now under review
RLEN - 15079
SY - 7440-47-3
SY - CHROMIC ION
SY - CHROMIUM
SY - Chromium(III)
SY - CHROMIUM (III) ION
SY - CHROMIUM, ION
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA
VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
No effects observed Rat Chronic Feeding Study Ivankovic and Preussmann, 1975	NOEL: 5% Cr2O3 in diet 5 days/week for 600 feedings (1800 g/kg bw average total dose) LOAEL: none	100	10	1E+0 mg/kg/day (as an insoluble salt)

*Dose Conversion Factors & Assumptions: 1800 g Cr2O3/kg bw x 1000 mg/g x 0.6849 Cr/g Cr2O3 / 600 feeding days x 5 feeding days/7 days = 1468 mg/kg/day

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o ORAL RFD STUDIES :

Ivankovic, S. and R. Preussmann. 1975. Absence of toxic and carcinogenic

effects after administration of high doses of chromic oxide pigment in subacute and long-term feeding experiments in rats. Food Cosmet. Toxicol. 13: 347-351.

Groups of 60 male and female rats were fed chromic oxide (Cr_2O_3) baked in bread at dietary levels of 0, 1, 2, or 5%, 5 days/week for 600 feedings (840 total days). The primary purpose of this study was to assess the carcinogenic potential of Cr_2O_3. Body weight and food consumption were monitored. The average total amounts of ingested Cr_2O_3 were given as 360, 720, and 1800 g/kg bw for the 1, 2, and 5% treatment groups, respectively. The animals were maintained on control diets following termination of exposure until they became moribund or died. All major organs were examined histologically. Other toxicologic parameters were not mentioned explicitly, but may have included some or all of those described for the accompanying subchronic study (see below). No effects due to Cr_2O_3 treatment were observed at any dose level.

Ivankovic and Preussmann (1975) also treated rats (both sexes, 12-19 rats/group) at dietary levels of 0, 2, or 5% Cr_2O_3 in bread, 5 days/week for 90 days. Food consumption and body weight were monitored. Toxicologic parameters included serum protein, bilirubin, hematology, urinalysis, organ weights, and histopathology. The only effects observed were reductions (12-37%) in the absolute weights of the livers and spleens of animals in the high-dose group. Organ weights relative to body weight were not reported. The high dose is equivalent to 1400 mg/kg/day (dose converted using reported data).

Other subchronic oral studies show no indication of adverse effects attributable to trivalent chromium compounds, but dose levels were considerably lower.

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o ORAL RFD UNCERTAINTY :

UF = 100. The factor of 100 represents two 10-fold decreases in mg/kg bw/day dose that account for both the expected interhuman and interspecies variability to the toxicity of the chemical in lieu of specific data.

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o ORAL RFD MODIFYING FACTOR :

MF = 10. The additional modifying factor of 10 is adopted to reflect uncertainty in the NOEL because: 1) the effects observed in the 90-day study were not explicitly addressed in the 2-year study and, thus, the highest NOAEL in the 2-year study may be a LOAEL; 2) the absorption of chromium is low (<1%) and is influenced by a number of factors; thus, a considerable potential variation in absorption exists; and 3) animals were allowed to die naturally after feeding stopped (2 years) and only then was histology performed.

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o ORAL RFD COMMENTS :

This RfD is limited to metallic chromium (III) of insoluble salts. Examples of insoluble salts include chromic III oxide (Cr_2O_3) and chromium III sulfate [$Cr_2(SO_4)_3$].

Very limited data suggest that Cr III may have respiratory effects on humans. No data on chronic or subchronic effects of inhaled Cr III in ani- mals can be found. Adequate teratology data do not exist, but reproductive effects are not seen at dietary levels of 5% Cr_2O_3.

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o ORAL RFD CONFIDENCE :

Study: Low
Data Base: Low
RfD: Low

The principal study is rated low because of the lack of explicit detail on study protocol and results. Low confidence in the data base reflects the lack of high-dose supporting data. The low confidence in the RfD reflects the foregoing, but also reflects the lack of an observed effect level. Thus, the RfD, as given, should be considered conservative, since the MF addresses only those factors which might lower the RfD.

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o ORAL RFD SOURCE DOCUMENT :

U.S. EPA. 1984. Health Effects Assessment for Trivalent Chromium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response.

The ADI in the 1984 Health Effects Assessment document received an Agency review with the help of two external scientists.

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o REVIEW DATES : 11/21/85, 02/05/86
o VERIFICATION DATE : 11/21/85
o EPA CONTACTS :

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

Robert Bruce / ORD -- (513)569-7553 / FTS 684-7553

RDI -
o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

HAONE-

NOTE: All chromium HAs are based on total chromium (III and VI).

Appropriate data for calculating a One-day HA are not available. It is recommended that the Ten-day HA of 1.4 mg/L be used as the One-day HA.

HATEN-

NOTE: All chromium HAs are based on total chromium (III and VI).

Ten-day HA -- 1.4E+0 mg/L

NOAEL -- 14.4 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Gross and Heller, 1946

Rats were exposed to drinking water containing Cr(VI) (K_2CrO_4) at levels of 80 or 134 mg Cr(VI)/L for 60 days (8.3 or 14.4 mg Cr(VI)/kg/day, respectively) without adverse effects. Therefore, a NOAEL of 14.4 mg/kg/day

is identified.

HALTC-

NOTE: All chromium HAs are based on total chromium (III and VI).

Longer-term (Child) HA -- 2.4E-1 mg/L

NOAEL -- 2.4 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal study -- MacKenzie et al., 1958

In a 1-year drinking water study, consumption of water containing either Cr(III) ($CrCl_3$) or Cr(VI) (K_2CrO_4) (0 to 1.87 mg/kg/day for male rats and 0 to 2.41 mg/kg/day for female rats) produced no significant differences in weight gain, appearance, or pathological changes in the blood or other tissue. Therefore, a NOAEL of 2.41 mg/kg/day is identified.

HALTA-

NOTE: All chromium HAs are based on total chromium (III and VI).

Longer-term (Adult) HA -- 8.4E-1 mg/L

NOAEL -- 2.4 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 2 L/day water consumption for a 70-kg adult

Principal study -- MacKenzie et al., 1958 (study described in HALTC)

HALIF-

NOTE: All chromium HAs are based on total chromium (III and VI).

Drinking Water Equivalent Level (DWEL) -- 1.7E-1 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date = 02/05/86 (see RDO)

Lifetime HA -- 1.2E-1 mg/L

Assumptions -- 71% exposure by drinking water

Principal study -- MacKenzie et al., 1958 (This study was used in the derivation of the chronic oral RfD; see RDO)

OLEP -

No data available

ALAB -

Determination of chromium is by an atomic absorption technique using either direct aspiration into a flame or a furnace.

TREAT-

The treatment technologies that are available to remove chromium from water include coagulation/filtration, lime softening, ion exchange, and reverse osmosis.

HADR -

o HEALTH ADVISORY SOURCE :

U.S. EPA. 1985. Draft of the Drinking Water Criteria Document on Chromium. Office of Drinking Water, Washington, DC.
DOCUMENT

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o HEALTH ADVISORY REVIEW :

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

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o EPA DRINKING WATER CONTACT :

Kenneth Bailey / ODW -- (202)260-5535 / FTS 260-5535

Edward V. Ohanian / ODW -- (202)260-7571 / FTS 260-7571

ACUTE- NO DATA
BCF - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption: 1.7E+5 ug/L

Fish Consumption Only: 3.433E+6 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 1.7E+5 ug/L is based on consumption of contaminated aquatic organisms and water. A WQC of 3.433E+6 ug/L has also been established based on consumption of contaminated aquatic organisms alone.

Reference -- 45 FR 79318 (11/28/80); 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute -- 9.8E+2 ug/L (hardness dependent)
Chronic -- 1.2E+2 ug/L (hardness dependent)

Marine:

Acute LEC -- 1.03 E+ 4 ug/L
Chronic LEC -- none

Considers technological or economic feasibility? -- NO

Discussion -- Criteria were derived from a minimum data base consisting of acute and chronic tests on a variety of species. For freshwater aquatic life the concentration (in ug/L) of total recoverable trivalent chromium should not exceed the numerical value given by the equations "e**(0.8190 [ln (hardness)]+3.688)" for acute exposure and "e**(0.8190 [ln (hardness)]+1.561)" for chronic exposure (** indicates exponentiation; hardness is in mg/L). For example, at a hardness of 50 mg/L, the acute and chronic WQC would be 980 and 120 ug/L, respectively. The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LEC's are given when the minimum data required to derive water quality criteria are not available.

Reference -- 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 0.1 mg/L [total chromium] (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.1 mg/L for total chromium (Cr III and Cr VI) is based on EPA's RfD methodology for Cr VI, the more toxic chromium species. The MCLG is based upon a DWEL of 0.17 mg/L calculated from available human and animal data and an assumed drinking water contribution of 20 percent. An uncertainty factor of 500 was applied. The MCLG also falls into the safe and adequate daily dietary intake range of 50 to 200 mg/day for Cr III established by the National Research Council in the National Academy of Sciences (NAS, 1989).

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value (status) -- 0.1 mg/L [total chromium] (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- The EPA has established an MCL equal to the MCLG of 0.1 mg/L.

Monitoring requirements -- Ground water systems monitored every three years; surface water systems monitored annually; systems out of compliance must begin monitoring quarterly until system is reliably and consistently below MCL.

Analytical methodology -- Atomic absorption/furnace technique (EPA 218.2; SM 304); inductively coupled plasma (EPA 200.7): PQL= 0.01 mg/L.

Best available technology -- Coagulation/filtration; ion exchange; lime softening; and reverse osmosis.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 1 pound (Statutory, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- Though "Chromium (III), insoluble salts" is not specifically designated as a CERCLA hazardous substance, insoluble chromium (III) salts would be considered hazardous substances under the CERCLA broad generic listing for "Chromium and Compounds." There is no corresponding reportable quantity (RQ) for this generic class of compounds. However, the releaser is still liable for cleanup costs if the designated Federal On-Scene Coordinator (OSC) decides to take response action with respect to the release of an insoluble chromium (III) salt that is not otherwise specifically listed as a CERCLA hazardous substance. There are two chromium (III) salts which are specifically listed as CERCLA hazardous substances, chromic acetate and chromic sulfate. Both have been assigned final RQs of 1000 pounds based on aquatic toxicity (as established under section 311(b)(4) of the Clean Water Act). Metallic chromium has been assigned a final RQ of 5000 pounds.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline (800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed (total chromium)

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - Ivankovic, S. and R. Preussmann. 1975. Absence of toxic and carcinogenic effects after administration of high doses of chromic oxide pigment in subacute and long-term feeding experiments in rats. Food Cosmet. Toxicol. 13: 347-351.
OREF - U.S. EPA. 1984. Health Effects Assessment for Trivalent Chromium. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH. OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.
IREF - None
CREF - None
HAREF- Gross, W.G., and V.G. Heller. 1946. Chromates in animal nutrition. J. Ind. Hyg. Toxicol. 28: 52-56.
HAREF- MacKenzie, R.D., R.U. Byerrum, C.F. Decker, C.A. Hoppert and R.F. Langham. 1958. Chronic toxicity studies. II. Hexavalent and trivalent chromium administered in drinking water to rats. Am. Med. Assoc. Arch. Ind. Health. 18: 232-234.
HAREF- U.S. EPA. 1985. Draft of the Drinking Water Criteria Document on Chromium. Office of Drinking Water, Washington, DC.

12 - IRIS
NAME - Chromium(VI)
RN - 18540-29-9
IRSN - 141
DATE - 930312
UPDT - 03/12/93, 2 fields
STAT - Oral RfD Assessment (RDO) on-line 03/01/88
STAT - Inhalation RfC Assessment (RDI) pending
STAT - Carcinogenicity Assessment (CAR) on-line 03/01/91
STAT - Drinking Water Health Advisories (DWHA) on-line 03/01/88
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 04/01/92
IRH - 09/30/87 CAREV Citation corrected
IRH - 03/01/88 CARI Confidence statement revised
IRH - 03/01/88 CARDR Contacts switched
IRH - 03/01/88 HADV Health Advisory added
IRH - 12/01/89 RDI Inhalation RfD now under review
IRH - 06/01/90 CAREV Basis - Text revised
IRH - 06/01/90 CARO Text revised
IRH - 06/01/90 CAA Area code for EPA contact corrected
IRH - 06/01/90 RCRA EPA contact changed
IRH - 06/01/90 REFS Bibliography on-line
IRH - 01/01/91 CAR Text edited
IRH - 01/01/91 CARI Inhalation slope factor removed (global change)
IRH - 03/01/91 CAREV Text revised
IRH - 03/01/91 CAREV Text revised
IRH - 03/01/91 CARO Text revised
IRH - 01/01/92 RDO Secondary contact changed
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 04/01/92 CAA CAA regulatory action withdrawn
RLEN - 31276
SY - 7440-47-3
SY - CHROMIC ION
SY - CHROMIUM
SY - CHROMIUM, ION
SY - Chromium(VI)
SY - CHROMIUM (VI) ION
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA
VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
No effects reported	NOAEL: 25 mg/L of chromium as K_2CrO_4	500	1	5E-3 mg/kg/day
Rat, 1-Year Drinking Study	(converted to 2.4 mg of chromium(VI)/kg/day)			
MacKenzie et al.,	LOAEL: none			

1958

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*Conversion Factors: Drinking water consumption = 0.097 L/kg/day (reported)

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o ORAL RFD STUDIES :

MacKenzie, R.D., R.U. Byerrum, C.F. Decker, C.A. Hoppert and R.F. Langham. 1958. Chronic toxicity studies. II. Hexavalent and trivalent chromium administered in drinking water to rats. Am. Med. Assoc. Arch. Ind. Health. 18: 232-234.

Groups of eight male and eight female Sprague-Dawley rats were supplied with drinking water containing 0-11 ppm (0-11 mg/L) hexavalent chromium (as K2CrO4) for 1 year. The control group (10/sex) received distilled water. A second experiment involved three groups of 12 males and 9 female rats. One group was given 25 ppm (25 mg/L) chromium (as K2CrO4); a second received 25 ppm chromium in the form of chromic chloride; and the controls again received distilled water. No significant adverse effects were seen on appearance, weight gain, or food consumption, and there were no pathologic changes in the blood or other tissues in any treatment group. The rats receiving 25 ppm of chromium (as K2CrO4) showed an approximate 20% reduction in water consumption. This dose corresponds to 2.4 mg chromium(VI)/kg/day based on actual body weight and water consumption data.

For rats treated with 0-11 ppm (in the diet), blood was examined monthly, and tissues (livers, kidneys and femurs) were examined at 6 months and 1 year. Spleens were also examined at 1 year. The 25 ppm groups (and corresponding controls) were examined similarly, except that no animals were killed at 6 months. An abrupt rise in tissue chromium concentrations was noted in rats treated with greater than 5 ppm. The authors stated that "apparently, tissues can accumulate considerable quantities of chromium before pathological changes result." In the 25 ppm treatment groups, tissue concentrations of chromium were approximately 9 times higher for those treated with hexavalent chromium than for the trivalent group.

Similar no-effect levels have been observed in dogs and humans. Anwar et al. (1961) observed no significant effects in female dogs (2/dose group) given up to 11.2 ppm chromium(VI) (as K2CrO4) in drinking water for 4 years. The calculated doses were 0.012-0.30 mg/kg of chromium(VI). In humans, no adverse health effects were detected (by physical examination) in a family of four persons who drank for 3 years from a private well containing chromium(VI) at approximately 1 mg/L (0.03 mg/kg/day for a 70-kg human).

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o ORAL RFD UNCERTAINTY :

UF = 500. The uncertainty factor of 500 represents two 10-fold decreases in dose to account for both the expected interhuman and interspecies variability in the toxicity of the chemical in lieu of specific data, and an additional factor of 5 to compensate for the less-than-lifetime exposure duration of the principal study.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

This RfD is limited to metallic chromium(VI) of soluble salts. Examples of soluble salts include potassium dichromate (K2CR2O7), sodium dichromate (Na2Cr2O7), potassium chromate (K2CrO4) and sodium chromate (Na2CrO4).

Trivalent chromium is an essential nutrient. There is some evidence to indicate that hexavalent chromium is reduced in part to trivalent chromium in vivo (Petrilli and DeFlora, 1977, 1978; Gruber and Jennette, 1978).

The literature available on possible fetal damage caused by chromium compounds is limited. No studies were located on teratogenic effects resulting from ingestion of chromium.

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o ORAL RFD CONFIDENCE :

Study: Low
Data Base: Low
RfD: Low

Confidence in the chosen study is low because of the small number of animals tested, the small number of parameters measured and the lack of toxic effect at the highest dose tested. Confidence in the data base is low because the supporting studies are of equally low quality, and teratogenic and reproductive endpoints are not well studied. Low confidence in the RfD follows.

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o ORAL RFD SOURCE DOCUMENT :

U.S. EPA. 1984. Health Effects Assessment for Hexavalent Chromium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985. Drinking Water Health Advisory for Chromium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (Draft)

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o REVIEW DATES : 11/21/85, 02/05/86
o VERIFICATION DATE : 02/05/86
o EPA CONTACTS :

Kenneth L. Bailey / ODW -- (202)260-5535 / FTS 260-5535

Sue Velazquez / ORD -- (513)569-7571 / FTS 684-7571

RDI -
o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

CAREV-
o CLASSIFICATION : A; human carcinogen
o BASIS FOR CLASSIFICATION : Results of occupational epidemiologic studies of chromium-exposed workers are consistent across investigators and study populations. Dose- response relationships have been established for chromium exposure and lung cancer. Chromium-exposed workers are exposed to both chromium III and chromium VI compounds. Because only chromium VI has been found to be carcinogenic in animal studies, however, it was concluded that only chromium VI should be classified as a human carcinogen.

o HUMAN CARCINOGENICITY DATA :

Sufficient. Epidemiologic studies of chromate production facilities in the United States (Machle and Gregorius, 1948; Brinton et al., 1952; Mancuso and Hueper, 1951, Mancuso, 1975; Baetjer, 1950; Taylor, 1966; Enterline, 1974; Hayes et al., 1979; Hill and Ferguson, 1979), Great Britain (Bidstrup, 1951; Bidstrup and Case, 1956; Alderson et al., 1981), Japan (Watanabe and Fukuchi, 1975; Ohsaki et al., 1978; Sano and Mitohara, 1978; Satoh et al., 1981) and West Germany (Korallus et al., 1982; Bittersohl, 1971) have established an association between chromium (Cr) exposure and lung cancer. Most of these studies did not attempt to determine whether Cr III or Cr VI compounds were the etiologic agents.

Three studies of the chrome pigment industry, one in Norway (Langard and Norseth, 1975), one in England (Davies, 1978, 1979), and the third in the Netherlands and Germany (Frentzel-Beyme, 1983) also found an association between occupational chromium exposure (predominantly to Cr VI) and lung cancer.

Results of two studies of the chromium plating industry (Royle, 1975; Silverstein et al., 1981) were inconclusive, while the findings of a Japanese study of chrome platers were negative (Okubo and Tsuchiya, 1979). The results of studies of ferrochromium workers (Pokrovskaya and Shabynina, 1973; Langard et al., 1980; Axelsson et al., 1980) were inconclusive as to lung cancer risk.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. Hexavalent chromium compounds were carcinogenic in animal assays producing the following tumor types: intramuscular injection site tumors in Fischer 344 and Bethesda Black rats and in C57BL mice (Furst et al., 1976; Maltoni, 1974, 1976; Payne, 1960; Heuper and Payne, 1959); intraplural implant site tumors for various chromium VI compounds in Sprague-Dawley and Bethesda Black rats (Payne, 1960; Heuper 1961; Heuper and Payne, 1962); intrabronchial implantation site tumors for various Cr VI compounds in Wistar rats (Levy and Martin, 1983; Laskin et al., 1970; Levy as quoted in NIOSH, 1975); and subcutaneous injection site sarcomas in Sprague-Dawley rats (Maltoni, 1974, 1976).

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o SUPPORTING DATA :

A large number of chromium compounds have been assayed in in vitro genetic toxicology assays. In general, hexavalent chromium is mutagenic in bacterial assays whereas trivalent chromium is not (Lofroth, 1978; Petrellie and Flora, 1977, 1978). Likewise Cr VI but not Cr III was mutagenic in yeasts (Bonatti et al., 1976) and in V79 cells (Newbold et al., 1979). Chromium III and VI compounds decrease the fidelity of DNA synthesis in vitro (Loeb et al., 1977), while Cr VI compounds inhibit replicative DNA synthesis in mammalian cells (Levis et al., 1978) and produce unscheduled DNA synthesis, presumably repair synthesis, as a consequence of DNA damage (Raffetto, 1977). Chromate has been shown to transform both primary cells and cell lines (Fradkin et al., 1975; Tsuda and Kato, 1977; Casto et al., 1979). Chromosomal effects produced by treatment with chromium compounds have been reported by a number of authors; for example, both Cr VI and Cr III salts were clastogenic for cultured human leukocytes (Nakamuro et al., 1978).

There are no long-term studies of ingested Cr VI. There appears to be significant in vivo conversion of Cr VI to Cr III and III to VI; Cr III is an essential trace element.

CARO - NO DATA
CARI -
o CLASSIFICATION : A; human carcinogen
o BASIS FOR CLASSIFICATION : Results of occupational epidemiologic studies

of chromium-exposed workers are consistent across investigators and study populations. Dose- response relationships have been established for chromium exposure and lung cancer. Chromium-exposed workers are exposed to both chromium III and chromium VI compounds. Because only chromium VI has been found to be carcinogenic in animal studies, however, it was concluded that only chromium VI should be classified as a human carcinogen.

o INHALATION UNIT RISK : 1.2E-2 per (ug/cu.m)
o DOSE EXTRAPOLATION METHOD : Multistage, extra risk
o RISK/AIR CONCENTRATIONS :

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	8E-3 ug/cu.m
E-5 (1 in 100,000)	8E-4 ug/cu.m
E-6 (1 in 1,000,000)	8E-5 ug/cu.m

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o INHALATION DOSE-RESPONSE DATA :

Species/Strain Tumor Type	Dose	Tumor Incidence		Reference
human	Route: Occupational exposure (inhalation)			
Age (years)	Midrange (ug/cu.m)	Deaths from Lung Cancer	Person Years	
50	5.66	3	1345	Mancuso, 1975
	25.27	6	931	
	46.83	6	299	
60	4.68	4	1063	
	20.79	5	712	
	39.08	5	211	
70	4.41	2	401	
	21.29	4	345	

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o ADDITIONAL COMMENTS :

The cancer mortality in Mancuso (1975) was assumed to be due to Cr VI, which was further assumed to be no less than one-seventh of total chromium. It was also assumed that the smoking habits of chromate workers were similar to those of the U.S. white male population. The unit risks of Langard et al. (1980), Axelsson et al. (1980), and Pokrovskaya and Shabynina (1973) are 1.3E-1, 3.5E-2 and 9.2E-2 per (ug/cu.m), respectively.

Hexavalent chromium compounds have not produced lung tumors in animals by inhalation. Trivalent chromium compounds have not been reported as carcinogenic by any route of administration.

The unit risk should not be used if the air concentration exceeds 8E-1 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

Results of studies of chromium exposure are consistent across investi-

gators and countries. A dose-relationship for lung tumors has been established. The assumption that the ratio of Cr III to Cr VI is 6:1 may lead to a 7-fold underestimation of risk. The use of 1949 hygiene data, which may underestimate worker exposure, may result in an overestimation of risk. Further overestimation of risk may be due to the implicit assumption that the smoking habits of chromate workers were similar to those of the general white male population, since it is generally accepted that the proportion of smokers is higher for industrial workers than for the general population.

CARDR-
o CARCINOGENICITY SOURCE :

Mancuso, T.F. 1975. International Conference on Heavy Metals in the Environment. Toronto, Ontario, Canada.

U.S. EPA. 1984. Health Assessment Document for Chromium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-83-014F.

The quantification of cancer risk in the 1984 Health Assessment Document has received peer review in public sessions of the Environmental Health Committee of the U.S. EPA's Science Advisory Board.
DOCUMENT

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o REVIEW DATES : 06/26/86
o VERIFICATION DATE : 06/26/86
o EPA CONTACTS :

Herman J. Gibb / ORD -- (202)260-5898 / FTS 260-5898

Chao W. Chen / ORD -- (202)260-5719 / FTS 260-5719

HAONE-

NOTE: All chromium HAs are based on total chromium (III and VI).

Appropriate data for calculating a One-day HA are not available. It is recommended that the Ten-day HA of 1.4 mg/L be used as the One-day HA.

HATEN-

NOTE: All chromium HAs are based on total chromium (III and VI).

Ten-day HA -- 1.4E+0 mg/L

NOAEL -- 14.4 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Gross and Heller, 1946

Rats were exposed to drinking water containing Cr(VI) (K_2CrO_4) at levels of 80 or 134 mg Cr(VI)/L for 60 days (8.3 or 14.4 mg Cr(VI)/kg/day, respectively) without adverse effects. Therefore, a NOAEL of 14.4 mg/kg/day is identified.

HALTC-

NOTE: All chromium HAs are based on total chromium (III and VI).

Longer-term (Child) HA -- 2.4E-1 mg/L

NOAEL -- 2.4 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal study -- MacKenzie et al., 1958

In a 1-year drinking water study, consumption of water containing either Cr(III) (CrCl3) or Cr(VI) (K2CrO4) (0 to 1.87 mg/kg/day for male rats and 0 to 2.41 mg/kg/day for female rats) produced no significant differences in weight gain, appearance, or pathological changes in the blood or other tissue. Therefore, a NOAEL of 2.41 mg/kg/day is identified.

HALTA-

NOTE: All chromium HAs are based on total chromium (III and VI).

Longer-term (Adult) HA -- 8.4E-1 mg/L

NOAEL -- 2.4 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 2 L/day water consumption for a 70-kg adult

Principal study -- MacKenzie et al., 1958 (study described in HALTC)

HALIF-

NOTE: All chromium HAs are based on total chromium (III and VI).

Drinking Water Equivalent Level (DWEL) -- 1.7E-1 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date = 02/05/86 (see RDO)

Lifetime HA -- 1.2E-1 mg/L

Assumptions -- 71% exposure by drinking water

Principal study -- MacKenzie et al., 1958 (This study was used in the derivation of the chronic oral RfD; see RDO)

OLEP -

No data available

ALAB -

Determination of chromium is by an atomic absorption technique using either direct aspiration into a flame or a furnace.

TREAT-

The treatment technologies that are available to remove chromium from water include coagulation/filtration, lime softening, ion exchange, and reverse osmosis.

HADR -
o HEALTH ADVISORY SOURCE :

U.S. EPA. 1985. Draft of the Drinking Water Criteria Document on Chromium. Office of Drinking Water, Washington, DC.
DOCUMENT

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o HEALTH ADVISORY REVIEW :

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

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o EPA DRINKING WATER CONTACT :

Kenneth Bailey / ODW -- (202)260-5535 / FTS 260-5535

Edward V. Ohanian / ODW -- (202)260-7571 / FTS 260-7571

ACUTE- NO DATA
BCF - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption -- 5.0E+1 ug/L

Fish Consumption Only -- None

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 5.0E+1 ug/L is based on consumption of contaminated aquatic organisms and water.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute -- 1.6E+1 ug/L (1-hour average)
Chronic -- 1.1E+1 ug/L (4-day average)

Marine:

Acute -- 1.1E+3 ug/L (1-hour average)
Chronic -- 5.0E+1 ug/L (4-day average)

Considers technological or economic feasibility? -- NO

Discussion -- Criteria were derived from a minimum data base on all forms of chromium consisting of acute and chronic tests on a variety of species. Requirements and methods are covered in the reference to the Federal Register.

Reference -- 50 FR 30784 (07/28/85)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 0.1 mg/L [total chromium] (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.1 mg/L for total chromium (Cr III and Cr VI) is based on the EPA's RfD methodology for Cr VI, the more toxic chromium species. The MCLG is based upon a DWEL of 0.17 mg/L calculated from available human and animal data and an assumed drinking water contribution of 20 percent. An uncertainty factor of 500 was applied. The MCLG also falls into the safe and adequate daily dietary intake range of 50 to 200 mg/day for Cr III established by the National Research Council in the National Academy of Sciences (NAS, 1989).

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value (status) -- 0.1 mg/L [total chromium] (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- The EPA has established an MCL equal to the MCLG of 0.1 mg/L.

Monitoring requirements -- Ground water systems monitored every three years; surface water systems monitored annually; systems out of compliance must begin monitoring quarterly until system is reliably and consistently below MCL.

Analytical methodology -- Atomic absorption/furnace technique (EPA 218.2; SM 304); inductively coupled plasma (EPA 200.7): PQL= 0.01 mg/L.

Best available technology -- Coagulation/filtration; ion exchange; reverse osmosis.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 10 pound (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The RQ for chromium (VI) is based on potential carcinogenicity. Available epidemiological data on inhalation of hexavalent chromium indicate a hazard ranking of high based on a potency factor of 388.99/mg/kg/day and assignment to weight-of-evidence group A. This corresponds to an RQ of 1 pound. In addition, a 10 pound adjustment has been applied based on BHP.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed (total chromium)

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

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OREF - Petrilli, F.L. and S. DeFlora. 1977. Toxicity and mutagencity of hexavalent chromium on Salmonella typhimurium. Appl. Environ. Microbiol. 33(4): 805-809.
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HAREF- U.S. EPA. 1985. Drinking Water Criteria Document on Chromium. Office of Drinking Water, Washington, DC. (Draft)

PRINT DL

1 - IRIS
IRSN - 37
DATE - 920120
UPDT - 01/20/92, 52 fields
STAT - Oral RfD Assessment (RDO) on-line 04/01/89
STAT - Inhalation RfC Assessment (RDI) pending
STAT - Carcinogenicity Assessment (CAR) on-line 02/01/91
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 03/31/87 CAR Carcinogenicity Section added
IRH - 03/01/88 RDO Dose conversion clarified
IRH - 03/01/88 RDO Contact changed
IRH - 03/01/88 CAREV Text added
IRH - 03/01/88 CARO Text revised
IRH - 03/01/88 CARO Confidence statement revised
IRH - 03/01/88 CARI Text added
IRH - 03/01/88 CARI Confidence statement revised
IRH - 06/30/88 RDO Changed primary contact's telephone number
IRH - 12/01/88 CAREV van Durren et al. citation year corrected
IRH - 04/01/89 RDO Oral RfD summary noted as pending change
IRH - 12/01/89 RDI Inhalation RfD now under review
IRH - 03/01/90 CAR Clarified NTP, 1982 citation
IRH - 03/01/90 REFS Bibliography on-line
IRH - 01/01/91 CAR Text edited
IRH - 01/01/91 CARI Inhalation slope factor removed (global change)
IRH - 02/01/91 CARI Information on extrapolation process included
IRH - 08/01/91 OREF References clarified
IRH - 08/01/91 CREF References clarified
IRH - 01/01/92 EXSR Regulatory actions updated
RLEN - 24762
NAME - 1,1-Dichloroethylene
RN - 75-35-4
SY - CHLORURE DE VINYLIDENE
SY - 1,1-DCE
SY - 1,1-DICHLOROETHENE
SY - Dichloroethylene, 1,1-
SY - ETHENE, 1,1-DICHLORO-
SY - ETHYLENE, 1,1-DICHLORO-
SY - NCI-C54262
SY - RCRA WASTE NUMBER U078
SY - SCONATEX
SY - UN 1303
SY - VDC
SY - Vinylidene Chloride
SY - VINYLIDENE DICHLORIDE
SY - VINYLIDINE CHLORIDE

-
RDO -
o ORAL RFD SUMMARY :

NOTE: The Oral RfD for 1,1,-dichloroethylene may change in the near future pending the outcome of a further review now being conducted by the Oral RfD Work Group.

Critical Effect	Experimental Doses*	UF	MF	RfD
Hepatic lesions	NOAEL: none	1000	1	9E-3 mg/kg/day

Rat Chronic Oral Bioassay	LOAEL: 50 ppm (converted to 9 mg/kg/day)

Quast et al., 1983

*Conversion Factors: Doses were calculated by the authors.

o ORAL RFD STUDIES :

Quast, J.F., C.G. Humiston, C.E. Wade, et al. 1983. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride. Fund. Appl. Toxicol. 3: 55-62.

Groups of 48 each male and female Sprague-Dawley rats (Spartan substrain) were administered 50, 100, or 200 ppm 1,1-dichloroethylene in drinking water for a period of 2 years. Control groups of 80 animals/sex were maintained for the same period. Daily intake was calculated by the authors to be 7, 10, or 20 mg/kg bw/day for males and 9, 14, or 30 mg/kg bw/day for females. There were no treatment-related effects on mortality, body or organ weight, clinical chemistry, urinalysis, hematology, or numbers of tumors. The only pathologic findings were of hepatic lesions, generally characterized by minimal mid-zonal hepatocellular fatty change and hepatocellular swelling. These findings were noted in rats of all female treatment groups. In male rats, only the 200 ppm treatment group showed a statistically significant increase in the incidence of hepatocellular swelling, but this trend was also observed in animals receiving 100 ppm 1,1-dichloroethylene.

As part of this same study, beagle dogs (4/sex/group) were administered 6.25, 12.5, or 25 mg/kg bw/day in gelatin capsules. Treatment for 97 days had no effect.

This study, as well as a review of the available data, indicate that the liver is the most sensitive target organ and, futhermore, that rats are the most sensitive species. The drinking water exposure reported by Quast et al. (1983) offers a more suitable model for potential human exposure to 1,1-dichloroethylene than does the NTP bioassay wherein animals were gavaged. It is, therefore, appropriate to set an RfD based on the LOAEL of 9 mg/kg bw/day for hepatic lesions in female rats.

o ORAL RFD UNCERTAINTY :

UF = 1000. A factor of 10 each was used for use of a LOAEL, for interspecies variation, and for protection of sensitive human subpopulations.

o ORAL RFD MODIFYING FACTOR :

MF = 1.

o ORAL RFD COMMENTS :

1,1-Dichloroethylene has been shown to be fetotoxic, but not teratogenic to rodents after exposure in drinking water or by inhalation (Short et al., 1977; Murray et al., 1979).

o ORAL RFD CONFIDENCE :

Study: Medium
Data Base: Medium
RfD: Medium

The study by Quast et al. (1983) was conducted using appropriate numbers of animals of two species, measured several endpoints, and was of chronic duration (rats). Since there are corroborative chronic and subchronic oral bioassays, confidence in the study, data base, and RfD are considered medium.

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o ORAL RFD SOURCE DOCUMENT :

U.S. EPA. 1985. Drinking Water Criteria Document for 1,1-Dichloroethylene (Vinylidene Chloride). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

This document has received a lengthy internal review and has undergone public comments.

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o REVIEW DATES : 01/22/85
o VERIFICATION DATE : 01/22/85
o EPA CONTACTS :

Charles Abernathy / ODW -- (202)260-5374 / FTS 260-5374

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

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RDI -
o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

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CAREV-
o CLASSIFICATION : C; possible human carcinogen
o BASIS FOR CLASSIFICATION : Tumors observed in one mouse strain after inhalation exposure is the basis for this classification. Other studies were of inadequate design. Vinylidene chloride is mutagenic, and a metabolite is known to alkylate and to bind covalently to DNA. It is structurally related to the known human carcinogen, vinyl chloride.
o HUMAN CARCINOGENICITY DATA :

Inadequate. An epidemiologic study of 138 workers showed no carcinogenic effect associated with vinylidene chloride exposure (Ott et al., 1976). Based on power considerations, this study is inadequate for assessing cancer risk in humans.

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o ANIMAL CARCINOGENICITY DATA :

Limited. Eighteen animal studies have been reported, which provide information about the carcinogenic potential of vinylidene chloride. Eleven of the studies involved inhalation exposure, five were oral, and one each was by skin application and subcutaneous injection. Most were not designed for maximum sensitivity to detect carcinogenic effects. None of the 11 inhalation exposures were for lifetime; all were 12 months or less. Three of the five oral studies were of lifetime exposures. Of all the studies, only one inhalation study produced a response as a complete carcinogen.

In the inhalation study by Maltoni et al. (1985) both sexes of Swiss mice were exposed to 10 and 25 ppm (MTD) for 4-5 days/week for 12 months. A statistically significant increase in kidney adenocarcinoma was noted in male mice. Although statistically significant increases in mammary carcinomas in female mice and pulmonary adenomas in both sexes were reported, dose-response relationships were unclear. A second Maltoni study exposed Sprague-Dawley rats to 10, 25, 50, 100, or 150 ppm, 4-5 days/week for 12 months and observed them until spontaneous death. A statistically significant increase in total mammary tumors, but not carcinomas alone, was seen only at 10 and 100 ppm. No dose-response relationship was apparent, and the overall interpretation of the mammary tumor incidence is inconclusive.

Four gavage studies (in rats and mice) and one drinking water study in rats have been negative (Maltoni et al., 1985; Quast et al., 1983; Humiston et al., 1978; NTP, 1982; Ponomarkov and Tomatis, 1980). Only the NTP (1982) corn oil gavage study in Fischer 344 rats and female 3F1 mice and the drinking water study in Sprague-Dawley rats were undertaken for 2 years dosing. The NTP study was apparently not conducted at the MTD and the drinking water study did not achieve a maximum dose of metabolite. All other oral studies were limited in design and, thus, lacking in sensitivity sufficient to detect a response.

Vinylidene chloride did not act as a comete carcinogen when applied topically or s.c. to ICR/Ha mice but did serve as an initiator when followed by phorbol myristate acetate treatment (Van Duuren et al., 1979).

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o SUPPORTING DATA :

Vinylidene chloride has been shown to be mutagenic for Salmonella typhimurium in multiple assays. This activity is largely dependent on the presence of microsomal enzymes. It has been used as a positive control in studies of chemicals that are gases at or near room temperature. Both conventional and host-mediated assays of Saccharomyces cerevisiae have been positive for mitotic gene conversion (Bronzetti et al., 1981). Vinylidene chloride was not mutagenic for V79 cells exposed to vapor in vitro (Drevon and Kuroki, 1979), nor did it produce chromosomal aberrations in bone marrow cells of ICR mice given single or repeated i.p. treatment in vivo (Cerna and Kypenova, 1977). CD-1 mice and Sprague-Dawley rats treated in vivo with labeled vinylidene

chloride showed evidence of DNA alkylation and subsequent repair which was specific to liver and kidney. Kidney in rat and mouse had higher alkylation than liver (Reitz et al., 1980). Covalent binding of vinylidene chloride closely correlates with metabolite formation. McKenna et al. (1977) observed greater binding in kidney than liver, and greater binding in mice than in rats. Vinylidene chloride failed to induce dominant lethal mutations in mice (Anderson et al., 1977) or rats (Short et al., 1977). Vinylidene chloride is structurally related to the known carcinogen, vinyl chloride.

CARO -

o CLASSIFICATION : C; possible human carcinogen

o BASIS FOR CLASSIFICATION : Tumors observed in one mouse strain after inhalation exposure is the basis for this classification. Other studies were of inadequate design. Vinylidene chloride is mutagenic, and a metabolite is known to alkylate and to bind covalently to DNA. It is structurally related to the known human carcinogen, vinyl chloride.

o ORAL SLOPE FACTOR : 6E-1 per (mg/kg)/day

o DRINKING WATER UNIT RISK : 1.7E-5 per (ug/L)

o DOSE EXTRAPOLATION METHOD : Linearized multistage procedure, extra risk

o RISK/WATER CONCENTRATIONS :

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	6E+0 ug/L
E-5 (1 in 100,000)	6E-1 ug/L
E-6 (1 in 1,000,000)	6E-2 ug/L

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o ORAL DOSE-RESPONSE DATA :

Species/Strain Tumor Type	Dose Administered	Dose Human Equivalent	Tumor Incidence	Reference
Rat, F344, male; adrenal pheochromocytomas	mg/kg/day	mg/kg/day		NTP, 1982
	0	0	6/50	
	0.71	0.120	5/48	
	3.57	0.603	13/47	

Human equivalent doses were determined by adjusting the administered animal dose by the cube root of the ratio of the weight of the animal (estimated 0.43 kg) to human weight (70 kg), and adjusting for length of exposure and length of the experiment.

The unit risk estimate chosen was derived from the highest of four slope factors calculated from two studies that did not show a statistically significant increase in tumor incidence attributable to oral exposure of vinylidene chloride. The drinking water study in rats (Quast et al., 1983) produced the lowest slope factor of 0.2 per (mg/kg)/day. The highest slope factor [0.6 per (mg/kg)/day] was based on male rat adrenal tumors from NTP (1982). Use of data from this study wherein there were no statistically significant increases in tumor incidence appears justified, since the slope

factor derived is within a factor of 2 of the slope factor based on data from the inhalation study of Maltoni et al. (1977, 1985).

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o ADDITIONAL COMMENTS :

Animal pharmacokinetic data show that metabolite elimination is dose-dependent and saturable at inhalation concentrations of 150-200 ppm, or approximately 50 mg/kg oral ingestion. Vinylidene chloride is rapidly absorbed, has limited solubility, and is not stored in body tissues. Pharmacokinetics and metabolism data indicate that the available assays were not of adequate design. The positive Maltoni inhalation study comes closest to achieving a maximum dose of metabolite, albeit less than lifetime exposure, but less than maximum dosing vis-a-vis metabolites. The water unit risk based on incidence data from a drinking water study was chosen because route of administration is appropriate to oral risk estimation.

The unit risk should not be used if the water concentration exceeds 6E+2 ug/L, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

The estimate is based on a data set in which there is no significant increase in tumor incidence. The confidence that the upper limit is not greater than 0.6 per (mg/kg)/day is high, since it is the largest value by a factor of 3 from four rat data sets in two studies. If drinking water exposure alone is considered the estimates might be reduced by a factor of 3.

The slope factors for the oral quantitative estimate based on data from inhalation exposure and based on the negative oral data are within a factor of 2.

CARI -

o CLASSIFICATION : C; possible human carcinogen

o BASIS FOR CLASSIFICATION : Tumors observed in one mouse strain after inhalation exposure is the basis for this classification. Other studies were of inadequate design. Vinylidene chloride is mutagenic, and a metabolite is known to alkylate and to bind covalently to DNA. It is structurally related to the known human carcinogen, vinyl chloride.

o INHALATION UNIT RISK : 5.0E-5 per (ug/cu.m)

o DOSE EXTRAPOLATION METHOD : Linearized multistage procedure, extra risk

o RISK/AIR CONCENTRATIONS :

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E+0 ug/cu.m
E-5 (1 in 100,000)	2E-1 ug/cu.m
E-6 (1 in 1,000,000)	2E-2 ug/cu.m

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o INHALATION DOSE-RESPONSE DATA :

Species/Strain Tumor Type	Dose Administered	Dose Human Equivalent	Tumor Incidence	Reference
Mouse/Swiss, male; kidney adenocarcinoma	Route: Inhalation			Maltoni et al., 1977, 1985
	ppm	mg/kg/day		
	0	0	0/56	
	0	0	0/70	
	10	0.078	0/25	
	25	0.195	3/21	
	25	0.195	25/98	

-

o ADDITIONAL COMMENTS :

Within each same dose pair there were no statistically significant differences between incidences in the two control and the 25 ppm groups. These groups were combined for modeling. The number of animals surviving to appearance of the first kidney adenocarcinoma was used as the denominator for incidence. Human equivalent doses were determined assuming 0.035 kg as the average weight of the male mice, adjusting for continuous lifetime exposure in the mice, accounting for metabolism and pharmacokinetics for mice, and using 70 kg weight and with 1.85 sq.m surface area for humans (U.S. EPA, 1985). A slope factor of 1.2E+0 per (mg/kg)/day was calculated using estimated animal administered doses.

The unit risk should not be used if the air concentration exceeds 2E+2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

Sufficient numbers of animals were used for treatment and control groups. Treatment was for approximately 50% of lifetime. Only two dose points provided data suitable for modeling.

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CARDR-

o CARCINOGENICITY SOURCE :

U.S. EPA. 1985. Health Assessment Document for Vinylidene Chloride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-83-031F.

The values in the 1985 Health Assessment Document for Vinylidene Chloride

received extensive peer and public review.
DOCUMENT

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o REVIEW DATES : 12/04/86, 01/07/87
o VERIFICATION DATE : 01/07/87
o EPA CONTACTS :

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Steven P. Bayard / ORD -- (202)260-5722 / FTS 260-5722

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WQCHU-

Water and Fish Consumption -- 3.3E-2 ug/L

Fish Consumption Only -- 1.85E+0 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, zero may not be attainable at this time, so the recommended criteria represents a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

-

-

WQCAQ-

Freshwater:

Acute LEC -- 1.16E+4 ug/L
Chronic LEC -- None

Marine:

Acute LEC -- 2.24E+5 ug/L
Chronic LEC -- None

Considers technological or economic feasibility? -- NO
Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the

minimum data required to derive water quality criteria are not available. The value given is for the class of dichloroethylenes, and not specifically for 1,1-dichlorolethylene.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 0.007 mg/L (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.007 mg/L for 1,1-dichloroethylene is proposed based on an RfD and an assumed drinking water contribution of 20%. The RfD was calculated based on the DWEL of 350 ug/L from an animal study in which liver effects were noted. An additional safety factor of 10 (for carcinogenicity) was applied.

Reference -- 50 FR 46880 (11/13/85)

EPA Contact -- Health and Ecological Criteria Division / OST / (202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value (status) -- 0.007 mg/L (Final, 1987)

Considers technological or economic feasibility? -- YES

Discussion -- EPA has set an MCL equal to the MCLG of 0.007 mg/L.

Monitoring requirements -- All systems to be monitored for four consecutive quarters; repeat monitoring dependent upon detection, vulnerability status and system size.

Analytical methodology -- Gas chromatography (EPA 502.1, 502.2, 503.1); gas chromatographic/mass spectrometry (EPA 524.1, 524.2).

Best available technology -- Packed tower aeration; granular activated carbon.

Reference -- 52 FR 25690 (07/08/87); 56 FR 30266 (07/01/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

1 - IRIS
NAME - cis-1,2-Dichloroethylene
RN - 156-59-2
IRSN - 444
DATE - 920122
UPDT - NO DATA
STAT - Oral RfD Assessment (RDO) pending
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 12/01/90
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 12/01/90 CAR Carcinogen assessment on-line
IRH - 12/01/90 REFS Bibliography on-line
IRH - 01/01/92 EXSR Regulatory Action section on-line
RLEN - 6429
SY - Ethene, 1,2-dichloro-, (Z)-
SY - (Z)-1,2-Dichloroethene
SY - (Z)-1,2-DICHLOROETHYLENE
SY - cis-DICHLOROETHYLENE
SY - CIS-1,2-DICHLORETHYLENE
SY - CIS-1,2-DICHLOROETHENE
SY - cis-1,2-DICHLOROETHYLENE
SY - Ethene, 1,2-dichloro-, (Z)-
SY - Ethylene, 1,2-dichloro-, (Z)-
SY - HSDB 5656
SY - NSC 6149
SY - 1,2-CIS-DICHLOROETHYLENE

RDO -
o ORAL RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

RDI - NO DATA
CAREV-
o CLASSIFICATION : D; not classifiable as to human carcinogenicity
o BASIS FOR CLASSIFICATION : Based on no data in humans or animals and generally nonpositive results in mutagenicity assays.
o HUMAN CARCINOGENICITY DATA :

None.

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o ANIMAL CARCINOGENICITY DATA :

None.

---

o SUPPORTING DATA :

cis-1,2-Dichloroethylene did not yield positive results for a Salmonella typhimurium spot test assay in the absence of mammalian liver homogenates; however, this compound did cause a dose-dependent increase in mutations in a host-mediated assay (Cerna and Kypenova, 1977). cis-1,2-Dichloroethylene at a medium concentration of 2.9 mM produced no positive results in a mutagenicity assay for Escherichia coli K12 (Greim et al., 1975). Galli et al. (1982a) reported no positive results for cis-1,2-dichloroethylene in point mutation, mitotic gene conversion and mitotic recombination assays (all for

Saccharomyces cerevisiae). In addition, it did not yield positive results in an in vivo (intravenous) host-mediated mutagenicity assay (Galli et al., 1982b). cis-1,2-Dichloroethylene did not induce chromosomal aberrations in mouse bone marrow in vivo (Cerna and Kypenova, 1977).

CARO - NO DATA
CARI - NO DATA
CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1984. Health Effects Assessment for cis-1,2-Dichloroethylene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

The 1984 Health Effects Assessment document has received Agency review and has been approved for publication as an EPA document.
DOCUMENT

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o REVIEW DATES : 09/07/89
o VERIFICATION DATE : 09/07/89
o EPA CONTACTS :

Lorenz Rhomberg / ORD -- (202)260-5723 / FTS 260-5723

Rita S. Schoeny / ORD -- (513)569-7544 / FTS 684-7544

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption -- 3.3E-2 ug/L

Fish Consumption Only -- 1.85E+0 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero.

However, zero may not be attainable at this time, so the recommended criteria represents a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute LEC -- 1.16E+4 ug/L
Chronic LEC -- None

Marine:

Acute LEC -- 2.24E+5 ug/L
Chronic LEC -- None

Considers technological or economic feasibility? -- NO
Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available. The value given is for the class of dichloroethylenes, and not specifically for 1,1-dichlorolethylene.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value -- 0.07 mg/L (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- A MCLG of 0.07 mg/L is promulgated based on potential adverse effects (hepatic toxicity) reported in compound specific data. The MCLG is based upon a DWEL of 0.4 mg/L and an assumed drinking water contribution of 20 percent.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 0.07 mg/L (Final, 1991)

Considers technological or economic feasibility? -- YES

Discussion -- EPA has set a MCL equal to the MCLG of 0.07 mg/L.

Monitoring requirements -- All systems initially monitored for four

consecutive quarters; repeat monitoring dependant upon detection, vulnerability status and system size.

Analytical methodology -- Purge and trap capillary gas chromatography (EPA 502.2): PQL=0.005 mg/L.

Best available technology -- Granular activated carbon; packed tower aeration

Reference -- 56 FR 3526 (01/30/91); 56 FR 30266 (07/01/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC - NO DATA

SARA - NO DATA

RCRA - NO DATA

TSCA -

No data available

OREF - None
IREF - None
CREF - Cerna, M. and H. Kypenova. 1977. Mutagenic activity of chloroethylenes analyzed by screening system tests. Mutat. Res. 46(3): 214-215.
CREF - Galli, A., C. Bauer, G. Bronzetti, et al. 1982a. Attivita genetica dell' 1,2-dichloroetilene. a) Studio in vitro. Boll. Soc. Ital. Biol. Sper. 58: 860-863. (Ital.)
CREF - Galli, A., C. Bauer, G. Bronzetti, et al. 1982b. Attivita genetica dell' 1,2-dichloroetilene. b) Studio in vivo: Effecto sugli enzimi microsomiali. Boll. Soc. Ital. Biol. Sper. 58: 864-869. (Ital.)
CREF - Greim, H., G. Bonse, Z. Radwan, D. Reichert and D. Henschler. 1975. Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. Biochem. Pharmacol. 24(21): 2013-2017.
CREF - U.S. EPA. 1984. Health Effects Assessment for cis-1,2-Dichloroethylene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the

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       Office of Solid Waste and Emergency Response, Washington, DC.
HAREF- None

[IRIS] SS 16 /cf?
USER:
find 7727-37-9

    Search in progress

NP (7727-37-9 (IRIS))
*NONE-

[IRIS] SS 16 /cf?
USER:
nfind nitrogen

    Search in progress

NITROGEN APPEARS IN THE FOLLOWING CATEGORIES IN IRIS:
   #      CATEGORY     POSTINGS
   1      ID    **           2
   2      NCAR  **          21
   3      CAR   **           1
   4      DWHA  **           9
   5      EXSR  **           8
   6      REFS  **           5
SPECIFY NUMBERS, EXPAND, ALL OR NONE-
USER:
```

1 - IRIS
NAME - Dichloromethane
RN - 75-09-2
IRSN - 68
DATE - 920120
UPDT - 01/20/92, 52 fields
STAT - Oral RfD Assessment (RDO) on-line 03/01/88
STAT - Inhalation RfC Assessment (RDI) pending 09/01/91
STAT - Carcinogenicity Assessment (CAR) on-line 01/01/91
STAT - Drinking Water Health Advisories (DWHA) on-line 03/01/88
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 04/20/87 CARI Unit Risk corrected from 4.1E-4 to 4.1E-6
IRH - 05/21/87 CAREV Missing text replaced in 3rd paragraph
IRH - 03/01/88 RDO Dose conversion clarified
IRH - 03/01/88 RDO Text revised
IRH - 03/01/88 CARO Text revised
IRH - 03/01/88 CARO Confidence statement revised
IRH - 03/01/88 CARI Text revised
IRH - 03/01/88 CARI Confidence statement revised
IRH - 03/01/88 CARDR Primary contact changed
IRH - 03/01/88 HADV Health Advisory added
IRH - 01/01/89 CAR Carcinogen summary noted as pending change
IRH - 10/01/89 CARO Inhalation rate corrected in paragraph 1
IRH - 10/01/89 CARI Dose corrections in mg/kg/day
IRH - 10/01/89 CARI Inhalation rate corrected in paragraph 1
IRH - 10/01/89 CARDR Contacts phone number changed
IRH - 08/01/90 RCRA EPA contact changed
IRH - 09/01/90 CAR Carcinogen assessment revised following re-evaluation
IRH - 09/01/90 CARI Inhalation unit risk changed
IRH - 09/01/90 REFS Bibliography on-line
IRH - 01/01/91 CARI Paragraph moved to II.C.3.
IRH - 01/01/91 CARI Inhalation slope factor removed (global change)
IRH - 08/01/91 CREF Citations clarified
IRH - 09/01/91 RDI Inhalation RfC now under review
IRH - 01/01/92 EXSR Regulatory actions updated
RLEN - 35600
SY - Aerothene MM
SY - Chlorure de methylene
SY - DCM
SY - Dichlormethan, uvasol
SY - Dichloromethane
SY - 1,1-Dichloromethane.
SY - Freon 30
SY - Methane dichloride
SY - Methane, dichloro-
SY - Methylene bichloride
SY - Methylene Chloride
SY - Methylene dichloride
SY - Metylenu chlorek
SY - Narkotil
SY - NCI-C50102
SY - R 30
SY - Solaesthin
SY - Solmethine
SY - WLN: G1G
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA

VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver toxicity 2-Year Rat Drinking Water Bioassay National Coffee Association, 1982	NOAEL: 5.85 and 6.47 mg/kg/day for males and females, respectively LOAEL: 52.58 and 58.32 mg/kg/day for males and females, respectively	100	1	6E-2 mg/kg/day

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*Conversion Factors: Doses reflect actual values and not nominal ones.

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o ORAL RFD STUDIES :

National Coffee Association. 1982. 24-Month chronic toxicity and oncogenicity study of methylene chloride in rats. Final Report. Prepared by Hazleton Laboratories America, Inc., Vienna, VA. (Unpublished)

The chosen study appears to have been very well conducted, with 85 rats/sex at each of four nominal dose groups (i.e., 5, 50, 125 and 250 mg/kg/day) for 2 years. A high-dose recovery group of 25 rats/sex, as well as two control groups of 85 and 50 rats/sex, was also tested. Many effects were monitored. Treatment related histological alterations of the liver were evident at nominal doses of 50 mg/kg/day or higher. The low nominal dose of 5 mg/kg/day was a NOAEL.

The supporting data base is limited. A NOAEL of 87 mg/cu.m was reported in one inhalation study (Haun et al., 1972). [The equivalent oral dose is about 28 mg/kg bw/day (i.e., 87 mg/cu.m x 0.5 x 0.223 cu.m/day/0.35 kg; these exposure values are for rats).]

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o ORAL RFD UNCERTAINTY :

UF = 100. (10a x 10h) The 100-fold factor accounts for both the expected intra- and interspecies variability to the toxicity of this chemical in lieu of specific data.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

None.

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o ORAL RFD CONFIDENCE :

Study: High
Data Base: Medium
RfD: Medium

The study is given a high confidence rating because a large number of animals of both sexes were tested in four dose groups, with a large number of controls. Many effects were monitored and a dose-related increase in severity was observed. The data base is rated medium to low because only a few studies support the NOAEL. Medium confidence in the RfD follows.

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o ORAL RFD SOURCE DOCUMENT :

U.S. EPA. 1985. Drinking Water Criteria Document for Methylene Chloride. Office of Drinking Water, Washington, DC.

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o REVIEW DATES : 06/24/85, 07/08/85, 11/06/85
o VERIFICATION DATE : 11/06/85
o EPA CONTACTS :

Krishan Khanna / ODW -- (202)260-7588 / FTS 260-7588

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

RDI -
o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

CAREV-
o CLASSIFICATION : Classification --B2; probable human carcinogen
o BASIS FOR CLASSIFICATION : Based on inadequate human data and sufficient evidence of carcinogenicity in animals; increased incidence of hepatocellular neoplasms and alveolar/bronchiolar neoplasms in male and female mice, and increased incidence of benign mammary tumors in both sexes of rats, salivary gland sarcomas in male rats and leukemia in female rats. This classification is supported by some positive genotoxicity data, although results in mammalian systems are generally negative.
o HUMAN CARCINOGENICITY DATA :

Inadequate. Neither of two studies of chemical factory workers exposed to dichloromethane showed an excess of cancers (Ott et al., 1983; Friedlander et al., 1978; Hearne and Friedlander, 1981). The Ott et al. (1983) study was designed to examine cardiovascular effects, and consequently the study period was too short to allow for latency of site-specific cancers. In the Friedlander et al. (1978) study, exposures were low, but the data provided some suggestion of an increased incidence of pancreatic tumors. This study was recently updated to include a larger cohort, followed through 1984, and an investigation of possible confounding factors (Hearne et al., 1986, 1987). A nonsignificant excess in pancreatic cancer deaths was observed, which was interpreted by EPA (1987a) as neither clear evidence of carcinogenicity in humans, nor evidence of noncarcinogenicity. An update of the Ott et al. (1983) study, based on longer follow-up, indicated possible elevation of liver and biliary tract cancers (TSCA section 8(e) submission no. 8eHQ-0198-0772 FLWP et seq., 1989).

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. Dichloromethane administered in the drinking water induced a

significant increase in combined hepatocellular carcinoma and neoplastic nodules in female F344 rats and a nonsignificant increase in combined hepatocellular carcinoma and neoplastic nodules in male B6C3F1 mice (NCA, 1982, 1983). Two inhalation studies with dichloromethane have shown an increased incidence of benign mammary tumors in both sexes of Sprague-Dawley (Burek et al., 1984) and F344 (NTP, 1986) rats. Male Sprague-Dawley rats had increased salivary gland sarcoma (Burek et al., 1984) and female F344 rats had increased leukemia incidence (NTP, 1986). Both sexes of B6C3F1 mice developed liver and lung tumors after dichloromethane treatment (NTP, 1986).

In a 2-year study by the National Coffee Association (1982, 1983), groups of 85 F344 rats/sex/dose received 5, 50, 125, or 250 (mg/kg)/day of dichloromethane in the drinking water. Control groups consisted of 135 rats/sex. In female rats the incidence of combined hepatocellular carcinoma and neoplastic nodules was statistically significantly increased in the 50 and 250 mg/kg dose groups when compared with matched controls (0/134, 1/85, 4/83, 1/85, and 6/85 in the five dose groups 0, 5, 50, 125, and 250 (mg/kg)/day, respectively). The incidence of hepatocellular carcinoma alone was not significantly increased (0/134, 0/85, 2/83, 0/85, 2/85). The combined incidence of hepatocellular carinoma and neoplastic nodules in controls and the 4 dose groups (472 rats: 4 with carcinoma and 8 with neoplastic nodules) was similar to that for historical controls (419 rats; 5 with carcinoma, 19 with neoplastic nodules). Male rats showed no increase in liver tumors.

In the same National Coffee Association study (1982, 1983), B6C3F1 mice received 0, 60, 125, 185, or 250 (mg/kg)/day of dichloromethane in drinking water. Treatment groups consisted of 50 female mice and 200, 100, 100, and 125 male mice (low to high dose). One hundred females and 125 males served as controls. Male mice had an increased incidence of combined neoplastic nodules and hepatocellular carcinoma (24/125, 51/200, 30/100, 31/99, 35/125). The increase was not dose-related, but the pairwise comparisons for the two mid-dose groups were reported to be statistically significant (U.S. EPA, 1985a). The hepatocellular carcinoma incidence alone for male mice (which was about 55 to 65% of the total) was not significantly elevated. Female mice did not have increased liver tumor incidence. The EPA (1985b) regarded this study as suggestive but not conclusive evidence for carcinogenicity of dichloromethane.

A gavage bioassay of dichloromethane conducted by NTP (1982) has not been published because of high mortality, much of which was attributed to gavage accidents.

Inhalation exposure of 107 to 109 Syrian hamsters/sex/dose to 0, 500, 1500, or 3500 ppm of dichloromethane for 6 hours/day, 5 days/week for 2 years did not induce neoplasia (Burek et al., 1984). Sprague-Dawley rats (129/sex/dose) were exposed under the same conditions. Female rats administered the highest dose experienced significantly reduced survival from 18-24 months. Female rats showed a dose-related increase in the average number of benign mammary tumors per rat (1.7, 2.3, 2.6, 3.0), although the numbers of rats with tumors were not significantly increased. A similar response was observed in male rats, but to a lesser degree. In the male rats there was a statistically significant positive trend in the incidence of sarcomas of the salivary gland (1/93, 0/94, 5/91, 11/88); the incidence was significantly elevated at the high dose. There is a question as to whether these doses reached the MTD, particularly in the hamsters and the male rats. In another study (Dow Chemical Co., 1982), 90 Sprague-Dawley rats/sex were exposed by inhalation to 0, 50, 200, or 500 ppm dichloromethane for 20 months (male) or 24 months (female). No salivary tumors were observed, but there was an exposure-related increase in the total number of benign mammary tumors in female rats, although the increase was not statistically significant in any individual exposure group.

Groups of 50 each male and female F344/N rats and B6C3F1 mice were exposed to dichloromethane by inhalation, 6 hours/day, 5 days/week for 2 years (NTP, 1986). Exposure concentrations were 0, 1000, 2000, or 4000 ppm for rats and

0, 2000, or 4000 ppm for mice. Survival of male rats was low; however, this apparently was not treatment-related. Survival was decreased in a treatment-related fashion for male and female mice and female rats. Mammary adenomas and fibroadenomas were significantly increased in male and female rats after survival adjustment, as were mononuclear cell leukemias in female rats. Among treated mice of both sexes there were significantly increased incidences of hepatocellular adenomas and carcinomas, and of alveolarbronchiolar adenomas and carcinomas, by life table tests. Adenomas and carcinomas were significantly increased alone as well as in combination. In addition, there were significant dose-related increases in the number of lung tumors per animal multiplicity in both sexes of mice.

Two inhalation assays using dogs, rabbits, guinea pigs, and rats showed no tumors, but were not conducted for the lifetime of the animals (Heppel et al., 1944; MacEwen et al., 1972). Theiss et al., (1977) injected Strain A male mice intraperitoneally with 0, 160, 400, or 800 mg/kg of dichloromethane 16 to 17 times, over 5 to 6 weeks. Survival of the animals was poor. The animals remaining 24 weeks after the first treatment were killed and examined for lung tumors; pulmonary adenomas were found.

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o SUPPORTING DATA :

Dichloromethane was mutagenic for Salmonella typhimurium with or without the addition of hepatic enzymes (Green, 1983) and produced mitotic recombination in yeast (Callen et al., 1980). Results in cultured mammalian cells have generally been negative, but dichloromethane has been shown to transform rat embryo cells and to enhance viral transformation of Syrian hamster embryo cells (Price et al., 1978; Hatch et al., 1983). Although chlorinated solvents have often been suspected of acting through a nongenotoxic mechanism of cell proliferation, Lefevre and Ashby (1989) found methylene chloride to be unable to induce hepatocellular division in mice.

CARO -

o CLASSIFICATION	: Classification --B2; probable human carcinogen
o BASIS FOR CLASSIFICATION	: Based on inadequate human data and sufficient evidence of carcinogenicity in animals; increased incidence of hepatocellular neoplasms and alveolar/bronchiolar neoplasms in male and female mice, and increased incidence of benign mammary tumors in both sexes of rats, salivary gland sarcomas in male rats and leukemia in female rats. This classification is supported by some positive genotoxicity data, although results in mammalian systems are generally negative.
o ORAL SLOPE FACTOR	: 7.5E-3 per (mg/kg)/day
o DRINKING WATER UNIT RISK	: 2.1E-7 per (ug/L)
o DOSE EXTRAPOLATION METHOD	: Linearized multistage procedure, extra risk
o RISK/WATER CONCENTRATIONS :	

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	5E+2 ug/L
E-5 (1 in 100,000)	5E+1 ug/L
E-6 (1 in 1,000,000)	5E+0 ug/L

---

o ORAL DOSE-RESPONSE DATA :

Tumor Type -- hepatocellular adenomas or carcinomas (NTP) and hepatocellular cancer and neoplastic nodules (NCA)
Test Animals -- mouse/B6C3F1 (female, NTP; male, NCA)
Route -- inhalation (NTP); oral/drinking water (NCA)
Reference -- NTP, 1986; National Coffee Association (NCA), 1983

Dose				
Administered (ppm)	mg/kg/day	Human Equivalent (mg/kg)/day	Tumor Incidence	Reference
0	0	0	3/50	NTP, 1986
2000	1582	122	16/48	
4000	3162	244	40/48	
	0	0	24/125	NCA, 1983
	60	4.5	51/200	
	125	9.4	30/100	
	185	14.0	31/99	
	250	18.9	35/125	

o ADDITIONAL COMMENTS :

The slope factor is an arithmetic mean of slope factors derived from NTP(1986) and the National Coffee Association (1983) data, 2.6E-3 per (mg/kg)/day and 1.2E-2 per (mg/kg)/day, respectively. The use of liver tumor data from the NTP inhalation bioassay was considered valid since dichloromethane is rapidly absorbed following either inhalation or ingestion.

Dose conversions used the mean body weight for female mice at the midpoint of the bioassay, and an estimated inhalation rate of 0.0407 cu.m/day. To obtain estimates of unit risk for humans, an inhalation rate of 20 cu.m/day was assumed. Dichloromethane was considered to be well-absorbed as a vapor at low doses. No pharmacokinetic or metabolism data have been used to modify the oral unit risk estimate, because such analyses have not yet been carried out.

The unit risk should not be used if the water concentration exceeds 5E+4 ug/L, since above this concentration the unit risk may not be appropriate.

o DISCUSSION OF CONFIDENCE :

Adequate numbers of animals were used in both assays. Risk estimates were based on the more sensitive sex in each study. The two risk estimates were within a factor of 5.

CARI -

o CLASSIFICATION : Classification --B2; probable human carcinogen

o BASIS FOR CLASSIFICATION : Based on inadequate human data and sufficient evidence of carcinogenicity in animals; increased incidence of hepatocellular neoplasms and alveolar/bronchiolar neoplasms in male and female mice, and increased incidence of benign mammary tumors in both sexes of rats, salivary gland sarcomas in male rats and leukemia in female rats. This

classification is supported by some positive genotoxicity data, although results in mammalian systems are generally negative.

o INHALATION UNIT RISK : 4.7E-7 per (ug/cu.m)
o DOSE EXTRAPOLATION METHOD : Linearized multistage procedure, extra risk
o RISK/AIR CONCENTRATIONS :

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E+2 ug/cu.m
E-5 (1 in 100,000)	2E+1 ug/cu.m
E-6 (1 in 1,000,000)	2E+0 ug/cu.m

---

o INHALATION DOSE-RESPONSE DATA :

Tumor Type -- combined adenomas and carcinomas
Test Animals -- mouse/B6C3F1, female
Route -- inhalation
Reference -- NTP, 1986

	Dose			
Tumor Type	Administered (ppm)	Transformed Animal (mg/kg)/day	Human Equivalent (mg/kg)/day	Tumor Incidence
Liver	0	0	0	3/45
	2000	1582	356	16/46
	4000	3162	712	40/46
Lung	0	0	0	3/45
	2000	1582	356	30/46
	4000	3162	712	41/46

---

o ADDITIONAL COMMENTS :

The unit risk of 4.7E-7 per (ug/cu.m), which incorporates information on pharmacokinetics and metabolism of dichloromethane, is approximately nine-fold lower than the previous applied dose estimate (U.S. EPA, 1987a,b). Internal dose estimates were based on the metabolism of dichloromethane by the glutathione-s-transferase pathway, as estimated by the model developed by Andersen et al. (1987). The internal dose was corrected for interspecies differences in sensitivity by using the surface area correction factor.

Calculation of a slope factor from the unit risk is inappropriate when pharmacokinetic models are used. (When dose-response relationships are figured on the basis of internal or metabolized dose, a slope factor in terms of per (mg/kg)/day represents a back calculation using different absorption assumptions than the pharmacokinetic models. This introduces possible contradictions.)

The unit risk should not be used if the air concentration exceeds 2E+4 ug/cu.m, since above this concentration the unit risk may differ from that stated. Since the unit risk is based on a pharmacokinetic model, the risk may change with alterations in exposure patterns. Thus, the unit risk presented here may not be applicable to acute, high exposures.

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o DISCUSSION OF CONFIDENCE :

Adequate numbers of animals were observed and tumor incidences were significantly increased in a dose-dependent fashion. Analysis excluding animals that died before observation of the first tumors produced similar

risk estimates, as did time-to-tumor analysis. The use of animal and human metabolism and pharmacokinetic data reduces some of the uncertainty typically associated with dose-risk extrapolation. A great deal of uncertainty still exists, however, in the estimates of internal dose generated by the model of Andersen et al. (1987). Important uncertainties remain regarding the pharmacokinetics, pharmacodynamics, and mechanisms of carcinogenicity for dichloromethane.

CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1985a. Health Assessment Document for Dichloromethane (Methylene Chloride). Final Report. Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-82/004F.

U.S. EPA. 1985b. Addendum to the Health Assessment Document for Dichloromethane (methylene chloride). Updated carcinogenicity assessment. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC. EPA/600/8-82/004FF.

U.S. EPA. 1987a. Update to the Health Assessment Document and Addendum for Dichloromethane (Methylene Chloride): Pharmacokinetics, Mechanism of Action and Epidemiology. Review Draft. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/030A.

U.S. EPA. 1987b. Technical Analysis of New Methods and Data Regarding Dichloromethane Hazard Assessments. Review Draft. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8- 87/029A.

The Addendum to the Health Assessment Document, the Update to the Health Assessment Document and Addendum, and the Technical Analysis of New Methods and Data for dichloromethane have received Agency and external review, including a review by the Science Advisory Board (SAB). Although the last two documents are not yet finalized and the SAB comments are not yet incorporated, these do not alter this document's analyses or conclusions.

DOCUMENT

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o REVIEW DATES : 11/12/86, 12/04/86, 04/06/89
o VERIFICATION DATE : 04/06/89
o EPA CONTACTS :

Lorenz Rhomberg / ORD -- (202)260-5723 / FTS 260-5723

Dharm V. Singh / ORD -- (202)260-5898 / FTS 260-5898

HAONE-

One-day HA -- 1.33E+1 mg/L

LOAEL -- 1326 mg/kg/day
UF -- 1000 (allows for interspecies and intrahuman variability with the use of a LOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Kimura et al., 1971

Single oral doses of dichloromethane were administered to young adult

Sprague-Dawley rats. An approximate dose of 1.3 g/kg was the lowest dose to induce the first observable gross signs of toxicity.

HATEN-

Ten-day HA -- 1.5E+0 mg/L

NOAEL -- 15 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Bornmann and Loeser, 1967

Male and female Wistar rats were administered dichloromethane in drinking water for 13 weeks at a dose of 15 mg/kg/day. No treatment-related effects were observed.

HALTC-

Appropriate data for calculating a Longer-term HA is not available. It is recommended that a modified DWEL (adjusted for a 10-kg child) of 0.5 mg/L be used as the Longer-term HA.

HALTA-

Appropriate data for calculating a Longer-term HA is not available. It is recommended that the DWEL of 1.75 mg/L be used as the Longer-term HA for the 70-kg adult.

HALIF-

Drinking Water Equivalent Level (DWEL) -- 1.75E+0 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date = 11/06/85

Lifetime HA -- None

Dichloromethane is considered to be a probable human carcinogen. Refer to CAR for information on the carcinogenicity of this substance.

Principal Study (DWEL) -- National Coffee Association, 1982 (This study was used in the derivation of the chronic oral RfD; see RDO)

OLEP -

No data available

ALAB -

Analysis of dichloromethane is by a purge-and-trap gas chromatographic procedure used for the detection of volatile organohalides in drinking water. Confirmatory analysis is by mass spectrometry.

TREAT-

The available information suggests that adsorption by granular activated carbon and air stripping are feasible technologies to remove dichloromethane from drinking water.

HADR -
o HEALTH ADVISORY SOURCE :

U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Dichloromethane. Office of Drinking Water, Washington, DC.
DOCUMENT

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o HEALTH ADVISORY REVIEW :

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

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o EPA DRINKING WATER CONTACT :

Krishan Khanna / ODW -- (202)260-7588 / FTS 260-7588

Edward V. Ohanian / ODW -- (202)260-7571 / FTS 260-7571

ACUTE- NO DATA
BCF - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption: 1.9E-1 ug/L

Fish Consumption Only: 1.57E+1 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- Methylene chloride is classified as a carcinogen, and under the assumption of no threshold for a carcinogen, the recommended WQC is zero. However, if zero cannot be obtained and exposure is via ingestion of water and aquatic organisms, 0.19 ug/L is associated with an upper-bound excess lifetime risk of 1.0E-6 [other risk levels to consider: 1.0E-5 (1.9 ug/L) and 1.0E-7 (0.019 ug/L)]. If exposure is only via ingestion of aquatic organisms, the WQC associated with an upper-bound excess lifetime risk of 1.0E-6 is 15.7 ug/L. The criteria are based on halomethanes as a class.

Reference -- 45 FR 79318 (11/13/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute LEC -- 1.1E+4 ug/L
Chronic -- None

Marine:

Acute LEC -- 1.2E+4 ug/L
Chronic LEC -- 6.4E+3 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available. The values given represent halomethanes as a class.

Reference -- 45 FR 79318 (11/13/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value -- 0 mg/L (Proposed, 1990)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed MCLG for dichloromethane is zero based on the evidence of carcinogenic potential (B2).

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 0.005 mg/L (Proposed, 1990)

Considers technological or economic feasibility? -- YES

Discussion -- The proposed MCL is equal to the PQL of 0.005 and is associated with a maximum lifetime individual risk of E-5.

Monitoring requirements -- All systems monitored every 3 or 5 years (dependent upon system size), except for non-vulnerable surface water systems with no detection of VOCs; vulnerable systems to be monitored quarterly; repeat monitoring dependent upon vulnerability, detection and system size.

Analytical methodology -- Purge and trap gas chromatography (EPA 503.1); purge and trap gas chromatographic/mass spectrometry (EPA 524.1): PQL= 0.005 mg/L.

Best available technology -- Packed tower aeration.

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

Status -- Listed (Final, 1987)

Discussion -- "Unregulated" contaminants are those contaminants for which EPA establishes a monitoring requirement but which do not have an associated final MCLG, MCL, or treatment technique. EPA may regulate these contaminants in the future.

Monitoring requirement -- Monitoring required for all water systems at a minimum frequency of once every 5 years.

Analytical methodology -- Gas chromatography (EPA 502.1, 502.2, 503.1); gas chromatographic/mass spectrometry (EPA 524.1, 524.2).

Reference -- 56 FR 25690 (07/08/87)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final adjusted RQ of 1000 pounds is based upon a chronic toxicity score of 10. This substance has recently been identified for assessment of carcinogenicity, and the RQ will be reevaluated when that assessment is completed.

Reference -- 50 FR 13456 (04/04/85); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

___IV.E.1. TSCA, SECTION 6

Status -- Advance Notice of Proposed Rulemaking (ANPR) (1985)

Discussion -- Initiated priority review under TSCA, sect. 6, of risks from cancer which may be associated with certain exposures to methylene chloride. Receipt of a positive NTP bioassay triggered an accelerated analysis under TSCA, sect. 4(f). Based on its preliminary analysis, the Agency decided that methylene chloride should be classified as a B2 probable human carcinogen under its Interim Cancer Guidelines. TSCA, sect. 4(f), requires that the Agency initiate appropriate action under sect. 5, 6, or 7 within a 180-day period of receipt of health effect information which triggers a sect. 4(f) decision. The sect. 6 ANPR initiated appropriate action.

Reference: 50 FR 42005 (10/17/85)

EPA Contact -- Chemical Control Division / OTS (202)260-3749 / FTS 260-3749

OREF - Haun, C.C., E.H. Vernot, K.I. Darmer Jr. and S.S. Diamond. 1972. Continous animal exposure to low levels of dichloromethane. AMRL-TR-72-13. In: Proceedings of the 3rd Annual Conference on Environmental Toxicology, Wright- Patterson Air Force Base, Ohio, Aerospace Medical Research Laboratory. p. 199-208.

OREF - National Coffee Association. 1982. 24-Month chronic toxicity and oncogenicity study of methylene chloride in rats. Final Report. Prepared by Hazleton Laboratories America, Inc., Vienna, VA. (Unpublished)

OREF - U.S. EPA. 1985. Drinking Water Criteria Document for Methylene Chloride. Office of Drinking Water, Washington, DC.

IREF - None

CREF - Andersen, M.E., H.J. Clewell, III, M.L. Gargas, F.A. Smith and R.H. Reitz. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol. Appl. Pharmacol. 87: 185-205.

CREF - Burek, J.D., K.D. Nitschke, T.J. Bell, et al. 1984. Methylene chloride: A two year inhalation toxicity and oncogenicity study in rats and hamsters. Fund. Appl. Toxicol. 4: 30-47.

CREF - Callen, D.F., C.R. Wolf and R.M. Philpot. 1980. Cytochrome P-450 mediated genetic activity and cytotoxicity of seven halogenated aliphatic hydrocarbons in Saccharomyces cerevisiae. Mutat. Res. 77: 55-63.

CREF - Dow Chemical Company. 1982. Methylene chloride: A two-year inhalation and oncogenicity study in rats. Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Company, Midland, MI.

CREF - Friedlander, B.R., F.T. Hearne and S. Hall. 1978. Epidemiologic investigation of employees chronically exposed to methylene chloride. J. Occup. Med. 20(10): 657-666.

CREF - Green, T. 1983. The metabolic activation of dichloromethane and chlorofluoromethane in a bacterial mutation assay using Salmonella typhimurium. Mutat. Res. 118(4): 277-288.

CREF - Hatch, G.G., P.D. Mamay, M.L. Ayer, B.C. Casto and S. Nesnow. 1983.

Chemical enhancement of viral transformation in Syrian hamster embryo cells by gaseous and volatile chlorinated methanes and ethanes. Cancer Res. 43: 1945-1950.

CREF - Hearne, F.T. and B.R. Friedlander. 1981. Follow-up of methylene chloride study. J. Occup. Med. 23: 660.

CREF - Hearne, F.T., F. Grose, J.W. Pifer and B.R. Friedlander. 1986. Methylene chloride mortality study update. Eastman Kodak Company, Rochester, NY. June 16.

CREF - Hearne, F.T., F Grose, J.W. Pifer, B.R. Friedlander and R.L. Raleigh. 1987. Methylene Chloride mortality study: dose-response characterization and animal model comparison. J. Occup. Med. 29 (3): 217-228.

CREF - Heppel, L.A., P.A. Neal, T.L. Perrin, M.L. Orr and V.T. Porterfield. 1944. Toxicology of dichloromethane (methylene chloride). I. Studies on effects of daily inhalation. J. Ind. Hyg. Toxicol. 26(1): 8-21.

CREF - Lefevre, P.A. and J. Ashby. 1989. Evaluation of dichloromethane as an inducer of DNA synthesis in B6C3F1 mouse liver. Carcinogenesis. 10(6): 1067-1072.

CREF - MacEwen, J.D., E.H. Vernot and C.C. Haun. 1972. Continuous animal exposure to dichloromethane. AMRL-TR-72-28, Systems Corporation Report No. W-71005. Wright Patterson Air Force Base, Ohio, Aerospace Medical Research. AD746295.

CREF - NCA (National Coffee Association). 1982. Twenty-four-month chronic toxicity and oncogenicity study of methylene chloride in rats. Final Report. Prepared by Hazleton Laboratories, America, Inc., Vienna, VA. Unpublished.

CREF - NCA (National Coffee Association). 1983. Twenty-four month oncogenicity study of methylene chloride in mice. Final Report. Prepared by Hazleton Laboratories, America, Inc., Vienna, VA.

CREF - NTP (National Toxicology Program). 1982. Draft technical report on the carcinogenesis bioassay of dichloromethane (methylene chloride) (CAS No. 75- 09-2) in F344/N rats and B6C3F1 mice (gavage study). Research Triangle Park, NC and Bethesda, MD. Unpublished. NTP-82-061.

CREF - NTP (National Toxicology Program). 1986. Toxicology and carcinogenesis studies of dichloromethane (methylene chloride) (CAS No. 75-09-2) in F344/N rats and B6C3F1 mice (inhalaltion studies). NTP-TRS-306.

CREF - Ott, M.G., L.K. Skory, B.B. Holder, J.M. Bronson and P.R. Williams. 1983. Health evaluation of employees occupationally exposed to methylene chloride: Mortality. Scand. J. Work Environ. Health. 9(Suppl. 1): 8-16.

CREF - Price, P.J., C.M. Hassett and J.I. Mansfield. 1978. Transforming activities of trichloroethylene and proposed industrial alternatives. In Vitro. 14(3): 290-293.

CREF - Thiess, J.C., G.D. Stoner, M.B. Shimkin and E.K. Weisburger. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res. 37: 2717-2720.

CREF - Toxic Substances Control Act. 1989. Section 8(e) submission no. 8eHQ-0198- 0772 FLWP et seq.

CREF - U.S. EPA. 1985a. Health Assessment Document for Dichloromethane (Methylene Chloride). Final Report. Office of Health and Environmental Assessment, Washington, D.C. EPA/600/8-82/004F.

CREF - U.S. EPA. 1985b. Addendum to the Health Assessment Document for Dichloromethane (methylene chloride). Updated carcinogenicity assessment. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC. EPA/600/8- 82/004FF.

CREF - U.S. EPA. 1987a. Update to the Health Assessment Document and Addendum for Dichloromethane (Methylene Chloride): Pharmacokinetics, Mechanism of Action and Epidemiology. Review Draft. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/030A.

CREF - U.S. EPA. 1987b. Technical Analysis of New Methods and Data Regarding Dichloromethane Hazard Assessments. Review Draft. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8- 87/029A.

HAREF- Bornmann, G., and A. Loeser. 1967. Zur Frage einer chronisch-toxischen

Wirkung von Dichloromethan. Z. Lebensm.-Unters. Forsch. 136: 14-18.
HAREF- Kimura, E.T., D.M. Ebert and P.W. Dodge. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19: 699-704.
HAREF- National Coffee Association. 1982. 24-Month chronic toxicity and oncogenicity study of methylene chloride in rats. Final Report. Prepared by Hazleton Laboratories America, Inc., Vienna, VA. (Unpublished)
HAREF- U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Dichloromethane. Office of Drinking Water, Washington, DC.

2 - IRIS
NAME - Formaldehyde
RN - 50-00-0
IRSN - 393
DATE - 920122
UPDT - NO DATA
STAT - Oral RfD Assessment (RDO) on-line 09/01/90
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 05/01/91
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 10/01/89 CAR Carcinogen summary on-line
IRH - 10/01/89 REFS Bibliography on-line
IRH - 12/01/89 RDO Oral RfD now under review
IRH - 02/01/90 REFS Supplementary data on-line
IRH - 09/01/90 RDO Oral RfD summary on-line
IRH - 09/01/90 CAR Text edited
IRH - 09/01/90 OREF Oral RfD references added
IRH - 01/01/91 CAR Text edited
IRH - 01/01/91 CARI Inhalation slope factor removed (global change)
IRH - 05/01/91 CARI Corrected units in risk level concentrations
IRH - 08/01/91 ? Citations clarified
IRH - 01/01/92 EXSR Regulatory Action section on-line
RLEN - 33771
SY - ALDEHYDE FORMIQUE (FRENCH)
SY - ALDEHYD MRAVENCI (CZECH)
SY - ALDEIDE FORMICA (ITALIAN)
SY - BFV
SY - FA
SY - FORMALDEHYD (CZECH, POLISH)
SY - FORMALDEHYDE
SY - FORMALDEHYDE SOLUTION (DOT)
SY - FORMALIN
SY - FORMALITH
SY - FORMIC ALDEHYDE
SY - FORMOL
SY - FYDE
SY - HOCH
SY - IVALON
SY - KARSAN
SY - LYSOFORM
SY - METHANAL
SY - METHYL ALDEHYDE
SY - METHYLENE GLYCOL
SY - METHYLENE OXIDE
SY - MORBICID
SY - NCI-C02799
SY - OPLOSSINGEN (DUTCH)
SY - OXOMETHANE
SY - OXYMETHYLENE
SY - PARAFORM
SY - POLYOXYMETHYLENE GLYCOLS
SY - RCRA WASTE NUMBER U122
SY - SUPERLYSOFORM
SY - UN 1198 (DOT)
SY - UN 2209 (DOT)
MF - Chemical Formula: CH2O
USE - Urea and melamine resins; polyacetal resins; phenolic resins; ethylene glycol; pentaerythritol; hexamethylenetetramine; fertilizer; dyes, medicine (disinfectant, germicide); embalming fluids; preservative; hardening agent; reducing agent, as in recovery of gold and silver; corrosion inhibitor in oil wells; durable-press treatment of textile fabrics; possible condensation to sugars and other carbohydrates for food use (experimental); industrial sterilant; treatment of grain smut

(Hawley, 1977, p. 395).
COFO - Appearance and Odor: Gas or liquid, strong, pungent odor, clear, water-white (Sax, 1984, p. 145).
ODOR - Appearance and Odor: Gas or liquid, strong, pungent odor, clear, water-white (Sax, 1984, p. 145).
BP - Boiling Point: -3.1F, -19.5C at 760 mmHg (Merck, 1976); commercial aqueous formaldehyde boils at 205F, 96C (Merck, 1983, p. 604)
MP - Melting Point: -134F, -92C (Merck, 1976), for anhydrous form
MW - Molecular Weight: 30.03
DEN - Specific Gravity (H2O=1): 1.067 (Merck, 1976); 0.815 at -20C/4C for anhydrous form (Merck, 1983, p. 604)
VAP - Vapor Pressure (mmHg): 10 at -88C (Patty, 1963), for anhydrous form
VAPD - Vapor Density (AIR=1): 1.03 for aqueous solution; 1.075 for gas (Environment Canada, 1982), 1.067 for gas (Merck, 1983, p. 604)
EVAP - Evaporation Rate (Butyl acetate=1): Not Found
SOLW - Solubility in Water: Very soluble in water, up to 55% (Merck, 1976)
FLPT - Flash Point (Method Used): 60C/40% solution (Merck, 1976)
FLMT - Flammable Limits: LEL: 7% (Sax, 1975) UEL: 73% (Sax, 1975)
AVOI - Avoid contact with oxidizing and alkaline materials (NFPA, 1978). Formaldehyde reacts with peroxide, nitrogen oxide, and performic acid causing explosions (Environment Canada, 1982). Formaldehyde can react with hydrogen chloride or other inorganic chlorides to form bis-chloromethylether (BCME), a known carcinogen (General Electric Co. 1981, MSDS 360). Formaldehyde is very reactive and combines readily with many substances; a 40% solution is a powerful reducing agent (Merck, 1976). Formaldehyde is incompatible with amines, azo compounds, dithiocarbamates, alkali and alkaline earth metals, nitrides, nitro compounds, unsaturated aliphatics and sulfides, organic peroxides, oxidizing agents, and reducing agents (Environment Canada 1982). This compound will polymerize with active organic materials such as phenol (General Electric Co., 1981, MSDS 360). Formaldehyde will polymerize violently in the presence of caustics and nitrides: (amines) exothermic reaction, (Azo compound) exothermic reaction giving off nitrogen gas, (caustics) heat generation and violent polymerization, (dithiocarbamates) formation of flammable gases and toxic fumes, formation of carbon disulfide may result, (alkali and alkaline earth metals) heat generation and formation of a flammable hydrogen gas (Environment Canada, 1982).
DCMP - Hazardous Decomposition or Byproducts: When heated, irritant formaldehyde gas is evolved from solution (Sax, 1984, p. 1452). The main products of decomposition are carbon monoxide and hydrogen. Metals such as platinum, copper, chromia, and alumina also catalyze the formation of methanol, methylformate, formic acid, carbon dioxide, and methane (Kirk-Othmer 1978).

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Reduced weight gain, histopathology in rats	NOAEL: 15 mg/kg/day LOAEL: 82 mg/kg/day	100	1	2E-1 mg/kg/day

Rat 2-Year Bioassay

Til et al., 1989

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* Conversion Factors: none

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o ORAL RFD STUDIES :

Til, H.P., R.A. Woutersen, V.J. Feron, V.H.M. Hollanders, H.E. Falke and J.J. Clary. 1989. Two-year drinking water study of formaldehyde in rats. Food Chem. Toxicol. 27: 77-87.

Formaldehyde was administered daily in drinking water to Wistar rats (70/sex/dose) for up to 24 months at mean doses of 0, 1.2, 15, or 82 mg/kg/day for males and 0, 1.8, 21, or 109 mg/kg/day for females. Up to 10 rats/sex/dose were sacrificed and examined after 12 months and 18 months of treatment; the remainder was sacrificed and examined at 24 months. Mean body weights of the high-dose group were decreased in males from week 1 and in females from week 24 through termination. Food intake was significantly decreased in all high-dose males with females showing a similar but less consistent decrease in food intake. A 40% decrease in drinking water intake was reported in all high-dose animals while those rats receiving the middle dose showed a slight but generally insignificant decrease in liquid intake. Changes in urinalyses, and hematological and clinical chemistry parameters, were not dose-related, so were not considered to be related to formaldehyde intake. Among the high-dose males, significant decreases were seen in the absolute heart and liver weights at 18 months and at termination; in testes weights at 18 months; and in kidney weights at termination. High-dose females showed significant increases in the relative kidney weights at 12 and 24 months. Relative brain weights were significantly increased in high-dose males at all three examination periods and in females at termination only. Relative testes weights were significantly increased in high-dose males at termination. These relative organ weight increases were generally ascribed to the decreased body weights observed. A significant increase in mortality among males receiving the 15 mg/kg/day dose was not considered toxicologically significant.

Gross examination at 12, 18, and 24 months revealed a raised, thickening of the limiting ridge of the forestomach in most high-dose rats and in some rats of both sexes from other groups. Irregular mucosal thickening of the forestomach and glandular stomach were seen in several rats of the high-dose group and in occasional rats of other groups. The incidence of discoloration and irregularity of the kidney surface and atrophy of the testes was lower in the high-dose group as compared with controls.

Significant histopathological changes of the gastrointestinal tract were found in high-dose males and females and included chronic atrophic gastritis of the glandular stomach from week 53 on, as well as focal ulceration and glandular hyperplasia at the terminal examination. The incidence of focal papillary epithelial hyperplasia and focal hyperkeratosis of the forestomach was significantly increased in both sexes at the terminal examination. These effects of formaldehyde on the gastric mucosa were considered cytotoxic in nature. A significant increase in the incidence of papillary necrosis of the kidneys was reported in both sexes of high-dose rats at the terminal examination. No treatment-related gastric tumors were observed in this study. The incidence and type of tumors observed in other organ systems were common to this strain and similar to those found in aging rats, 30 were not considered toxicologically significant. A NOAEL of 15 mg/kg/day in male rats was indicated in this study.

Formaldehyde was administered daily in the drinking water of Sprague-Dawley rats (15/sex/dose) at doses equivalent to 0, 50, 100, or 150 mg/kg/day for 90 days (Johannsen et al., 1986). Male and female high-dose rats (150 mg/kg/day) and male rats receiving the 100 mg/kg/day dose showed a significant decrease in body weight gain. A dose-related decrease in the intake of drinking water was reported in both sexes of treated rats. Food intake and feed efficiency was comparable among all groups. No statistically significant differences were seen in urinalyses, or hematological and blood chemistry parameters. No treatment-related histopathological findings were observed. A NOAEL of 50 mg/kg/day was indicated for rats.

Similarly, formaldehyde was administered in the diet of pure-bred beagle dogs (4/sex/dose) at doses of 0, 50, 75, or 100 mg/kg/day for 90 days. A significant decrease in body weight gain was reported in the high-dose dogs of both sexes with no effect on weight gain at the two lower dose levels. A

reduced food consumption and feed efficiency was observed in dogs at all treatment levels. No treatment-related effects were seen on hematological, blood chemistry, or urinalysis parameters, nor were any treatment-related lesions observed. The gastrointestinal mucosa was not affected by formaldehyde intake. A NOAEL of 75 mg/kg/day was indicated.

Marks et al. (1980) administered formaldehyde as an aqueous solution to pregnant CD-1 mice at oral doses of 74, 148, and 185 mg/kg on days 6 to 15 of gestation. The high dose was lethal to most of the treated mice by day 18. Mortality was 1/35 and 22/34 among dams treated at 148 and 185 mg/kg/day, respectively. In the high-dose group, the number of resorption sites was increased and mean litter size was slightly decreased. No effects on fetus size, and no gross or microscopic skeletal or soft tissue abnormalities were observed.

Hurni and Ohder (1973) exposed pregnant beagle dogs (9 to 11/group) to formaldehyde in the diet at levels of 125 or 375 ppm from 4 days after mating through day 56. Assuming that 1 ppm in the diet of a 10-kg dog consuming 250 g of dry chow/day equals 0.025 mg/kg/day (Lehman, 1959), this would correspond to doses of 3 or 9 mg/kg/day. The dogs were weighed weekly, and the pups were weighed at birth and twice weekly thereafter. Feeding of formaldehyde had no effect on pregnancy rate, maternal body weight, or duration of gestation. Mean litter sizes were within normal ranges. No effects were reported on growth or mortality. All pups were inspected for defects at birth and at 8 weeks postpartum. Stillborns, as well as pups dying before weaning, were autopsied and examined for internal and skeletal anomalies. Normal behavior, appearance, mobility and muscular coordination were reported for all dogs observed for up to 9 months.

Seidenberg et al. (1987) evaluated formaldehyde in the Chernoff/Kavlock developmental toxicity screen. Formaldehyde was administered by gavage at 540 mg/kg/day to pregnant ICR/SIM mice on gestation days 8 through 12. The mice were allowed to deliver, then several neonatal growth and viability parameters were measured in the offspring. Comparative statistical analysis of these parameters between treated animals and concurrent (vehicle-treated) controls revealed no significant effect on any perinatal parameter examined.

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o ORAL RFD UNCERTAINTY :

UF = 100. An uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

Based on this 2-year study in rats in which a NOAEL is identified, the uncertainty factor of 100 is considered appropriate for extrapolating results to humans. This study consisted of adequate numbers of animals of both sexes as well as a thorough examination of toxicological and histological parameters.

Takahashi et al. (1986) conducted a two-stage carcinogenesis bioassay in male Wistar rats. The animals were administered N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) at 100 mg/L in the drinking water for the first 8 weeks of the study, followed by administration of 0.5% formalin (dose not specified) in the drinking water during weeks 8 through 40. Other groups of animals received just MNNG or formalin (dose not specified). The animals were sacrificed at the termination of dosing and the stomachs were examined grossly and microscopically. The actual doses of formaldehyde received by the test animals is not known, because dose concentrations were not reported, and drinking water consumption was not measured. Formalin did not produce

malignant tumors when given alone. In animals receiving just formalin, forestomach papillomas occurred in 8/10 animals. In rats given MNNG alone, adenocarcinoma of the pylorus occurred in 1/30 rats, preneoplastic hyperplasia of the pylorus occurred in 7/30 rats, and adenocarcinoma of the duodenum occurred in 3/30 rats. In the group administered both MNG and formalin, forestomach papillomas occurred in 15/17 animals, adenocarcinoma of the pylorus in 4/17, preneoplastic hyperplasia of the pylorus in 7/17, and adenocarcinoma of the duodenum in 1/17.

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o ORAL RFD CONFIDENCE :

Study: High
Data Base: Medium
RfD: Medium

Confidence in the critical study is high since it consisted of adequate numbers of animals of both sexes, as well as a thorough examination of toxicological and histological parameters. Confidence in the data base is medium as several additional chronic bioassays and reproductive and developmental stuides support the critical effect and study. Medium confidence in the RfD follows.

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o ORAL RFD SOURCE DOCUMENT :

U.S. EPA. 1989. Draft Drinking Water Health Advisory for Formaldehyde. Office of Drinking Water, Washington, DC.

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o REVIEW DATES : 11/17/89, 05/17/90, 06/20/90
o VERIFICATION DATE : 06/20/90
o EPA CONTACTS :

Jennifer Orme / ODW -- (202)260-7586 / FTS 260-7586

Charles Abernathy / ODW -- (202)260-5374 / FTS 260-5374

RDI - NO DATA
CAREV-
o CLASSIFICATION : B1; probable human carcinogen, based on limited evidence in humans, and sufficient evidence in animals. Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products. An increased incidence of nasal squamous cell carcinomas was observed in long-term inhalation studies in rats and in mice. The classification is supported by in vitro genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes such as acetaldehyde.

o HUMAN CARCINOGENICITY DATA :

Limited. At least 28 relevant epidemiologic studies have been conducted. Among these, two cohort studies (Blair et al., 1986, 1987; Stayner et al., 1988) and one case-control study (Vaughan et al., 1986a,b) were well-conducted and specifically designed to detect small to moderate increases in formaldehyde-associated human risks. Blair et al. studied workers at 10 plants who were in some way exposed to formaldehyde (largely through resin formation) and observed significant excesses in lung and nasopharyngeal cancer

deaths. Despite a lack of significant trends with increasing concentration or cumulative formaldehyde exposure, lung cancer mortality was significantly elevated in analyses with or without a 20-year latency allowance. No explicit control was made for smoking status. Stayner et al. reported statistically significant excesses in mortality from buccal cavity tumors among formaldehyde-exposed garment workers. The highest SMR was for workers with long employment duration (exposure) and follow-up period (latency). The Vaughan et al. nasal and pharyngeal cancer case-control study examined occupational and residential exposures, controlling for smoking and alcohol consumption. It showed a significant association between nasopharyngeal cancer and having lived 10 or more years in a mobile home, especially for mobile homes built in the 1950s to 1970s, a period of increasing formaldehyde-resin usage. No exposure measurements were available.

The 25 other reviewed studies had limited ability to detect small to moderate increases in formaldehyde risks owing to small sample sizes, small numbers of observed site-specific deaths, and insufficient follow-up. Even with these potential limitations, 6 of the 25 studies (Acheson et al., 1984; Hardell et al., 1982; Hayes et al., 1986; Liebling et al., 1984; Olsen et al., 1984; Stayner et al., 1985) reported significant associations between excess site-specific respiratory (lung, buccal cavity, and pharyngeal) cancers and exposure to formaldehyde. Some of these studies looked at potential confounders (such as wood-dust exposure) in greater detail; they did not discern sinonasal cancer incidence excesses of the size predicted. Others (Liebling et al., 1984; Stayner et al., 1985) overlapped the Acheson et al. (1984), Hardell et al. (1982) and Hayes et al. (1986) studies; the improved design and nonoverlapping portions of the later studies (Blair et al., 1986; Stayner et al., 1988) reinforce the conclusions of the earlier studies. Analysis of the remaining 19 studies indicate that leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure. The biological support for such postulates, however, has not yet been demonstrated. Although the common exposure in all of these studies was formaldehyde, the epidemiologic evidence is categorized as "limited" primarily because of the possible exposures to other agents. Such exposures could have contributed to the findings of excess cancers.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. Consequences of inhalation exposure to formaldehyde have been studied in rats, mice, hamsters and monkeys. The principal evidence comes from positive studies in both sexes of two strains of rats (Kerns et al., 1983; Albert et al., 1982; Tobe et al., 1985) and males of one strain of mice (Kerns et al., 1983), all showing squamous cell carcinomas.

For the CIIT, Kerns et al. (1983) exposed about 120 animals/sex/species (Fischer 344 rats and B6C3F1 mice) to 0, 2, 5.6 or 14.3 ppm, 6 hours/day, 5 days/week for 24 months. Five animals per group were sacrificed at 6 and 12 months and 20 per group were killed at 18 months. At 24 and 27 months the number sacrificed is unclear. The studies were terminated at 30 months. From the 12th month on, male and female rats in the highest dose group (14.3 ppm) showed significantly increased mortality compared with controls. In the 5.6-ppm group, male rats showed a significant increase in mortality from 17 months on. Female mice showed generally comparable survival across dose groups, as did male mice, but the male mice as a whole showed increased mortality because of housing problems. Squamous cell carcinomas were seen in the nasal cavities of 51/117 male rats and 52/115 female rats at 14.3 ppm (HDT) by experiment's end (as many as 35 carcinomas had been identified in males by month 18 based on EPA analysis notes and Kerns (Chart 8). At 5.6 ppm, 1/119 male rats and 1/116 female rats showed squamous cell carcinomas of the nasal cavity. No such tumors were seen at 0 or 2 ppm. Polypoid adenomas of the nasal mucosa were seen in rats at all doses (0 ppm: 1/118 M, 0/114 F; 2 ppm: 4/118 M, 4/118 F; 5.6 ppm: 6/119 M, 0/116 F; 14.3 ppm: 4/117 M, 1/115 F) in a significant dose-related trend, albeit one that falls off after a peak. Among the mice, squamous cell carcinomas were seen in two males at 14.3 ppm. No other lesions

were noteworthy.

Sellakumar et al. (1985) exposed male Sprague-Dawley rats, 100/group, 6 hours/day, 5 days/week for lifetime to 10 ppm HCl and to 14 ppm formaldehyde. This was a combined exposure HCl and formaldehyde were administered simultaneously, and each was administered separately. An equal number of rats received an air control. HCl was administered to determine if tumor response was enhanced by an additional irritant effect or by the combining of formaldehyde and HCl to form bis-(chloromethyl)ether (BCME). Groups receiving formaldehyde alone or with HCl showed an increase in nasal squamous cell carcinomas; those without formaldehyde were free of carcinomas and other tumors (0/99 in each group), although rhinitis and hyperplasia were of comparable incidence.

Tobe et al. (1985) conducted a 28-month study of male Fischer 344 rats (about 2 weeks younger than those in Kerns et al., 1983). Groups of 32 rats were exposed 6 hours/day, 5 days/week to 0, 0.3, 2.0, 3,3, or 15 ppm formaldehyde in aqueous solution methanol; another group of 32 was exposed to methanol only (vehicle control). Animals were sacrificed at 12, 18, and 24 months. Exposure to 15 ppm ended at 24 months; at that point, mortality was 88%. At 28 months mortality was 60% in the control group and 32% in the 0.3 dose group. Squamous cell carcinomas were seen at 15 ppm in 14/27 rats surviving past 12 months, compared with 0/27 in the controls. No polypoid adenomas were observed; the increased incidences of rhinitis and hyperplasia were dose-related.

While these three rodent studies are principal in the weight of evidence, inhalation studies have been carried out in other strains and species. Dalbey (1982), as part of a promotion experiment, exposed male Syrian golden hamsters to 10 ppm formaldehyde 5 times/week, 5 hours/day throughout their lifetimes, 132 animals were untreated controls. Although survival time was significantly reduced in the treated group, no tumors were observed in either treated or control groups. Rusch et al. (1983) carried out a 6-month toxicity study in 6 male cynomolgus monkeys, 40 F344 rats (20M, 20F), and 20 Syrian golden hamsters (10M, 10F) with 22 hours/day, 7 days/week exposure to three levels of formaldehyde with corresponding controls. The highest dose tested was 2.95 ppm. The short duration of the assay, the small sample sizes, and, possibly, the low concentrations tested, limited the sensitivity of the assay to detect tumors. In the highest dose group in both rats and monkeys, incidences of squamous metaplasia/hyperplasia of the nasal turbinates were significantly elevated.

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o SUPPORTING DATA :

Mutagenic activity of formaldehyde has been demonstrated in viruses, Escherichia coli, Pseudomonas fluorescens, Salmonella typhimurium and certain strains of yeast, fungi, Drosophila, grasshopper and mammalian cells (Ulsamer et al., 1984). Formaldehyde has been shown to cause gene mutations, single strand breaks in DNA, DNA-protein crosslinks, sister chromatid exchanges and chromosomal aberrations. Formaldehyde produces in vitro transformation in BALB/c 3T3 mouse cells, BHK21 hamster cells and C3H-10T1/2 mouse cells, enhances the transformation of Syrian hamster embryo cells by SA7 adenovirus, and inhibits DNA repair (Consensus Workshop on Formaldehyde, 1984).

When inhaled, acetaldehyde, the closest aldehyde to formaldehyde in structure, causes cancers in the nose and trachea of hamsters, and nasal cancers in rats.

CARO - NO DATA
CARI -
o CLASSIFICATION : B1; probable human carcinogen, based on

limited evidence in humans, and sufficient evidence in animals. Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products. An increased incidence of nasal squamous cell carcinomas was observed in long-term inhalation studies in rats and in mice. The classification is supported by in vitro genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes such as acetaldehyde.

o INHALATION UNIT RISK : 1.3E-5 per (ug/cu.m)
o DOSE EXTRAPOLATION METHOD : Linearized multistage procedure, additional risk

o RISK/AIR CONCENTRATIONS :

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	8E+0 ug/cu.m
E-5 (1 in 100,000)	8E-1 ug/cu.m
E-6 (1 in 1,000,000)	8E-2 ug/cu.m

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o INHALATION DOSE-RESPONSE DATA :

Tumor Type -- squamous cell carcinoma
Test Animals -- Rat/F344, males
Route -- inhalation
Reference -- Kerns et al., 1983

Dose		Tumor
Administered (ppm)	Human Equivalent (mg/kg/day)	Incidence
0	0	0/156
2	2	0/159
5.6	5.6	2/153
14.3	14.3	94/140

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o ADDITIONAL COMMENTS :

In the Kerns et al. (1983) study, rats that died at 11 months (prior to appearance of the first squamous cell carcinoma) were not considered at risk. Those sacrificed at 12 and 18 months were treated as though they would have responded in the same proportion as rats remaining alive at the respective sacrifice times and those living beyond 24 months were included with animals sacrificed at 24 months. From the estimates of the probability of death with tumor within 24 months and its variance, the number of animals at risk and the number with tumors were derived for a 24-month study with no 12- or 18-month kills. These rounded numbers are shown above and were used for significance tests and modeling.

The unit risk should not be used if the air concentration exceeds 8E+2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

The experimental range is close to expected human exposures. Estimated

lifetime excess risks from six epidemiologic studies are close to upper bound risks based on animal data (usually within 1 order of magnitude for four types of estimated occupational and residential exposure). Animal-based estimates derived using time in the model were similar but would have required the use of more assumptions in the calculations. Three non-zero doses were used in addition to controls in the study on which calculations are based, with a large number of animals per group. Male and female incidences were close throughout the exposure groups.

CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1987. Assessment of Health Risk to Garment Workers and Certain Home Residents from Exposure to Formaldehyde. Office of Toxic Substances, Washington, DC.

The OTS Assessment of Health Risk has received wide internal and external review.
DOCUMENT

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o REVIEW DATES : 02/03/88
o VERIFICATION DATE : 02/03/88
o EPA CONTACTS :

R. Hefter / OPTS -- (202)260-6712 / FTS 260-6712

E. Margosches / OTS -- (202)260-1511 / FTS 260-1511

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE-
o ACUTE TOXICITY :

The probable oral lethal dose for humans is 0.5-5 g/kg, or etwen1 ounce and 1 pint for a 150 pound person (Gosselin, 1976). Acute -- below 1 ppm, odor perceptible to most. 2-3 ppm, mild tingling of eyes. 4-5 ppm, increased discomfort, mild lacrimation. 10 ppm, profuse lacrimation; can be withstood only for few minutes. 10-20 ppm, breathing difficult, cough, severe burning of nose and throat. 50-100 ppm, acute irritation of respiratory tract, very serious injury likely. Skin -- primary irritation from strong solutions, gas. Delayed -- sensitization dermatitis (Proctor and Hughes, 1978,

pp. 272-273). Suspected carcinogen (Kirk-Othmer, 1978). Effects in women include menstrual disorders and secondary sterility (IARC, 1972-1985). Solutions splashed in eyes have caused injuries ranging from severe, permanent corneal opacification and loss of vision to minor discomfort (Grant, 1974).

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o SIGNS AND SYMPTOMS :

Irritation of eyes, nose and throat, tearing, cough, bronchospasm, pulmonary irritation, dermatitis (Proctor and Hughes, 1978, p. 273). Severe pain, vomiting and diarrhea result from ingestion. After absorption, formaldehyde depresses the central nervous system and symptoms similar to alcohol intoxication (i.e., vertigo, depression and coma) result. It can also cause a reduction in body temperature (Environment Canada, 1982).

BCF - NO DATA

CAA - NO DATA

WQCHU- NO DATA

WQCAQ- NO DATA

MCLG - NO DATA

MCL - NO DATA

SMCL - NO DATA

FISTD-

Status -- Issued (1986)

Reference -- Formaldehyde Pesticide Registration Standard. September, 1986. (NTIS No. not available) as Amended in May, 1988 (NTIS No. PB88-231543).

EPA Contact -- Registration Branch / OPP
(703)557-7760 / FTS 557-7760

FIREV-

No data available

CERC -

Value (status) -- 100 pounds (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for formaldehyde is based on potential carcinogenicity and adjusted after consideration of the BHP processes. Available data indicate a ranking of medium and a weight of evidence classification of Group B1, which corresponds to an RQ of 10 pounds. The BHP processes adjusts the RQ ranking upward one level corresponding to an RQ of 100 pounds.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline

(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA - NO DATA

TSCA -

No data available

OREF - Hurni, H. and H. Ohder. 1973. Reproduction study with formaldehyde and hexamethylenetetramine in beagle dogs. Food Cosmet. Toxicol. 11: 459-462.

OREF - Johannsen, F.R., G.J. Levinskas and A.S. Tegeris. 1986. Effects of formaldehyde in the rat and dog following oral exposure. Toxicol. Lett. 30: 1-6.

OREF - Marks, T.A., W.C. Worthy and R.E. Staples. 1980. Influence of formaldehyde and sonacide (potentiated acid glutaraldehyde) on embryo and fetal development in mice. Teratology. 22: 51-58.

OREF - Seidenberg, J.M., D.G. Anderson and R.A. Becker. 1986. Validation of an in vivo developmental toxicity screen in the mouse. Teratol. Carcinogen. Mutagen. 6: 361-374.

OREF - Takahashi, M., R. Hasegawa, F. Furukawa, K. Toyoda, H. Sato and Y. Hayashi. 1986. Effects of ethanol, potassium metabisulfite, formaldehyde and hydrogen peroxide on gastric carcinogenesis in rats after initiation with N-methyl- N'nitro-N'nitrosoguanidine. Jap. J. Cancer Res. 77: 118-124.

OREF - Til, H.P., R.A. Woutersen, V.J. Feron, V.H.M. Hollanders, H.E. Falke and J.J. Clary. 1989. Two-year drinking water study of formaldehyde in rats. Food Chem. Toxicol. 27(2): 77-87.

OREF - U.S. EPA. 1989. Draft Drinking Water Health Advisory for Formaldehyde. Office of Drinking Water, Washington, DC.

IREF - None

CREF - Acheson, E.D., M.J. Gardner, B. Pannett, H.R. Barnes, C. Osmond and C.P. Taylor. 1984. Formaldehyde in the British Chemical Industry. The Lancet. p. 611-615.

CREF - Albert, R.E., A.R. Sellakumar, S. Laskin, M. Kuschner, N. Nelson and C.A. Snyder. Gaseous formaldehyde and hydrogen chloride induction of nasal cancer in the rat. J. Natl. Cancer Inst. 68(4): 597-603.

CREF - Blair, A., P.A. Stewart, R.N. Hoover, et al. 1986. Mortality among industrial workers exposed to formaldehyde. J. Natl. Cancer Inst. 76(6): 1071-1084.

CREF - Blair, A., P. Stewart, P.A. Hoover, et al. 1987. Cancers of the nasopharynx and oropharynx and formaldehyde exposure. J. Natl. Cancer Inst. 78(1): 191-193.

CREF - Consensus Workshop on Formaldehyde. 1984. Deliberations of the Consensus Workshop on Formaldehyde, October 3-6, 1983. Little Rock, AK. (Final report)

CREF - Dalbey, W.E. 1982. Formaldehyde and tumors in hamster respiratory tract. Toxicology. 24: 9-14.

CREF - Hardell, L., B. Johansson and O. Axelson. 1982. Epidemiological study of nasal and nasopharyngeal cancer and their relation to phenoxy acid or chlorophenol exposure. Am. J. Ind. Med. 3: 247-257.

CREF - Hayes, R.B., J.W. Raatgever, A. de Bruyn and M. Gerin. 1986. Cancer of the nasal cavity and paranasal sinuses, and formaldehyde exposure. Int. J. Cancer. 37: 487-492.

CREF - Kerns, W.D., K.L. Pavkov, D.J. Donofrio, E.J. Gralla and J.A. Swenberg. 1983. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Res. 43: 4382-4392.

CREF - Liebling, T., K.D. Rosenman, H. Pastides, R.G. Griffith and S.

Lemeshow. 1984. Cancer mortality among workers exposed to formaldehyde. Am. J. Ind. Med. 5: 423-428.
CREF - Olsen, J.H., S.P. Jensen, M. Hink, K. Faurbo, N.O. Breum and O.M. Jensen. 1984. Occupational formaldehyde exposure and increased nasal cancer risk in man. Int. J. Cancer. 34: 639-644.
CREF - Rusch, G.M., J.J. Clary, W.E. Rinehart and H.F. Bolte. 1983. A 26-week inhalation toxicity study with formaldehyde in the monkey, rat and hamster. Toxicol. Appl. Pharmacol. 68: 329-343.
CREF - Sellakumar, A.R., C.A. Snyder, J.J. Solomon and R.E. Albert. Carcinogenicity of formaldehyde and hydrogen chloride in rats. Toxicol. Appl. Pharmacol. 81: 401-406.
CREF - Stayner, L.S., A.B. Smith, G. Reeve, et al. 1985. Proportionate mortality study of workers in the garment industry exposed to formaldehyde. Am. J. Ind. Med. 7: 229-240.
CREF - Stayner, L.T., L. Elliott, L. Blade, R. Keenlyside and W. Halperin. 1988. A retrospective cohort mortality study of workers exposed to formaldehyde in the garment industry. Am. J. Ind. Med. 13(6): 667-682.
CREF - Tobe, M., T. Kaneko, Y. Uchida, et al. 1985. Studies of the inhalation toxicity of formaldehyde. National Sanitary and Medical Laboratory Service (Japan). p. 1-94.
CREF - Ulsamer, A.G., K.C. Gupta, M.S. Cohn and P.W. Preuss. 1982. Formaldehyde in indoor air: Toxicity and risk. In: Proceed. 75th Ann. Meet. Air Pollut. Control Assoc. 16 p.
CREF - U.S. EPA. 1987. Assessment of Health Risk to Garment Workers and Certain Home Residents from Exposure to Formaldehyde. Office of Toxic Substances, Washington, DC.
CREF - Vaughn, T.L., C. Strader, S. Davis and J.R. Daling. 1986a. Formaldehyde and cancers of the pharynx, sinus and nasal cavity: I. Occupational exposures. Int. J. Cancer. 38: 677-683.
CREF - Vaughn, T.L., C. Strader, S. Davis and J.R. Daling. 1986b. Formaldehyde and cancers of the pharynx, sinus and nasal cavity: II. Residential exposures. Int. J. Cancer. 38: 685-688.
HAREF- None

2 - IRIS
NAME - Hydrazine/Hydrazine sulfate
RN - 302-01-2
IRSN - 351
DATE - 920604
UPDT - 06/04/92, 52 fields
STAT - Oral RfD Assessment (RDO) no data
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 04/01/91
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 09/07/88 CAR Carcinogen summary on-line
IRH - 06/01/89 CARDR Secondary contact deleted
IRH - 12/01/89 CAREV 2nd para, deleted Biancifiori et al., 1968
IRH - 12/01/89 REFS Bibliography on-line
IRH - 01/01/91 CAR Text edited
IRH - 01/01/91 CARI Inhalation slope factor removed (global change)
IRH - 02/01/91 CARI Information on extrapolation process included
IRH - 02/01/91 CARDR Title corrected for U.S. EPA, 1986
IRH - 02/01/91 CREF Title corrected for U.S. EPA, 1986
IRH - 04/01/91 CAR Text edited
IRH - 01/01/92 EXSR Regulatory Action section on-line
RLEN - 23494
SY - hydrazine
SY - hydrazine, anhydrous
SY - Hydrazine/Hydrazine sulfate
MF - Chemical Formula: H4N2
USE - Hydrazine is a chemical intermediate for pesticides, blowing agents, photography chemicals, pharmaceuticals, antituberculants, and textile dyes (SRI).
COFO - Appearance and Odor: Colorless, oily liquid with penetrating ammonia-like odor (Merck, 1983).
ODOR - Appearance and Odor: Colorless, oily liquid with penetrating ammonia-like odor (Merck, 1983).
BP - Boiling Point: 236.3F, 113.5C (Merck, 1983)
MP - Melting Point: 36F, 2.0C (Merck, 1983)
MW - Molecular Weight: 32.05
DEN - Specific Gravity (H2O=1): 1.011 at 15C/4C (Merck, 1983)
VAP - Vapor Pressure (mmHg): 14.4 at 25C (Sunshine, 1969)
VAPD - Vapor Density (AIR=1): Not Found
EVAP - Evaporation Rate (Butyl acetate=1): Not Found
SOLW - Solubility in Water: Miscible (Merck, 1983)
FLPT - Flash Point (Method Used): 52C (Merck, 1983)
FLMT - Flammable Limits: LEL: 4.7% (NFPA, 1978) UEL: 100% (NFPA, 1978)
AVOI - Conditions and Materials to Avoid: Hydrazine can catch fire when in contact with porous materials such as wood, asbestos, cloth, earth, and rusty metals (Weiss, 1980, p. 509). This substance is incompatible with oxidizers, hydrogen peroxide, nitric acid, metal oxides, and strong acids (NIOSH/OSHA, 1978, p. 110).
DCMP - Hazardous Decomposition or Byproducts: Decomposition of hydrazine gives off toxic nitrogen compound fumes (Rumack, 1975 to Present).

RDO - NO DATA

RDI - NO DATA

CAREV-

- o CLASSIFICATION : B2; probable human carcinogen.
- o BASIS FOR CLASSIFICATION : Tumors have been induced in mice, rats and hamsters following oral, inhalation or intraperitoneal administration of hydrazine and hydrazine sulfate. Hydrazine is mutagenic in numerous assays.
- o HUMAN CARCINOGENICITY DATA :

Inadequate. A Letter to the Editor by Roe (1978) is the only available report on effects of hydrazine exposure in humans. Mortality data from two hydrazine manufacturing plants (from one company of nine in the field) are presented. Between 1963 and 1975, one company reported two deaths. Both were due to heart disease and were presumed to be unrelated to hydrazine exposure. A second company reported 26 deaths among 272 workers who had been employed at the plant between 1945 and 1970. Two of these deaths were due to stomach cancer. The author noted that the observed and expected deaths were similar and that these occupational exposures to hydrazine are not associated with an increased risk of cancer.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. Biancifiori (1970) conducted a multiple-dose study in which hydrazine sulfate was administered by gavage to groups of 24 to 30 8-week-old CBA/Cb/Se mice of each sex at doses of 0.0, 0.14, 0.28, 0.56, or 1.13 mg/day, 6 days/week for 25 weeks. Animals were observed throughout their lifetimes. Liver carcinomas were induced in a dose-related manner in both sexes and lung metastases were observed in some of the mice treated with 1.13 mg/kg/day. Pulmonary tumors were reportedly present in many of the treated mice, but incidences were not reported because the purpose of the study was to describe hepatic tumors.

Many other water gavage studies of hydrazine sulfate in mice have resulted in increased incidence of lung adenomas/carcinomas. Strains tested included BALB/c (Biancifiori and Ribacchi, 1962), CBA/Cb/Se (Biancifiori et al., 1964; Severi and Biancifiori, 1968), BALB/c x DBA/2 (Kelly et al., 1969) and Swiss (Roe et al., 1967). Hepatomas and hepatocarcinomas were also observed in some strains as a consequence of treatment. Cb/Se rats gavaged with 18 (males) or 12 (females) mg hydrazine sulfate/day showed an increased incidence of lung tumors in both sexes and hepatomas in males only (Severi and Biancifiori, 1968).

Toth (1969) administered 0.012% hydrazine sulfate in the drinking water to groups of 6-week old Swiss, C3H, and AKR mice (40 to 50/sex) for their lifetimes. Groups of 110 Swiss mice and 30 C3H and AKR mice of each sex served as untreated controls. Lung adenomas and adenocarcinomas were reported in 46-50% of the treated Swiss mice (25/50 males and 24/50 females), compared with 9-11% in the controls (11/110 males and 14/110 females). Hydrazine sulfate did not induce significantly increased incidence of tumors at other sites in the Swiss mice, or at any site in the C3H or AKR mice. In a later study, Toth (1972) administered 0.001% hydrazine continuously in the drinking water to 50 Swiss mice/sex for their lifetimes. Lung adenomas and adenocarcinomas were induced in 24/50 of the males and 27/50 of the females (48-54%). Yamamoto and Weisburger (1970) reported a 100% induction of lung adenomas and adenocarcinomas (38/38 by comparison with 12/20 in the controls) in A/J male mice given 325 mg/L hydrazine sulfate in the drinking water for 48 weeks.

MacEwen et al. (1981) reported on the carcinogenic effect of inhaled hydrazine in C57BL/6 mice, F344 rats, Syrian golden hamsters and beagle dogs. Hydrazine vapor (97% pure) was administered to 400 female mice at 0.05, 0.25 or 1.0 ppm; to 100 rats of each sex at 0.05, 0.25, 1.0, or 5.0 ppm; to 160 male hamsters at 0.25, 1.0 or 5.0 ppm; and to 4 dogs of each sex at 0.25 or 1.0 ppm. Exposure was 6 hours/day, 5 days/week for 1 year, followed by a variable observation period (12-38 months). Appropriate controls were maintained for each species. Significantly increased incidences of tumors were reported at the highest exposures administered in mice (lung adenoma), male and female rats (nasal cavity adenoma and adenocarcinoma), and hamsters (nasal cavity polyp) as well as in male and female rats treated with 1.0 ppm hydrazine (nasal cavity adenoma and adenocarcinoma). No significant increase in tumor induction was observed at the lower doses nor were treatment-related neoplasms reported in the dogs. The observation period is considered to be insufficient for dogs.

Juhasz et al. (1966) injected white mice of both genders with hydrazine (0.5 mg x 16 injections) over a period of 46 days, then observed the animals for 1 year. Mediastinum reticulum-cell sarcomas were observed in 4/34 mice, and 9/34 had myeloid leukemias. A single thymic leukemia was reported out of 60 control animals. Kelly et al. (1969) injected (BALB/c\x DBA/2)F1 male mice i.p. with a total dose of 20.8 mg hydrazine sulfate/animal (given in 8 weekly injections). Lung tumors were reported in 6/30 of the treated animals and 1/9 of the control animals.

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o SUPPORTING DATA :

The mutagenicity of hydrazine has been demonstrated in both in vitro and in vivo assays tested as hydrazine sulfate, hydrazine hydrate or hydrazine hydrochloride. Hydrazine induced reverse mutations in histidine auxotrophs of S. typhimurium (Kimball, 1977; Anderson and Styles, 1978; McMahon et al., 1979; Tosk et al., 1979; Parodi et al., 1981; Rogan et al., 1982), in tryptophan auxotrophs of E. coli (McMahon et al., 1979; Von Wright and Tikkanen, 1980), and in a host-mediated assay with mice given a single dose of hydrazine sulfate by gavage (Simmon et al., 1979). Intraperitoneal treatment of mice with hydrazine sulfate and radiolabeled formate or methionine produced radiolabeled 7-methylguanine in liver DNA and RNA, indicating that hydrazine mediated indirect alkylation of nucleic acids in vivo (Quintero-Ruiz et al., 1970). Hydrazine induces DNA strand breaks in rat hepatocytes treated in vitro (Sina et al., 1983) and in the liver and lung of mice treated intraperitoneally with hydrazine hydrate (Parodi et al., 1981). sister chromatid exchange was induced by in vitro treatment with hydrazine in Chinese hamster V-79 cells (Speit et al., 1980), Chinese hamster ovary cells (MacRae and Stitch, 1979), and Chinese hamster Don (lung) cells (Baker et al., 1983). Hydrazine induced specific locus and recessive lethal mutations in D. melanogaster (Jain and Shukla, 1972; Shukla, 1972) but did not induce dominant lethal mutations in mice (Epstein and Shafner, 1968; Epstein et al., 1972).

CARO -

o CLASSIFICATION	: B2; probable human carcinogen.
o BASIS FOR CLASSIFICATION	: Tumors have been induced in mice, rats and hamsters following oral, inhalation or intraperitoneal administration of hydrazine and hydrazine sulfate. Hydrazine is mutagenic in numerous assays.
o ORAL SLOPE FACTOR	: 3.0 per (mg/kg)/day
o DRINKING WATER UNIT RISK	: 8.5E-5 per (ug/L)
o DOSE EXTRAPOLATION METHOD	: Linearized multistage procedure, extra risk

o RISK/WATER CONCENTRATIONS :

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+0 ug/L
E-5 (1 in 100,000)	1E-1 ug/L
E-6 (1 in 1,000,000)	1E-2 ug/L

---

o ORAL DOSE-RESPONSE DATA :

Tumor Type -- hepatoma
Test Animals -- mouse, CBA/Cb/Se; male
Route -- gavage (hydrazine sulfate in water)
Reference -- Biancifiori, 1970

Administered	Human Equivalent	Tumor

Dose (ppm)	Dose (mg/kg)/day	Incidence
0	0	3/30
0.14	0.044	1/26
0.28	0.103	7/25
0.56	0.222	12/25
1.13	0.403	15/25

---

o ADDITIONAL COMMENTS :

Human equivalent doses were calculated to reflect a treatment period of 175 days and an experimental period of 607 days, the mean length of the experiment for each treatment group. Mouse body weight was assumed to be 0.03 kg and the animal lifespan was assumed to be 730 days. A slope factor of 9.01E-1 per (mg/kg)/day was derived from the lung tumor response in male Swiss mice in the single-dose lifetime drinking water study with 0.012% (0.74 mg/day) hydrazine sulfate (Toth, 1969). The values for hydrazine would be expected to be less than these values for hydrazine sulfate because of the smaller molecular weight of the molecule. Although it is likely that hydrazine is responsible for the tumorigenic response in these experiments, the slope factor calculated on the basis of this compound may not be appropriate for hydrazine, even after converting the dose rate from hydrazine sulfate to that of hydrazine. The absorption rates in the body are likely to differ between the two compounds. The lifetime drinking water study with hydrazine in Swiss mice (Toth, 1972) is inappropriate for the calculation of a slope factor because of the lack of concurrent controls.

The unit risk should not be used if the water concentration exceeds 1E+2 ug/L, since above this concentration the unit risk may not be appropriate.

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o DISCUSSION OF CONFIDENCE :

The study showed a dose-response and encompassed the lifespan of the animal. Two independent slope factors are within a factor of 4.

CARI -

o CLASSIFICATION : B2; probable human carcinogen.

o BASIS FOR CLASSIFICATION : Tumors have been induced in mice, rats and hamsters following oral, inhalation or intraperitoneal administration of hydrazine and hydrazine sulfate. Hydrazine is mutagenic in numerous assays.

o INHALATION UNIT RISK : 4.9E-3 per (ug/cu.m)

o DOSE EXTRAPOLATION METHOD : Linearized multistage procedure, extra risk

o RISK/AIR CONCENTRATIONS :

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E-2 ug/cu.m
E-5 (1 in 100,000)	2E-3 ug/cu.m
E-6 (1 in 1,000,000)	2E-4 ug/cu.m

---

o INHALATION DOSE-RESPONSE DATA :

Tumor Type -- nasal cavity adenoma or adenocarcinoma
Test Animals -- rat/F344, male
Route -- inhalation (hydrazine)
Reference -- MacEwen et al., 1981

---- Dose ----- Administered (ppm)	Human Equivalent (mg/kg/day)	Tumor Incidence
0.0	0.00	0/149
1.0	0.01	11/98
5.0	0.05	72/99

---

o ADDITIONAL COMMENTS :

Data in CARI. were described in the Evaluation of the Potential Carcinogenicity of Hydrazine (U.S. EPA, 1986). Global 82 was used to calculate a slope factor of 1.7E+1 per (mg/kg)/day, which was the basis for the inhalation unit risk.

Human equivalent doses reflect a treatment period of 365 days and an experimental period of 910 days. Rat body weight was assumed to be 350 g, and the animal lifespan was assumed to be 910 days.

The unit risk should not be used if the air concentration exceeds 2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

---

o DISCUSSION OF CONFIDENCE :

A sufficient number of animals were treated for less than lifetime and observed until death; a dose-related increase in incidence was observed.

CARDR-

o CARCINOGENICITY SOURCE :

U.S. EPA. 1984. Health and Environmental Effects Profile for Hydrazine and Hydrazine Sulfate. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1986. Evaluation of the Potential Carcinogenicity of Hydrazine. Prepared by the Carcinogen Assessment Group, Office of Health and Environmental Assessment, Washington, DC for the Office of Emergency and Remedial Response and the Office of Solid Waste and Emergency Response, Washington, DC.

The values in the 1986 Reportable Quantity Document for Hydrazine (review draft) have received limited Agency review. The values in the 1984 Health and Environmental Effects Profile for Hydrazine and Hydrazine Sulfate (final draft) have received Agency review.

DOCUMENT

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o REVIEW DATES : 06/03/87
o VERIFICATION DATE : 06/03/87
o EPA CONTACTS :

William E. Pepelko / ORD -- (202)260-5904 / FTS 260-5904

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE-
o ACUTE TOXICITY :

Target organs affected by hydrazine include the central nervous system, respiratory system, skin, and eyes (NIOSH/OSHA, 1978, p. 110).

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o SIGNS AND SYMPTOMS :

Symptoms include irritation of eyes, nose, and throat; temporary blindness; dizziness; nausea; dermatitis and burning skin (NIOSH/OSHA, 1978, p. 110). Inhalation may cause nausea, headache, facial numbness, twitching, sore throat, and pulmonary edema. Acute exposure may cause seizures and coma, and increased blood sugar levels (Rumack, 1975 to Present). Chemical burns result from skin contact (ACGIH, 1980).

BCF - NO DATA

CAA - NO DATA

WQCHU- NO DATA

WQCAQ- NO DATA

MCLG -

Value -- 400 mg/L (sulfate) (Proposed, 1990)

Considers technological or economic feasibility? -- NO

Discussion -- EPA is proposing two alternate options of 400 or 500 mg/L for the sulfate MCLG based on the available health information in humans.

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Health and Ecological Criteria Division / OST / (202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 400 mg/L (sulfate) (Proposed, 1990)

Considers technological or economic feasibility? -- YES

Discussion -- EPA is proposing a MCL equal to the MCLG of 400 or 500 mg/L.

Monitoring requirements -- Ground water systems every 3 years; surface

water systems annually; will allow monitoring at up to 10-year intervals after the system completes 3 rounds of sampling at <50% of the MCL.

Analytical methodology -- Ion chromatography (EPA 300.0; ASTM D-4327-88; SM 429); automated, chloranilate (EPA 375.1; SM 426D); Gravimetric (EPA 375.3; ASTM D-516-82A; SM 426A,B); turbidimetric (EPA 375.4; ATSM D-516-82B; SM 426C). PQL= 10.0 mg/L.

Best available technology -- Reverse osmosis; ion exchage.

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

Value -- 250 mg/L [sulfate] (Proposed, 1990)

Considers technological or economic feasibility? -- NO

Discussion -- SMCLs are non-enforceable and establish limits for contaminants which may affect the aesthetic qualities (e.g. taste and odor) of drinking water. It is recommended that systems monitor for these contaminants every three years. More frequent monitoring for contaminants such as pH, color, odor or others may be appropriate under certain circumstances.

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

Status -- Listed [sulfate] (Proposed, 1991)

Discussion -- "Unregulated" contaminants are those contaminants for which EPA establishes a monitoring requirement but which do not have an associated final MCLG, MCL, or treatment technique. EPA may regulate these contaminants in the future.

Monitoring requirement -- All systems to be monitored unless a vulnerability assessment determines the system is not vulnerable.

Analytical methodology -- Colorimetric (EPA 340.1; ASTM D1179-72A; SM 43A and C).

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 1 pound (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for hydrazine is based on potential carcinogenicity. Available data indicate a hazard ranking of high and a weight of evidence classification of Group B2, which corresponds to an RQ of 1 pound.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA - NO DATA

TSCA -

No data available

OREF - None

IREF - None

CREF - Anderson, D. and J.A. Styles. 1978. An evaluation of four short-term tests for detecting organic chemical carcinogens. Appendix 2. The bacterial mutation test. Br. J. Cancer. 37: 924-930.

CREF - Baker, R.S.U., G.A. Mitchell, K.M. Meher-Homji and E. Podobna. 1983. Sensitivity of two Chinese hamster cell lines to SCE induction by a variety of chemical mutagens. Mutat. Res. 118(1-2): 103-116.

CREF - Biancifiori, C. 1970. Hepatomas in CBA/Cb/Se mice and liver lesions in golden hamsters induced by hydrazine sulfate. J. Natl. Cancer Inst. 44: 943.

CREF - Biancifiori, C. and R. Ribacchi. 1962. Pulmonary tumors in mice induced by oral isoniazid and its metabolites. Nature. 194: 488-489.

CREF - Biancifiori, C., E. Bucciarelli, D.B. Clayson and F.E. Santilli. 1964. Induction of hepatomas in CBA/Cd/Se mice by hydrazine sulphate and the lack of effect of croton oil on tumor induction in BALB/c/Cd/Se mice. Br. J. Cancer. 18: 543-550.

CREF - Epstein, S.S. and H. Shafner. 1968. Chemical mutagens in the human environment. Nature. 219: 385-387.

CREF - Epstein, S.S., E. Arnold, J. Andrea, W. Bass and Y. Bishop. 1972. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23: 288-325.

CREF - Jain, H.K. and P.T. Shukla. 1972. Locus specificity of mutagens in Drosophila. Mutat. Res. 14: 440-442.

CREF - Juhasz, J., J. Balo and B. Szende. 1966. Tumor-inducing effects of hydrazine in mice. Nature. 121: 1377.

CREF - Kelly, M.G., R.W. O'Gara, S.T. Yancey, K. Gadekar, C. Botkin and V.T. Oliverio. 1969. Comparative carcinogenicity of N-isopropyl-alpha- (2-methylhydrazine)-p-toluamide-HCl (procarbazine hydrochloride), its degradation products, other hydrazines, and isonicotinic acid hydrazine. J. Natl. Cancer Inst. 42: 337-344.

CREF - Kimball, R.F. 1977. The mutagenicity of hydrazine and some of its derivatives. Mutat. Res. 39(2): 11-126.

CREF - MacEwen, J.D., E.H. Vernot, C.C. Haun, E.R. Kinkead and A. Hall, III. 1981. Chronic Inhalation Toxicity of Hydrazine: Oncogenic Effects. Air

Force Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio. NTIS, Springfield, VA.
CREF - MacRae, W.D. and H.F. Stich. 1979. Induction of sister-chromatid exchanges in Chinese hamster ovary cells by thiol and hydrazine compounds. Mutat. Res. 68(4): 351-366.
CREF - McMahon, R.E., J.C. Cline and C.Z. Thompson. 1979. Assay of 855 test chemicals in ten tester strains using a new modification of the Ames test for bacterial mutagens. Cancer Res. 39(3): 682-693.
CREF - Parodi, S., S. DeFlora, M. Cavanna, et al. 1981. DNA-damaging activity in vitro and bacterial mutagenicity of 16 hydrazine derivatives as related quantitatively to their carcinogenicity. Cancer Res. 41(4): 1469-1482.
CREF - Quintero-Ruiz, A., L.L. Paz-Neri and S. Villa-Trevino. 1981. Indirect alkylation of CBA mouse live DNA and RNA by hydrazine in vivo. A possible mechanism of action as a carcinogen. J. Natl. Cancer Inst. 67(3): 613-618.
CREF - Roe, F.J.C., G.A. Grant and D.M. Millican. 1967. Carcinogenicity of hydrazine and 1,1-dimethylhydrazine for mouse lung. Nature (London). 216: 375-376.
CREF - Roe, F.J.C. 1978. Letter to the Editor. Ann. Occup. Hyg. 21: 323-325.
CREF - Rogan, E.G., B.A. Walker, R. Gingell, D.L. Nagel and B. Toth. 1982. Microbial mutagenicity of selected hydrazines. Mutat. Res. 102(4): 413-424.
CREF - Severi, L. and C. Biancifiori. 1968. Hepatic carcinogenesis in CBA/Cb/Se mice and Cb/Se rats by isonicotinic acid hydrazine and hydrazone sulfate. J. Natl. Cancer Inst. 41: 331-340.
CREF - Shukla, P.T. 1972. Analysis of mutagen specificity in Drosophila melanogaster. Mutat. Res. 16: 363-371.
CREF - Simmon, V.F., H.S. Rosenkranz, E. Zeiger and L.A. Poirier. 1979. Mutagenic activity of chemical carcinogens and related compounds in the intraperitoneal host-mediated assay. J. Natl. Cancer Inst. 62(4): 911-918.
CREF - Sin, J.F., C.L. Bean, G.R. Dysart, V.I. Taylor and M.O. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat. Res. 113(5): 357-391.
CREF - Speit, G., C. Wick and M. Wolf. 1980. Induction of sister chromatid exchanges by hydroxylamine, hydrazine and isoniazid and their inhibition by cysteine. Human Genet. 52(2): 155-158.
CREF - Tosk, J., I. Schemeltz and D. Hoffman. 1979. Hydrazines as mutagens in a histidine-requiring auzotroph of Salmonella typhimurium. Mutat. Res. 66(3): 247-252.
CREF - Toth, B. 1969. Lung tumor induction and inhibition of breast adenocarcinomas by hydrazine sulfate in mice. J. Natl. Cancer Inst. 42: 469-475.
CREF - Toth, B. 1972. Hydrazine, methylhydrazine and methylhydrazine sulfate carcinogenesis in Swiss mice. Failure of ammonium hydroxide to interfere in the development of tumors. Int. J. Cancer. 9: 109-118.
CREF - U.S. EPA. 1984. Health and Environmental Effects Profile for Hydrazine and Hydrazine Sulfate. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.
CREF - U.S. EPA. 1986. Evaluation of the Potential Carcinogenicity of Hydrazine. Prepared by the Carcinogen Assessment Group, Office of Health and Environmental Assessment, Washington, DC for the Office of Emergency and Remedial Response and the Office of Solid Waste and Emergency Response, Washington, DC.
CREF - Von Wright, A. and L. Tikkanen. 1980. Hydrazine and methylhydrazine as recA+-independent mutagens in Escherichia coli. Mutat. Res. 71(2): 269-271.
CREF - Yamamoto, R.S. and J.H. Weisburger. 1970. Failure of arginine glutamate to inhibit lung rumor formation by isoniazid and hydrazine in mice. Life Sci. 9: 285.
HAREF- None

1 - IRIS
NAME - Hydrogen chloride
RN - 7647-01-0
IRSN - 455
DATE - 920122
UPDT - NO DATA
STAT - Oral RfD Assessment (RDO) no data
STAT - Inhalation RfC Assessment (RDI) on-line 01/01/91
STAT - Carcinogenicity Assessment (CAR) no data
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 01/01/91 RDI Inhalation RfC summary on-line
IRH - 01/01/91 REFS Bibliography on-line
IRH - 01/01/92 EXSR Regulatory Action section on-line
RLEN - 16472
SY - ACIDE CHLORHYDRIQUE (French)
SY - ACIDO CLORIDRICO (Italian) 362
SY - CHLOORWATERSTOF (Dutch)
SY - CHLOROHYDRIC ACID
SY - CHLOROWODOR (Polish)
SY - CHLORWASSERSTOFF (German)
SY - HYDROCHLORIC ACID
SY - HYDROCHLORIDE
SY - HYDROGEN CHLORIDE
SY - MURIATIC ACID
SY - SPIRITS of SALT
SY - UN 1050
SY - UN 1789
SY - UN 2186
MF - HCl
USE - Major uses of hydrogen chloride include refining metal ore, lab reagent, and removing scale from boilers (Merck, 1983). Hydrogen chloride is also a metal treating agent; it is used in food processing, and to neutralize waste streams (Hawley, 1981). Hydrogen chloride is used in the manufacture of fertilizers and dyes, in electroplating, in the textile industry, and in the rubber industry (Encyc. Occupat. Safety and Health, 1983).
COFO - Colorless gas or liquid (Weast, 1979). Irritating pungent odor (NFPA, 1978). May be colored yellow by traces of iron, chlorine, and organic matter (Merck, 1983).
ODOR - Colorless gas or liquid (Weast, 1979). Irritating pungent odor (NFPA, 1978). May be colored yellow by traces of iron, chlorine, and organic matter (Merck, 1983).
BP - Constant boiling azeotrope with water 227F, 109C containing 20.22% hydrogen chloride (Merck 1983, p. 692); -121F, -85C (gas) (Weast, 1979)
MP - Freezing point -13.7F, -25.4C (39.17% weight/weight solution) (Merck, 1983; p. 692); -174.6F, -114.8C (gas) (Weast, 1979)
MW - 36.46
DEN - 1.05 at 15C/4C for 10.17% weight/weight solution (Merck, 1983; p. 692)
VAP - Not Found
VAPD - 1.268 (Merck, 1983)
EVAP - Not Found
SOLW - 82.3 g/100 mL at 32F (gas) (Weast, 1979)
FLPT - Not Found
FLMT - Flammable Limits: LEL -- Not Found UEL -- Not Found
AVOI - Avoid heat; at high temperatures hydrogen chloride will decompose into hydrogen and chlorine (Encyc. Occupat. Health and Safety, 1983). Materials to avoid: mercuric sulfate -- violent reaction with gaseous hydrochloric acid at 250F; sodium -- reacts vigorously with gaseous hydrochloric acid; acetic anhydride, 2-aminoethanol, ammonium hydroxide, chlorosulfonic acid, ethylene diamine, ethyleneimine, oleum, propiolactone, sodium hydroxide, sulfuric acid, and vinyl acetate -- increase in temperature and pressure when mixed with hydrochloric acid; calcium phosphide -- energetic reaction with hydrochloric acid; silver

perchlorate and carbon tetrachloride - - when mixed in combination with hydrochloric acid forms a compound that detonates at 105F (NFPA, 1978); formaldehyde -- when mixed with hydrochloric acid forms a human carcinogen (NRC, 1981). Hydrogen chloride reacts violently with bases and is corrosive with the generation of heat. Hydrogen chloride reacts with base metals, forming combustible gas (hydrogen). It also reacts violently with strong oxidants forming toxic gas (chlorine) (DASE, 1980; p. 541).

DCMP - At high temperatures, hydrogen chloride decomposes into hydrogen and chlorine (Encyc. Occupat. Health and Safety, 1983).

RDO - NO DATA

RDI -

o INHALATION RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfC
Hyperplasia of nasal mucosa, larynx and trachea	NOAEL: None LOAEL: 15.0 mg/cu.m (10 ppm)	1000	1	7E-3 mg/cu.m
Chronic Rat Inhalation Study	LOAEL(ADJ): 2.5 mg/cu.m (1.7 ppm)			
Sellakumar et al., 1985	LOAEL(HEC): 6.5 mg/cu.m (4.4 ppm)			

*Conversion Factors: MW = 36.46. Assuming 25C and 760 mm Hg, LOAEL (mg/cu.m) = 10 ppm x 36.67/24.45 = 15 mg/cu.m. LOAEL(ADJ) = 15 x 6 hours/day x 4.7 days/7 days = 2.5 mg/cu.m. The LOAEL(HEC) was calculated for a gas: respiratory effect in the ExtraThoracic and tracheobronchial region. MVa = 0.5 cu.m/day, MVh = 20 cu.m/day, Sa = (37.6 ET + 11.6 TB) = 49.2 sq.cm., Sh = (5036 ET + 177 TB) = 5213 sq.cm. RGDR(ET+TB) = (MVa/Sa) / (MVh/Sh) = 2.6. LOAEL(HEC) = LOAEL(ADJ) x RGDR = 2.5 mg/cu.m x 2.6 = 6.5 mg/cu.m.

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o INHALATION RFD STUDIES :

Sellakumar, A.R., C.A. Snyder, J.L. Solomon and R.E. Albert. 1985. Carcinogenicity for formaldehyde and hydrogen chloride in rats. Toxicol. Appl. Pharmacol. 81: 401-406.

The Albert et al. (1982) study, discussed in detail by Sellakumar et al. (1985), reported data from a chronic inhalation exposure study in rats. One hundred male Sprague-Dawley rats were exposed to 10 ppm HCl 6 hours/day, 4.7 (adjusted according to the authors) days/week (2.5 mg/cu.m adjusted for duration and assuming 25 degrees C and 760 mm Hg) for their lifetime. All animals were observed daily, weighed monthly, and allowed to die naturally, or were killed when moribund. Complete necropsy was performed on all animals and particular attention was given to the respiratory tract. Histologic sections were prepared from each nasal cavity, lung, trachea, larynx, liver, kidneys, testes and other organs where gross pathological signs were present. However, Sellakumar et al. (1985) did not discuss histopathological events in organs other than the respiratory tract. HCl-exposed animals showed no differences in body weights or survival when compared with air controls. The histopathology data indicated 62/99 exposed animals with epithelial or squamous hyperplasia of the nasal mucosa versus 51/99 in the concurrent control group. Additionally, however, there was approximately 24% incidence of hyperplasia of laryngeal-tracheal segments in HCl-exposed rats (larynx 2/22, trachea 6/26) versus 6% in the controls. The authors did not make any comments concerning the severity of these changes.

In a 90-day inhalation study using B6C3F1 mice, and SD and Fisher 344 rats (Toxigenics, Inc, 1984), groups of 31 males and 31 females of each

species and strain were exposed to hydrogen chloride at 10, 20, or 50 ppm (15, 30, or 150 mg/cu.m, respectively) 6hors/ay, 5 days/week for 90 days. Several animals died during the study; however, the deaths did not appear to be exposure-related. There was a slight but significant decrease in body weight gain in male and female mice and in male Fischer 344 rats in the high-exposure groups. There was no effect on hematology, clinical chemistry, or urinalysis. Histologic examination showed minimum to mild rhinitis in both strains of rats. Lesions occurred in the anterior portion of the nasal cavity and were concentration- and time-related. In mice exposed to 50 ppm there was cheilitis and accumulation of macrophages in the peripheral tissues after 90 days. Mice in all exposure groups developed eosinophilic globules in the epithelial lining of the nasal tissues.

Based on the findings of both the chronic and the 90-day studies the 10 ppm (15 mg/cu.m) concentration can be considered a LOAEL [LOAEL(HEC) = 6.5 mg/cu.m].

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o INHALATION RFD UNCERTAINTY :

UF = 1000. The UF includes a factor of 10 for interspecies differences, 10 for intraspecies extrapolations and 10 to extrapolate from a LOAEL to NOAEL. Because of the expected portal-of-entry effect of HCl, an uncertainty factor to account for the lack of both a second species chronic bioassay and an adequate reproductive bioassay was not considered necessary.

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o INHALATION RFD MODIFYING :

MF = 1.
FACTOR

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o INHALATION RFD COMMENTS :

Reproductive and development effects of hydrogen chloride are limited. Pavlova (1976) exposed two groups of 8 to 15 female rats to 302 ppm (450 mg/cu.m) hydrogen chloride for 1 hour. One group was exposed 12 days prior to mating and the other group on day 9 of gestation. In both groups signs of severe dyspnea and cyanosis were noted, and mortality occurred in one-third of the animals. Fetal mortality was significantly higher in rats exposed during pregnancy. When the progeny were subjected to an additional exposure of 35 ppm (52 mg/cu.m) at the age of 2 to 3 months, functional abnormalities in the organs of the progeny were similar to those found in the mothers.

In another study from the same laboratory, female rats were exposed to 302 ppm (450 mg/cu.m) hydrogen chloride for 1 hour prior to mating. Exposure killed 20 to 30% of the rats. In rats surviving 6 days after exposure, a decrease in blood oxygen saturation was noted, as was kidney, liver, and spleen damage. In addition, treatment altered the estrus cycles. In rats mated 12 to 16 days postexposure and killed on day 21 of pregnancy, fewer live fetuses, a decrease in fetal weight, and an increase in relative lung weights of the fetuses were observed (GEOMET Technologies, Inc., 1981).

In a short-term study, Kaplan et al. (1988) exposed baboons (3 males/group) to 0, 500, 5000, or 10,000 ppm HCl for 15 minutes and observed for 3 months. The results indicated dose-related increased frequency of respiratory rate and minute volume following exposure. The higher doses caused decreased arterial PO2 but follow-up measurements at 3 days or 3 months following exposure did not show any abnormalities. The upper airways of the baboon, compared to other mammalian species (rodents), have the greatest similarity to those of human child and the complexity of the respiratory tract increases with age. It can reasonably be expected that the more complex structure of the upper airways of the human would remove more of an airborne chemical than those of other mammalian species (rodents). Based on the results of this study, the authors suggested that the human is probably much less sensitive to hydrogen chloride than the mouse.

Burleigh-Flayer et al. (1985) exposed male guinea pigs to 0, 320, 680, 1040, and 1380 ppm HCl for 1 to 6 minutes and measured respiratory rate and induction of sensory or pulmonary irritations. This study indicated sensory irritation at 320 ppm (477 mg/cu.m) when exposed for 6 minutes while less severe effects were observed at 680 ppm or higher during 1-minute exposure. The concentration of HCl exposure was inversely related to the onset interval of pulmonary irritations.

Buckley et al. (1984) attempted to determine the potential for pathologic damage following exposure to sensory irritants at concentrations eliciting a 50% decrease in respiratory rate in the mouse. The mouse RD50 for HCl was reported to be 309 ppm. The TWA exposure consisted of three exposures (295-310 ppm) for 5 days (6 hours/day). The lesions noted were confined to upper respiratory epithelium. No abnormalities were noted in the lungs.

Darmer et al. (1974), in an attempt to determine the HCl hazard at a missile test firing site, reported 30-minute LC50 values for rats and mice of 4701 and 2644 ppm, respectively; the LC50 values for 5-minute exposures were 40,989 (rat) and 13,745 ppm (mice). Thus, it appeared that mice are 2 to 3 times more sensitive than rats to HCl exposure.

A thorough search of literature failed to reveal any additional long-term human or animal data. Based on the chronic and subchronic rat studies, the 10 ppm (15 mg/cu.m) rat concentration seems appropriate at this time as an interim LOAEL due to the reactive nature of the agent and the documented portal-of-entry effects.

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o INHALATION RFD CONFIDENCE : Study: Low Data Base: Low RfC: Low The chronic study used only one dose and limited toxicological measurements. The supporting data consist of two subchronic bioassays; the data base does not provide any additional chronic or reproductive studies. was recommended for the study, data base and the RfC.

o INHALATION RFD SOURCE :

Source Document -- This assessment is not presented in any existing U.S. EPA document

Other EPA Documentation -- U.S. EPA, 1988
DOCUMENT

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o REVIEW DATES : 01/19/89, 02/16/89
o VERIFICATION DATE : 02/16/89
o EPA CONTACTS :

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

W. Bruce Peirano / ORD -- (513)569-7553 / FTS 684-7553

CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE-

o ACUTE TOXICITY :

Gas concentrations of 50 to 100 ppm are tolerable for 1 hour. Concentrations of 1000 to 2000 ppm are dangerous, even for brief exposures. More severe exposures will result in serious respiratory distress and prolonged exposures will result in death. Mists of hydrogen chloride are considered less harmful than anhydrous hydrochloric acid, because droplets have no dehydrating action (Sax 1975).

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o SIGNS AND SYMPTOMS :

Inhalation of hydrogen chloride may cause coughing and choking, and inflammation and ulceration of the respiratory tract. Ingestion causes corrosion of the mucous membranes, esophagus and stomach; nausea; vomiting; intense thirst and diarrhea. Concentrated solutions can cause severe burns to the skin. Occupational exposures have led to dermatitis, photosensitization (Merck 1983), gastritis, and chronic bronchitis (ACGIH 1980). Contact may cause burns to skin and eyes. Concentrated solutions can cause severe burns and permanent visual damage may occur (Rumack 1975 to Present).

BCF - NO DATA

CAA - NO DATA

WQCHU-

No data available

WQCAQ-

Freshwater:

Acute -- 8.6E+5 ug/L (1-hour average) [chloride]
Chronic -- 2.3E+5 ug/L (4-day average) [chloride]

Marine:

Acute -- None
Chronic -- None

Considers technological or economic feasibility? -- NO

Discussion -- Criterion were derived from a minimum database consisting of acute and chronic tests on a variety of species. Requirements and methods are covered in the reference to the Federal Register. This criterion will probably not be adequately protective when the chloride is associated with potassium, calcium or magnesium, rather than sodium. In addition, because freshwater animals have a narrow range of acute suceptibilities to chloride, excursions above this criterion might affect a substantial number of species.

Reference -- 53 FR 19028 (05/26/88)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG - NO DATA

MCL - NO DATA

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 5000 pounds (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- No data have been found to permit the ranking of this hazardous substance. The available data for acute hazards may lie above the upper limit for the 5000 pound RQ, but since it is a designated hazardous substance, the largest assignable RQ is 5000 pounds.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA Superfund Hotline
(800) 424-9346 / (703) 920-9810 / FTS 260-3000

SARA - NO DATA

RCRA - NO DATA

TSCA -

No data available

OREF - None

IREF - Albert, R.E., A.R. Sellakumar, S. Laskin, M. Kuschner, N. Nelson and C.A. Snyder. 1982. Gaseous formaldehyde and hydrogen chloride induction of nasal cancer in rats. J. Natl. Cancer Inst. 68(4): 597-603.

IREF - Buckley, L., X.Z. Jiang, R.A. James, K.T. Morgan and C.S. Barrow. 1984. Respiratory tract lesions induced by sensory irritants at the RD50 concentration. Toxicol. Appl. Pharmacol. 74: 417-429.

IREF - Burleigh-Flayer, H., K.L. Wong and Y. Alarie. 1985. Evaluation of the pulmonary effects of hydrochloric-acid using carbon dioxide challenges in guinea-pigs. Fund. Appl. Toxicol. 5(5): 978-985.

IREF - Darmer, K.I., E.R. Kinkead and L.C. Dipasquale. 1974. Acute toxicity in rats and mice exposed to hydrogen chloride gas and aerosols. Am. Ind. Hyg. Assoc. J. 35(10): 623-631.

IREF - GEOMET Technologies, Inc. 1981. Hydrogen chloride: Report 4, Occupational Hazard Assessment. U.S. Department of Health and Human Services, NIOSH, Cincinnati, OH. NTIS PB83-105296.

IREF - Kaplan, H.L., A. Anzueto, W.G. Switzer and R.K. Hinderer. 1988. Effects

of hydrogen chloride on respiratory response and pulmonary function of the baboon. J. Toxicol. Environ. Health. 23(4): 473-493.
IREF - Pavlova, T.E. 1976. Disturbance of development of the progeny of rats exposed to hydrogen chloride. Bull. Exp. Biol. Med. 82: 1078-1081.
IREF - Sellakumar, A.R., C.A. Snyder, J.L. Solomon and R.E. Albert. 1985. Carcinogenicity of formaldehyde and hydrogen chloride in rats. Toxicol. Appl. Pharmacol. 81: 401-406.
IREF - Toxigenics, Inc. 1984. 90-Day inhalation study of hydrogen chloride gas in B6C3F1 mice, Sprague-Dawley rats and Fischer-344 rats. Study conducted for CIIT, Research Triangle Park, NC. CIIT Docket No. 20915.
IREF - U.S. EPA. 1988. Health Assessment Document for Chlorine and Hydrogen Chloride. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-87- 041A. (External Review Draft)
CREF - None
HAREF- None

4 - IRIS
NAME - Lead and compounds (inorganic)
RN - 7439-92-1
IRSN - 271
DATE - 930701
UPDT - 07/01/93, 4 fields
STAT - Oral RfD Assessment (RDO) message 02/01/91
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 07/01/93
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 06/01/92
IRH - 09/26/88 CAR Carcinogen summary on-line
IRH - 02/01/89 MCLG Effect level corrected in discussion
IRH - 06/01/89 CARDR Primary contact changed
IRH - 06/01/89 CAA Reference corrected - changed number for part in CFR
IRH - 12/01/89 CAREV Last paragraph - Correct Van Esch 1969 citation
IRH - 12/01/89 REFS Bibliography on-line
IRH - 07/01/90 RDO Changed contact J. Cohen's office and telephone number
IRH - 07/01/90 RCRA EPA contact changed
IRH - 02/01/91 RDO Message revised to include new EPA document
IRH - 02/01/91 RDO EPA contacts changed
IRH - 05/01/91 CAREV Text edited
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 06/01/92 MCL MCL monitoring reqs. and BAT corrected
IRH - 07/01/93 CARDR Secondary contact's phone number changed
IRH - 07/01/93 CREF References alphabetized correctly
RLEN - 18720
SY - Lead
SY - Lead and compounds
SY - plumbum
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA
VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

RDO -
o ORAL RFD SUMMARY :

A great deal of information on the health effects of lead has been obtained through decades of medical observation and scientific research. This information has been assessed in the development of air and water quality criteria by the Agency's Office of Health and Environmental Assessment (OHEA) in support of regulatory decision-making by the Office of Air Quality Planning and Standards (OAQPS) and by the Office of Drinking Water (ODW). By comparison to most other environmental toxicants, the degree of uncertainty about the health effects of lead is quite low. It appears that some of these effects, particularly changes in the levels of certain blood enzymes and in aspects of children's neurobehavioral development, may occur at blood lead levels so low as to be essentially without a threshold. The Agency's RfD Work Group discussed inorganic lead (and lead compounds) at two meetings (07/08/85 and 07/22/85) and considered it inappropriate to develop an RfD for inorganic lead. For additional information, interested parties are referred to the 1986

Air Quality Criteria for Lead (EPA-600/8-83/028a-dF) and its 1990 Supplement (EPA/600/8-89/049F) or the following Agency scientists:

Harlal Choudhury / OHEA -- (513)569-7536

J. Michael Davis / OHEA -- (919)541-4162

Jeff Cohen / OST -- (202)260-5456

John Haines / OAQPS -- (919)541-5533

RDI - NO DATA
CAREV-

o CLASSIFICATION : B2; probable human carcinogen

o BASIS FOR CLASSIFICATION : Sufficient animal evidence. Ten rat bioassays and one mouse assay have shown statistically significant increases in renal tumors with dietary and subcutaneous exposure to several soluble lead salts. Animal assays provide reproducible results in several laboratories, in multiple rat strains with some evidence of multiple tumor sites. Short term studies show that lead affects gene expression. Human evidence is inadequate.

o HUMAN CARCINOGENICITY DATA :

Inadequate. There are four epidemiologic studies of occupational cohorts exposed to lead and lead compounds. Two studies (Dingwall-Fordyce and Lane, 1963; Nelson et al., 1982) did not find any association between exposure and cancer mortality. Selevan et al. (1985), in their retrospective cohort mortality study of primary lead smelter workers, found a slight decrease in the total cancer mortality (SMR=95). Apparent excesses were observed for respiratory cancer (SMR=111, obs=41, $p>0.05$) and kidney cancer (SMR=204, obs=6, $p>0.05$). Cooper and Gaffey (1975) and Cooper (1985 update) performed a cohort mortality study of battery plant workers and lead smelter workers. They found statistically significant excesses for total cancer mortality (SMR=113, obs=344), stomach cancer (SMR=168, obs=34), and lung cancer (SMR=124, obs=109) in the battery plant workers. Although similar excesses were observed in the smelter workers, they were not statistically significant. Cooper and Gaffey (1975) felt it was possible that individual subjects were monitored primarily on the basis of obvious signs of lead exposure, while others who showed no symptoms of lead poisoning were not monitored.

All of the available studies lacked quantitative exposure information, as well as information on the possible contribution from smoking. All studies also included exposures to other metals such as arsenic, cadmium, and zinc for which no adjustment was done. The cancer excesses observed in the lung and stomach were relatively small (<200). There was no consistency of site among the various studies, and no study showed any dose-response relationship. Thus, the available human evidence is considered to be inadequate to refute or demonstrate any potential carcinogenicity for humans from lead exposure.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. The carcinogenic potential of lead salts (primarily phosphates and acetates) administered via the oral route or by injection has been demonstrated in rats and mice by more than 10 investigators. The most characteristic cancer response is bilateral renal carcinoma. Rats given lead acetate or subacetate orally have developed gliomas, and lead subacetate also

produced lung adenomas in mice after i.p. adminstration. Most of these investigations found a carcinogenic response only at the highest dose. The lead compounds tested in animals are almost all soluble salts. Metallic lead, lead oxide and lead tetralkyls have not been tested adequately. Studies of inhalation exposure have not been located in the literature.

Azar et al. (1973) administerd 10, 50, 100, and 500 ppm lead as lead acetate in dietary concentrations to 50 rats/sex/group for 2 years. Control rats (100/sex) received the basal laboratory diet. In a second 2-year feeding study, 20 rats/group were given diets containing 0, 1000, and 2000 ppm lead as lead acetate. No renal tumors were reported in the control groups or in treated animals of either sex receiving 10 to 100 ppm. Male rats fed 500, 1000, and 2000 ppm lead acetate had an increased renal tumor incidence of 5/50, 10/20, and 16/20, while 7/20 females in the 2000-ppm group developed renal tumors.

The Azar et al. (1973) study is limited by the lack of experimental detail. The possibility of environmental contamination from lead in the air or drinking water was not mentioned. The strains of rats used were not specified in the study, but the Health Effects Assessment for Lead (U.S. EPA, 1984) indicates the rats were Wistar strain. The weight gain at 1000 and 2000 ppm was reported to be depressed, but details were not given.

Kasprzak et al. (1985), in investigating the interaction of dietary calcium on lead carcinogenicity, fed 1% lead subacetate (8500 ppm Pb) to male Sprague-Dawley rats in the diet for 79 weeks. Of the rats surviving (29/30) in this treatment group beyond 58 weeks, 44.8% had renal tumors. Four rats had adenocarcinomas; the remainaing nine had adenomas. Bilateral tumors were noted. No renal tumors were noted among the controls.

As part of a study to determine interactions between sodium nitrite, ethyl urea and lead, male Sprague-Dawley rats were given lead acetate in their drinking water for 76 weeks (Koller et al., 1986). The concentration of lead was 2600 ppm. No kidney tumors were detected among the 10 control rats. Thirteen of 16 (81%) lead-treated rats had renal tubular carcinoma; three tumors were detected at 72 weeks and the remainder detected at the termination of the study.

Van Esch and Kroes (1969) fed basic lead acetate at 0, 0.1%, and 1.0% in the diet to 25 Swiss mice/sex/group for 2 years. No renal tumors developed in the control group, but 6/25 male mice of 0.1% basic lead acetate group had renal tumors (adenomas and carcinomas combined). In the 1.0% group, one female had a renal tumor. The authors thought that the low incidence in the 1.0% group was due to early mortality.

Hamsters given lead subacetate at 0.5% and 1% in the diet had no significant renal tumor response (Van Esch and Kroes, 1969).

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o SUPPORTING DATA :

Lead acetate induces cell transformation in Syrian hamster embryo cells (DiPaolo et al., 1978) and also enhances the incidence of simian adenovirus induction. Lead oxide showed similar enhanced adenovirus induction (Casto et al., 1979).

Under certain conditions lead compounds are capable of inducing chromosomal aberrations in vivo and in tissue cultures. Grandjean et al. (1983) showed a relationship between SCE and lead exposure in exposed workers. Lead has been shown, in a number of DNA structure and function assays, to affect the molecular processes associated with the regulation of gene expression (U.S. EPA, 1986).

CARO -

o CLASSIFICATION : B2; probable human carcinogen

o BASIS FOR CLASSIFICATION : Sufficient animal evidence. Ten rat bioassays and one mouse assay have shown statistically significant increases in renal tumors with dietary and subcutaneous exposure to several soluble lead salts. Animal assays provide reproducible results in several laboratories, in multiple rat strains with some evidence of multiple tumor sites. Short term studies show that lead affects gene expression. Human evidence is inadequate.

o ORAL DOSE-RESPONSE DATA :

Not available.

Quantifying lead's cancer risk involves many uncertainties, some of which may be unique to lead. Age, health, nutritional state, body burden, and exposure duration influence the absorption, release, and excretion of lead. In addition, current knowledge of lead pharmacokinetics indicates that an estimate derived by standard procedures would not truly describe the potential risk. Thus, the Carcinogen Assessment Group recommends that a numerical estimate not be used.

CARI - NO DATA

CARDR-

o CARCINOGENICITY SOURCE :

Source Document -- U.S. EPA, 1984, 1986, 1987

The review of the carcinogenic potential of lead associated with oral exposure (U.S. EPA, 1987) has received Agency review.

The 1986 Air Quality Criteria Document for Lead has received Agency and External Review.

DOCUMENT

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o REVIEW DATES : 05/04/88

o VERIFICATION DATE : 05/04/88

o EPA CONTACTS :

William Pepelko / OHEA -- (202)260-5898

Jim Cogliano / OHEA -- (202)260-3814

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE- NO DATA
BCF - NO DATA

CAA -

Considers technological or economic feasibility? -- No

Discussion -- Under Section 109 of the CAA, EPA has set a primary (health-based) NAAQS for lead of 1.5 ug/cu.m, calendar quarter average not to be exceeded (43 FR 41258, 10/05/78). The secondary (welfare-based) NAAQS is identical to the primary standard. EPA is currently reviewing these standards to determine if changes are warranted.

Reference -- 40 CFR 50.12

U.S. EPA Contact -- Air Quality Management Division / OAQPS /
(919)541-5656 / FTS 629-5656

WQCHU-

Water and Fish Consumption -- 5.0E+1 ug/L

Fish Consumption Only -- None

Considers technological or economic feasibility? -- NO

Discussion -- The criterion was set at the existing drinking water standard in 1980.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute -- 8.2E+1 ug/L (1-hour average)
Chronic -- 3.2E+0 ug/L (4-day average)

Marine:

Acute -- 1.40E+2 ug/L (1-hour average)
Chronic -- 5.6E+0 ug/L (4-day average)

Considers technological or economic feasibility? -- NO

Discussion -- Criteria were derived from a minimum data base consisting of acute and chronic tests on a variety of species. The toxicity of this compound in freshwater is hardness dependent. The values given are for a hardness of 100 mg/L CaCO3. For a more complete discussion, see the referenced notice.

Reference -- 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 0 mg/L (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- The MCLG for lead is zero based on (1) occurrence of low level effects and difficulties in identifying clear threshold levels, (2) the overall Agency goal of reducing total lead exposures, and (3) the classification of lead as a group B2 carcinogen.

Reference -- 56 FR 26460 (06/07/91); 56 FR 32112 (07/15/91)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- None (Final, 1991)

Considers technological or economic feasibility? -- YES

Discussion -- EPA concluded that setting an MCL for lead is not feasible and believes that the treatment approach contained in the final rule (corrosion control, source water reduction, public education and lead service line problems associated with establishing MCL's.

Monitoring requirements -- Tap water monitoring for lead and copper to determine whether a system is subject to the treatment technique requirements. Water quality parameter sampling to determine the effectiveness of optional corrosion control treatment. Source water monitoring for lead and copper to determine source water's contribution to total tap water lead and copper levels, and the need for treatment. Monitoring schedules vary by system size and type of monitoring.

Analytical methodology -- Atomic absorption/furnace technique (EPA 239.2; ASTM D-3559-85D; SM 3113); inductively-coupled plasma/mass spectrometry (EPA 200.8); atomic absorption/platform furnace technique (EPA 200.9).

Best available technology --

Optimal corrosion control treatment: pH/akalinity adjustment, calcium adjustment; addition of corrosion inhibitor.

Source water treatment: Coagulation/filtration; ion exchange; lime softening; reverse osmosis.

Public education.

Lead service line replacement.

Reference -- 45 FR 57332 (08/27/80); 53 FR 31517 (08/18/88); 56 FR 26460 (06/07/91); 56 FR 32112 (07/15/91).

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 1 pound (Statutory, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The statutory 1-pound RQ for lead is retained pending assessment of its potential carcinogenicity and may be adjusted in a future notice of proposed rulemaking when the evaluation of available data is completed. Lead was evaluated for chronic toxicity, but was not ranked for toxicity because of insufficient data.

Reference -- 52 FR 8140 (03/16/87); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed (total lead)

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - None

FICHE # 4

IREF - None
CREF - Anderson, E.L., and CAG (Carcinogenic Assessment Group). 1983. Quantitative approaches in use to assess cancer risk. Risk Analysis. 3: 277-295.
CREF - Azar, A., H.J. Trochimowicz and M.E. Maxfield. 1973. Review of lead studies in animals carried out at Haskell Laboratory - Two year feeding study and response to hemorrhage study. In: Barth D., A. Berlin, R. Engel, P. Recht and J. Smeets, Ed. Environmental health aspects of lead: Proceedings International Symposium; October 1972; Amsterdam, The Netherlands. Commission of the European Communities, Luxemberg. p. 199-208.
CREF - Casto, B.C., J. Meyers and J.A. DiPaolo. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res. 39: 193-198.
CREF - Cooper, W.C. 1985. Mortality among employees of lead battery plants and lead producing plants, 1947-1980. Scand. J. Work Environ. Health. 11: 331-345.
CREF - Cooper, W.C. and W.R. Gaffey. 1975. Mortality of lead workers. In: Proceedings of the 1974 Conference on Standards of Occupational Lead Exposure, J.F. Cole, Ed., February, 1974. Washington, DC. J. Occup. Med. 17: 100-107.
CREF - Dingwall-Fordyce, I. and R.E. Lane. 1963. A follow-up study of lead workers. Br. J. Ind. Med. 20: 313-315.
CREF - DiPaolo, J.A., R.L. Nelson and B.C. Casto. 1978. In vitro neoplastic transformation of Syrian hamster cells by lead acetate and its relevance to environmental carcinogenesis. Br. J. Cancer. 38: 452-455.
CREF - Grandjean, P., H.C. Wulf and E. Niebuhr. 1983. Sister chromatid exchange in response to variations in occupational lead exposure. Environ. Res. 32: 199-204.
CREF - Kasprzak, K.S., K.L. Hoover and L.A. Poirier. 1985. Effects of dietary calcium acetate on lead subacetate carcinogenicity in kidneys of male Sprague- Dawley rats. Carcinogenesis. 6(2): 279-282.
CREF - Koller, L.D., N.I. Kerkvliet and J.H. Exon. 1986. Neoplasia induced in male rats fed lead acetate, ethyl urea and sodium nitrate. Toxicol. Pathol. 13: 50-57.
CREF - Nelson, D.J., L. Kiremidjian-Schumacher and G. Stotzky. 1982. Effects of cadmium, lead, and zinc on macrophage-mediated cytotoxicity toward tumor cells. Environ. Res. 28: 154-163.
CREF - Selevan, S.G., P.J. Landrigan, F.B. Stern and J.H. Jones. 1985. Mortality of lead smelter workers. Am. J. Epidemiol. 122: 673-683.
CREF - U.S. EPA. 1984. Health Effects Assessment for Lead. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-86/055. NTIS PB85-163996/AS.
CREF - U.S. EPA. 1986. Air Quality Criteria Document for Lead. Volumes III, IV. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC, for the Office of Air Quality Planning and Standards. EPA-600/8-83/028dF.
CREF - U.S. EPA. 1987. Preliminary review of the carcinogenic potential of lead associated with oral exposure. Prepared by the Office of Health and Environmental Assessment, Carcinogenic Assessment Group, Washington DC, for the Office of Drinking Water, Office of Solid Waste and the Office of Emergency and Remedial Response (Superfund). OHEA-C-267. Internal Review Draft.
CREF - Van Esch, G.J. and R. Kroes. 1969. The induction of renal tumors by feeding of basic lead acetate to mice and hamsters. Br. J. Cancer. 23: 265-271.
HAREF- None

6 - IRIS
NAME - Mercury (Inorganic)
RN - 7439-97-6
IRSN - 369
DATE - 920122
UPDT - NO DATA
STAT - Oral RfD Assessment (RDO) pending
STAT - Inhalation RfC Assessment (RDI) pending
STAT - Carcinogenicity Assessment (CAR) on-line 05/01/91
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 09/07/88 CAR Carcinogen summary on-line
IRH - 09/01/89 REFS Bibliography on-line
IRH - 12/01/89 RDI Inhalation RfD now under review
IRH - 05/01/91 CAREV Text edited
IRH - 01/01/92 EXSR Regulatory Action section on-line
RLEN - 7139
SY - hydragyrum
SY - Mercury
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA
VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

RDO -
o ORAL RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

RDI -
o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

CAREV-
o CLASSIFICATION : D; not classifiable as to human carcinogenicity
o BASIS FOR CLASSIFICATION : No human data are available. Animal and supporting data are inadequate.
o HUMAN CARCINOGENICITY DATA :

None.

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o ANIMAL CARCINOGENICITY DATA :

When 39 BD III and BD IV rats were injected i.p. over 2 weeks with 0.1 ml metallic mercury and observed for their lifetimes, sarcomas were seen only in those tissues that had been in direct contact with the metal (Druckrey et al., 1957). No concurrent controls were reported.

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o SUPPORTING DATA :

Mitsumori et al. (1981) fed groups of 60 male and 60 female SPF ICR mice 0, 15 or 30 ppm methyl mercury chloride in the diet for up to 78 weeks. The majority of the 30 ppm groups died from neurotoxicity by week 26. Histopathology on kidney tissue from all animals surviving after 53 weeks revealed renal tumors in 13/16 males in the 15 ppm group (2 adenomas, 11 adenocarcinomas). One adenoma was detected among 37 controls surviving to week 53 or beyond, and no tumors were seen in either control or exposed females. The possible presence of tumors at other sites was not reported in this preliminary communication.

Methyl mercury hydroxide administered in the diet to Drosophila melanogaster at 5 mg/L induced chromosomal nondisjunction. Methyl and phenyl mercury produced small increases in the rate of point mutations (Ramel, 1972).

The relevance of data from studies of organic mercury to the possible carcinogenicity of inorganic mercury is uncertain.

CARO - NO DATA
CARI - NO DATA
CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1987. Drinking Water Criteria Document for Mercury. Prepared for the Office of Drinking Water, Washington, DC. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-025, February, 1987.

The 1987 Drinking Water Criteria Document for Mercury has received Agency and external review.
DOCUMENT

---

o REVIEW DATES : 01/13/88
o VERIFICATION DATE : 01/13/88
o EPA CONTACTS :

W. Bruce Peirano / ORD -- (513)569-7540 / FTS 684-7540

Krishan Khanna / ODW -- (202)260-7588 / FTS 260-7588

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE- NO DATA
BCF - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption: 1.44E-1 ug/L

Fish Consumption Only: 1.46E-1 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 1.44E-1 ug/L is based on consumption of contaminated aquatic organisms and water. A WQC of 1.46E-1 ug/L has also been established based on consumption of contaminated aquatic organisms alone.

Reference -- 45 FR 79318 (11/28/80); 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute -- 2.4E+0 ug/L (1-hour average)
Chronic -- 1.2E-2 ug/L (4-day average)

Marine:

Acute -- 2.1E+0 ug/L (1-hour average)
Chronic -- 2.5E-2 ug/L (4-day average)
Considers technological or economic feasibility? -- NO

Discussion -- Criteria were derived from a minimum data base consisting of acute tests on a variety of species. Requirements and methods are covered in the reference to the Federal Register. The Agency recommends an exceedence frequency of no more than 3 years.

Reference -- 45 FR 79318 (11/28/80); 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value -- 0.002 mg/L (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- EPA has promulgated a MCLG of 0.002 mg/L based on potential

adverse effects (renal toxicity) in three major studies. The MCLG is based upon a DWEL of 0.01 mg/L and an assumed drinking water contribution of 20 percent.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST / (202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 0.002 mg/L (Final, 1991)

Considers technological or economic feasibility? -- YES

Discussion -- EPA has set an MCL equal to the MCLG of 0.002 mg/L.

Monitoring requirements -- Ground water systems monitored every three years; surface water systems monitored annually; systems out of compliance must begin monitoring quarterly until system is reliably and consistently below MCL.

Analytical methodology -- Manual cold vapor technique (EPA 245.1; ASTM D3223-80; SM 303F); automated cold vapor technique (EPA 245.2): PQL=0.0005 mg/L.

Best available technology -- Coagulation/filtration; Lime softening; Reverse osmosis; Granular activated carbon.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 1 pound (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for mercury is based on aquatic toxicity. The available data indicate that the aquatic 96-Hour Median Threshold Limit is less than 0.1 ppm, which corresponds to an RQ of 1 pound.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed (total mercury)

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - None
IREF - None
CREF - Druckrey, H., H. Hamperl and D. Schmahl. 1957. Carcinogenic action of metallic mercury after intraperitoneal administration in rats. Z. Krebs- forsch. 61: 511-519.
CREF - Mitsumori, K., K. Maita, T. Saito, S. Tsuda and Y. Shikasu. 1981. Carcinogenicity of methylmercury chloride in ICR mice: Preliminary note on renal carcinogens. Cancer Lett. 12: 305-310.
CREF - Ramel, C. 1972. Genetic effects. In: Mercury in the Environment -- An Epidemiological and Toxicological Appraisal, L. Friberg and J. Vostal, Ed. CRC Press, Cleveland, OH. p. 169-181.
CREF - U.S. EPA. 1987. Drinking Water Criteria Document for Mercury. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.
HAREF- None

print all

1 - IRIS
NAME - Naphthalene
RN - 91-20-3
IRSN - 445
DATE - 931101
UPDT - 11/01/93, 3 fields
STAT - Oral RfD Assessment (RDO) pending 11/01/93
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 09/01/92
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 12/01/90 CAR Carcinogen assessment on-line
IRH - 12/01/90 REFS Bibliography on-line
IRH - 01/01/92 EXSR Regulatory Action section on-line
IRH - 09/01/92 CAR Classification noted as pending change
IRH - 09/01/92 CARDR Work group review date added
IRH - 11/01/93 RDO Work group review date added
RLEN - 14912
CONTINUE PRINTING? (YES/NO/CONT)
USER:
cont

SY - Naphthalene
SY - Albocarbon
SY - Caswell No. 587
SY - Dezodorator
SY - EPA Pesticide Chemical Code 055801
SY - HSDB 184
SY - MOTH BALLS
SY - MOTH FLAKES
SY - Naftalen [Polish]
SY - Naftaleno [Spanish]
SY - Naphtalene [French]
SY - Naphthalene
SY - Naphthalin
SY - Naphthaline
SY - Naphthene
SY - NAPTHALENE, molten
SY - NCI-C52904
SY - NSC 37565
SY - RCRA WASTE NUMBER U165
SY - TAR CAMPHOR
SY - UN 1334
SY - UN 2304
SY - WHITE TAR

-
RDO -
o ORAL RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

-
o REVIEW DATES : 03/19/87, 10/19/89, 09/22/93

-
RDI - NO DATA
CAREV-

o CLASSIFICATION : D; not classifiable as to human carcinogenicity

o BASIS FOR CLASSIFICATION : Based on no human data and inadequate data from animal bioassays.

o HUMAN CARCINOGENICITY DATA :

None.

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o ANIMAL CARCINOGENICITY DATA :

Inadequate. The National Toxicology Program is currently evaluating naphthalene for carcinogenicity in mice by the inhalation route; final results are not yet available.

A group of 28 rats (in-house strains BDI and BDIII) was exposed to a diet supplemented with naphthalene, 6 times/week (Schmahl, 1955). Treatment was stopped when total dose was 10 g/rat. The average daily dose was approximately 10 to 20 mg/day (approximately 30 to 60 mg/kg/day). Tumors were evaluated in animals that died spontaneously at about 700 to 800 days of age. No carcinogenic responses were reported.

In a short-term pulmonary tumor bioassay, Adkins et al. (1986) exposed groups of 30 female A/J strain mice by inhalation to 0, 10, or 30 ppm naphthalene for 6 hours/day, 5 days/week for 6 months. While naphthalene caused a statistically significant increase in the number of adenomas per mouse lung, there was no apparent dose-response. This assay is considered to be a short-term, in vivo, lung tumor assay.

Tsuda et al. (1980) administered a single gavage dose of 100 mg/kg naphthalene in corn oil to a group of 10 F344 rats (sex not specified) at 12 hours after partial hepatectomy. A vehicle control group of 10 rats was included. At 2 weeks after surgery, 2-acetylaminofluorene was added to the diet at 200 ppm to inhibit proliferation of "nonresistant" hepatocytes. After 1 week of dietary 2-acetylaminofluorene, a single 2.0 mL/kg dose of carbon tetrachloride was given to necrotize "nonresistant" hepatocytes and permit proliferation of "resistant" hepatocytes. Feeding of 2-acetylaminofluorene continued for 1 week, followed by a basal diet for 1 week. The rats were then sacrificed and livers were sectioned and histochemically examined for the number and size of gamma-glutamyl transpeptidase (GGT) positive foci. These foci contain cells that are "resistant" to the necrotizing effects of carbon tetrachloride and to the proliferation-inhibiting effects of 2-acetylaminofluorene and are considered to represent an early stage in the process of neoplastic transformation. Neither the number nor the size of GGT foci appeared to be increased in naphthalene-treated rats compared with vehicle controls.

A group of 10 rats (in-house strains BDI and BDIII) received intraperitoneal injections of naphthalene (20 mg/rat) once a week for 40 weeks (Schmahl, 1955). Another group of 10 rats served as a control group. Animals were evaluated after spontaneous death. No carcinogenic responses were reported.

Coal tar-derived naphthalene that contained approximately 10% unidentified

impurities was administered to 40 white rats (sex unspecified) by seven subcutaneous injections of 500 mg/kg naphthalene in sesame oil at 2-week intervals. Lymphosarcomas were found in 5/34 surviving rats at 18 months (14.7%), whereas vehicle controls had a 2% incidence of these tumors. This study is of limited value because of the presence of potentially carcinogenic impurities in the naphthalene and because prior to injection carbofuchsin was applied dermally to the injection site (Knake, 1956).

Inbred black mice (25/group) were painted with 0.5% coal tar-derived naphthalene (10% unidentified impurities) in benzene 5 days/week for life. Four treated mice develoed leukemias in contrast to 0/21 vehicle controls; the untreated control incidence was 0.4%. The value of this study for assessing carcinogenicity is very limited due to the presence of potentially carcinogenic impurities. Moreover, the vehicle in the study has been shown to cause leukemias (Knake, 1956). Other mouse skin-painting tests of naphthalene as a complete carcinogen and as an initiator of carcinogenicity were negative or inconclusive (Kennaway, 1930; Schmeltz et al., 1978).

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o SUPPORTING DATA :

With one exception naphthalene was not positive when tested in a variety of genotoxicity assays. In reverse mutation assays using Salmonella typhimurium strains TA97, TA98, TA100, TA1535, TA1537, TA1538, UTH8413 and UTH8414, naphthalene at concentrations of up to 2.5 mg/plate was not positive either with or without hepatic homogenates (McCann et al., 1975; Anderson and Styles, 1978; Florin et al., 1980; Gatehouse, 1980; Connor et al., 1985; Ho et al., 1981; Sakai et al., 1985; Mortelmans et al., 1986; Bos et al., 1988). Narbonne et al. (1987) reported that in the presence of hepatic homogenates naphthalene at 5 and 10 ug/plate was mutagenic for S. typhimurium TA1538; however, naphthalene was not positive at concentrations of 50, 100 and 1000 ug/plate. There was no increase in forward mutation frequency for Salmonella.

At concentrations of up to 1.6 mM, naphthalene was not positive in S. typhimurium forward mutation assays (Kaden et al. 1979; Seixas et al., 1982).

In a DNA damage assay using S. typhimurium TA1535 Nakamura et al. (1987) reported that naphthalene at concentrations of up to 83 ug/mL was not positive. In phage induction assays using Escherichia coli as a host, naphthalene at concentrations of up to 2 mg/mL did not yield positive results (Ho and Ho, 1981; Mamber et al. 1984). DNA damage assays with naphthalene were not positive in E. coli (Mamber et al., 1983) or in primary rat hepatocyte cultures (Sina et al., 1983). Transformation assays in Swiss mouse embryo cells (Rhim et al., 1974) and in rat embryo cells (Freeman et al., 1973) were not positive.

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CARO - NO DATA
CARI - NO DATA
CARDR-
o CARCINOGENICITY SOURCE :

Source Document -- U.S. EPA, 1986, 1990

The 1990 Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons has undergone Agency and external review.

DOCUMENT

-

o REVIEW DATES : 02/07/90, 08/05/92
o VERIFICATION DATE : 02/07/90
o EPA CONTACTS :

Rita S. Schoeny / OHEA -- (513)569-7544

Robert E. McGaughy / OHEA -- (202)260-5889

-

-

HAONE- NO DATA

-

HATEN- NO DATA

-

HALTC- NO DATA

-

HALTA- NO DATA

-

HALIF- NO DATA

-

OLEP - NO DATA

-

ALAB - NO DATA

-

TREAT- NO DATA

-

HADR - NO DATA

-

CAA - NO DATA

-

WQCHU-

No data available

-

-

WQCAQ-

Freshwater:

Acute -- 2.3E+3 ug/L
Chronic -- 6.2E+2 ug/L

Marine:

Acute -- 2.3E+3 ug/L
Chronic -- None

Considers technological or economic feasibility? -- NO

Discussion -- Criteria were derived from a minimum data base consisting of acute and chronic tests on a variety of species. Requirements and methods are covered in the reference to the federal register.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

No data available

MCL -

No data available

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

Status -- Listed (Final, 1987)

Discussion -- "Unregulated" contaminants are those contaminants for which EPA establishes a monitoring requirement but which do not have an associated final MCLG, MCL, or treatment technique. EPA may regulate these contaminants in the future.

Monitoring requirement -- Monitoring required at the state's discretion; repeat monitoring at minimum 5 year intervals.

Analytical methodology -- Capillary gas chromatography (EPA 502.2); capillary gas chromatographic/mass spectrometry (EPA 524.2).

Reference -- 56 FR 25690 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

SMCL - NO DATA

FISTD-

Status -- Issued (1981)

Reference -- Naphthalene Pesticide Registration Standard. September, 1981 [NTIS No. PB82-139437].

EPA Contact -- Registration Branch / OPP
(703)557-7760 / FTS 557-7760

FIREV-

No data available

CERC -

Value (status) -- 100 pounds (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for naphthalene is based on aquatic toxicity as established under CWA Section 311 (40 CFR 117.3). The available data indicate that the aquatic 96-Hour Median Threshold Limit is between 1-10 ppm, which corresponds to an RQ of 100 pounds.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - None
IREF - None
CREF - Adkins, B., E.W. Van Stee, J.E. Simmons and S.L. Eustis. 1986. Oncogenic response of strain A/J mice to inhaled chemicals. J. Toxicol. Environ. Health. 17: 311-322.
CREF - Anderson, D. and J.A. Styles. 1978. An evaluation of 6 short-term tests for detecting organic chemical carcinogens. Appendix 2. The bacterial mutation test. Br. J. Cancer. 37(6): 924-930.
CREF - Bos, R.P., J.L.G. Theuws, F.J. Jongeneelen and P.Th. Henderson. 1988. Mutagenicity of bi-, tri- and tetra-cyclic aromatic hydrocarbons in the "taped-plate assay" and in the conventional Salmonella mutagenicity assay. Mutat. Res. 204: 203-206.
CREF - Connor, T.H., J.C. Theiss, H.A. Hanna, D.K. Monteith and T.S. Matney. 1985. Genotoxicity of organic chemicals frequently found in the air of mobile homes. Toxicol. Lett. 25: 33-40.
CREF - Florin, I., L. Rutberg, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology. 18: 219-232.
CREF - Freeman, A.E., E.K. Weisburger, J.H. Weisburger, R.G. Wolford, J.M. Maryak and R.J. Huebner. 1973. Transformation of cell cultures as an indication of the carcinogenic potential of chemicals. J. Natl. Cancer Inst. 51: 799-808.
CREF - Gatehouse, D. 1980. Mutagenicity of 1,2 ring-fused acenaphthenes against S. typhimurium TA1537 and TA1538: Structure-activity relationships. Mutat. Res. 78: 121-135.
CREF - Ho, Y.L. and S.K. Ho. 1981. Screening of carcinogens with the prophage lambda CLTS857 induction test. Cancer Res. 41: 532-536.
CREF - Ho, C.H., B.R. Clark, M.R. Guerin, B.D. Barkenbus, T.K. Rao and J.L. Epler. 1981. Analytical and biological analyses of test materials from the synthetic fuel technologies. IV. Studies of chemical structure-mutagenic activity relationships of aromatic nitrogen compounds relevant to synfuels. Mutat. Res. 85: 335-345.
CREF - Kaden, D., R. Hites and W. Thilly. 1979. Mutagenicity of soot and associated polycyclic aromatic hydrocarbons to Salmonella typhimurium. Cancer Res. 39: 4152-4159.
CREF - Kennaway, E.L. 1930. Further experiments on cancer-producing substances. Biochem. J. 24: 497-504.
CREF - Knake, E. 1956. Uber schache geschwulsterzeugende wirkung von naphthalin und benzol. Virchows Archiv. Pathol. Anat. Physiol. 329: 141-176. (Ger.)
CREF - Mamber, S.W., V. Bryson and S.E. Katz. 1983. The Escherichia coli WP2/WP100 rec assay for detection of potential chemical carcinogens. Mutat. Res. 119: 135-144.
CREF - Mamber, S.W., V. Bryson and S.E. Katz. 1984. Evaluation of the Escherichia coli K12 inductest for detection of potential chemical caricnogens. Mutat. Res. 130: 141-151.

CREF - McCann, J.E., E. Choi, E. Yamasaki and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. USA. 72(12): 5135-5139.
CREF - Mortelmans, K., S. Haworth, T. Lawlor, W. Speck, B. Tainer and E. Zeiger. 1986. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ. Mutagen. 8(Suppl. 7): 1-119.
CREF - Nakamura, S., Y. Oda, T. Shimada, I. Oki and K. Sugimoto. 1987. SOS-inducing activity of chemical carcinogens and mutagens in Salmonella typhimurium TA1535/pSK1002: Examination with 151 chemicals. Mutat. Res. 192: 239-246.
CREF - Narbonne, J.F., P. Cassand, P. Alzieu, P. Grolier, G. Mrlina and J.P. Calmon. 1987. Structure-activity relationships of the N-methylcarbamate series in Salmonella typhimurium. Mutat. Res. 191: 21-27.
CREF - Rhim, J.S., D.K. Park, E.K. Weisburger and J.H. Weisburger. 1974. Evaluation of an in vitro assay system for carcinogens based on prior infection of rodent cells with nontransforming RNA tumor virus. J. Natl. Cancer Inst. 52(4): 1167-1173.
CREF - Sakai, M., D. Yoshida and S. Mizusaki. 1985. Mutagenicity of polycylic aromatic hydrocarbons and quinones on Salmonella typhimurium TA97. Mutat. Res. 156: 61-67.
CREF - Schmahl, D. 1955. Examination of the carcinogenic action of naphthalene and anthracene in rats. Z. Krebsforsch. 60: 697-710.
CREF - Schmeltz, I., J. Tosk, J. Hilfrich, N. Hirota, D. Hoffmann and E.L. Wynder. 1978. Bioassays of naphthalene and alkylnaphthalenes for co-carcinogenic activity. Relation to tobacco carcinogenesis. Carcinog. 3(Polynul. Aromat. Hydrocarbons). p. 47-60.
CREF - Seixas, G.M., B.M. Andon, P.G. Hollingshead and W.G. Thilly. 1982. The aza- arenes as mutagens for Salmonella typhimurium. Mutat. Res. 102: 201-212.
CREF - Sina, J.F., C.L. Bean, G.R. Dysart, V.I. Taylor and M.O. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat. Res. 113: 357-391.
CREF - Tsuda, H., G. Lee and E. Farber. 1980. Induction of resistant hepatocytes as a new principle for a possible short-term in vivo test for carcinogens. Cancer Res. 40(4): 1157-1164.
CREF - U.S. EPA. 1986. Health and Environmental Effects Profile for Naphthalene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. Final Draft. ECAO-CIN-P192, August, 1986.
CREF - U.S. EPA. 1990. Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft. ECAO-CIN-D010, September, 1990.
HAREF- None

[IRIS] SS 4 /cf?
USER:
find nitric acid

Search in progress

NP (NITRIC ACID (IRIS))
*NONE-

[IRIS] SS 4 /cf?
USER:
find 52583-42-3

Search in progress

NP (52583-42-3 (IRIS))
*NONE-

4 - IRIS
NAME - Nickel, soluble salts
RN - 7440-02-0
IRSN - 265
DATE - 920122
UPDT - NO DATA
STAT - Oral RfD Assessment (RDO) on-line 01/01/92
STAT - Inhalation RfC Assessment (RDI) pending
STAT - Carcinogenicity Assessment (CAR) message
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 03/01/88 RDO Text clarified paragraph 1
IRH - 12/01/89 RDI Inhalation RfD now under review
IRH - 04/01/90 RDO ABC, 1986 corrected to U.S. EPA, 1986
IRH - 04/01/90 REFS Bibliography on-line
IRH - 06/01/90 RDO Oral RfD summary noted as pending change
IRH - 06/01/90 RCRA EPA contact changed
IRH - 09/01/91 RDO Oral RfD no longer pending change; no changes made
IRH - 12/01/91 RDO Text revised; additional study added
IRH - 12/01/91 RDO Text significantly revised; additional studies added
IRH - 12/01/91 OREF Oral RfD references revised to reflect new text
IRH - 01/01/92 RDO Citation year corrected for Schnegg and Kirchgessner
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 01/01/92 OREF Citation year corrected for Schnegg and Kirchgessner
RLEN - 29210
SY - C.I. 77775
SY - NICHEL
SY - Nickel
SY - Nickel, soluble salts
MF - Ni
USE - Nickel is used in nickel-plating; for various alloys such as new silver, Chinese silver, and German silver; for coins, electrotypes, lighting-rod tips, electrical contacts and electrodes, spark plugs, machinery parts; as a catalyst for hydrogenation of organic substances; in manufacturing of Monel metal, stainless steels, and nickel-chrome resistance wire; and in alloys for electronic and space applications (Merck, 1983).
COFO - Silvery metal (Weast, 1979); lustrous white metal (Merck, 1983)
ODOR - Silvery metal (Weast, 1979); lustrous white metal (Merck, 1983)
BP - 5139F, 2837C (Merck, 1983)
MP - 2831F, 1555C (Merck, 1983)
MW - 58.70
DEN - 8.90 (Sax, 1979)
VAP - 1 at 1810C (Sax, 1979)
VAPD - Not Found
EVAP - Not Found
SOLW - Insoluble (Weast, 1979)
FLPT - Not Found
FLMT - Not Found
AVOI - Finely divided nickel (e.g. Raney nickel catalysts) may become hot enough to ignite if exposed to air or moisture (Student, 1981, p. 363). Materials containing potassium perchlorate with nickel and titanium powders and infusional earth give severe explosions during a friction test. Dioxane reacts explosively with hydrogen and Raney nickel above 210C (NFPA, 1978). Also, aluminum; aluminum trichloride; ethylene; hydrogen; methanol; non-metals; oxidants; sulfur compounds (Sax, 1984, p. 1990), and selenium metal (Weiss, 1980, p. 1105) are incompatible with nickel.
DCMP - Not Found

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD

Decreased body and organ weights	NOAEL: 100 ppm diet (5 mg/kg/day)	300	1	2E-2 mg/kg/day
Rat Chronic Oral Study	LOAEL: 1000 ppm diet (50 mg/kg/day)			

Ambrose et al., 1976

*Conversion Factors: 1 ppm = 0.05 mg/kg/day (assumed rat consumption)

o ORAL RFD STUDIES :

Ambrose, A.M., D.S. Larson, J.R. Borzelleca and G.R. Hennigar, Jr. 1976. Long-term toxicologic assessment of nickel in rats and dogs. J. Food Sci. Technol. 13: 181-187.

Ambrose et al. (1976) reported the results of a 2-year feeding study using rats given 0, 100, 1000 or 2500 ppm nickel (estimated as 0, 5, 50 and 125 mg Ni/kg bw) in the diet. Body weights in the high-dose male and female rats were significantly decreased compared with controls. Body weight was also reduced at 1000 ppm. This reduction was significant for females at week 6 and from weeks 26 through 104, whereas males showed body weight reduction only at 52 weeks. Groups of female rats on the 1000 or 2500 ppm nickel diets (50 and 125 mg Ni/kg bw) had significantly higher heart-to-body weight ratios and lower liver-to-body weight ratios than controls. No significant effects were reported at 100 ppm (5 mg Ni/kg bw). The dose of 1000 ppm (50 mg Ni/kg bw) represents a LOAEL for this study, while the dose of 100 ppm (5 mg Ni/kg bw) is a NOAEL. In this study, 2-year survival was poor, particularly in control rats of both sexes (death: 44/50), raising some concern about the interpretation of the results of this study. A subchronic study conducted by American Biogenics Corp. (ABC, 1986) also found 5 mg/kg/day to be a NOAEL, which supports the Ambrose et al. (1976) chronic NOAEL of 5 mg/kg/day.

Dietary exposure of dogs to 2500 ppm Ni (about 63 mg/kg/day) resulted in depressed body weight gain; no effects were seen at either 100 ppm (about 2.5 mg/kg/day) or 1000 ppm Ni (about 25 mg/kg/day) in the diet (Ambrose et al., 1976). This study demonstrates that rats are the more sensitive of the two species.

ABC (1986) conducted the 90-day study with nickel chloride in water (0, 5, 35 and 100 mg/kg/day) administered by gavage to both male and female CD rats (30 animals/sex/group). The data generated in this study included clinical pathology, ophthalmological evaluations, serum biochemistry, body and organ weight changes and histopathological evaluations of selected organs (heart, kidney, liver).

The body weight and food consumption values were consistently lower than those of controls for the 35 and 100 mg/kg/day dosed males. Female rats in both high-dose groups had lower body weights than controls, but food consumption was unaffected by the test article. Clinical signs of toxicity, such as lethargy, ataxia, irregular breathing, cool body temperature, salivation and discolored extremities, were seen primarily in the 100 mg/kg/day group; these signs were less severe in the 35 mg/kg/day group. The 5 mg/kg/day group did not show any significant clinical signs of toxicity. There was 100% mortality in the high-dose group; 6/30 males and 8/30 females died in the mid-dose group (35 mg/kg/day). Histopathologic evaluation indicated that deaths of 3/6 males and 5/8 females in the mid-dose group were due to gavage errors. At sacrifice, kidney, liver and spleen weights for 35 mg/kg/day treated males and right kidney weights for 35 mg/kg/day treated females were significantly lower than controls. Based on the results obtained in this study, the 5 mg/kg/day nickel dose was a NOAEL, whereas 35 mg/kg/day was a LOAEL for decreased body and organ weights.

o ORAL RFD UNCERTAINTY :

UF = 300. An uncertainty factor of 10 is used for interspecies extrapolation and 10 to protect sensitive populations. An additional uncertainty factor of 3 is used to account for inadequacies in the reproductive studies (RTI, 1987; Ambrose et al., 1976; Smith et al., 1990) (see Additional Comments section). During the gestation and postnatal development of F1b litters in the RTI (1987) study, temperatures were about 10 degrees F higher than normal at certain times, which makes evaluation of this part of the reproductive study impossible. In the Ambrose et al. (1976) study, statistical design limitations included small sample size and use of pups rather than litters as the unit for comparison. There were also problems with the statistical analysis of the Smith et al. (1990) study.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

In addition to the effects on organ weights described in the critical study, two other sensitive endpoints exist: neonatal mortality and dermatotoxicity. While no reproductive effects have been associated with nickel exposure to humans, several studies in laboratory animals have demonstrated fetotoxicity. These studies are described below.

Following the reproductive studies is a discussion of nickel-induced dermatotoxicity in hypersensitive humans. While nickel has long been recognized as a contact irritant, many studies have also demonstrated dermal effects in sensitive humans resulting from ingested nickel. The weight-of-evidence from these studies indicates that ingested nickel may invoke an eruption or worsening of eczema; however, a dose-response relationship is difficult to establish. A few representative studies and review articles are cited below.

While the systemic toxicity data (as manifested in organ weight changes) was used as the critical study for the RfD determination, the reproductive/fetotoxicity and the dermatotoxicity were both considered as possible endpoints upon which to base the quantitative risk assessment of nickel. The data for effects on the latter two endpoints do not demonstrate consistent dose-response relationships, and in both cases the available studies are sufficiently flawed so as to prevent their selection as the basis for the oral RfD. It is noted, however, that the RfD based on the Ambrose et al. (1976) study is considered to be protective of all endpoints with the possible exception of hypersensitive individuals as described below.

In addition to the 2-year feeding study used as the basis for the RfD, Ambrose et al. (1976) also reported reproductive toxicity of nickel. The study had some statistical design limitations including small sample size and use of pups rather than litters as the unit for comparison. Furthermore, the results were equivocal and did not clearly define a NOAEL or LOAEL. Because nickel was administered in a laboratory chow diet rather than drinking water, quantifying analogous nickel exposure via drinking water was problematic.

In a 2-generation study (RTI, 1987) nickel chloride was administered in drinking water to male and female CD rats (30/sex/dose) at dose levels of 0, 50, 250 and 500 ppm (0, 7.3, 30.8 and 51.6 mg/kg/day, estimated) for 90 days before breeding (10 rats/sex/group comprised a satellite subchronic nonbreeder group). At the 500 ppm dose level there was a significant decrease in the Po maternal body weight, along with absolute and relative liver weights. Thus, 250 ppm (30.8 mg/kg/day) was a NOAEL for Po breeders. Histopathology was performed for liver, kidney, lungs, heart, pituitary, adrenals and reproductive organs to make this assessment. This NOAEL is higher than the NOAEL derived from the chronic Ambrose et al. (1976) and subchronic gavage

(ABC, 1986) assays.

In the RTI (1987) F1a generation (postnatal days 1-4) at the 500 ppm dose level the number of live pups/litter was significantly decreased, pup mortality was significantly increased, and average pup body weight was significantly decreased in comparison with controls. Similar effects were seen with F1b litters of Po dams exposed to 500 ppm nickel. In the 50 and 250 ppm dose groups increased pup mortality and decreased live litter size was observed in the F1b litters. However, these effects seen with F1b litters are questionable because the room temperature tended to be 10 degrees F higher than normal at certain times (gestation-postnatal days) along with much lower levels of humidity. As evidenced in the literature, temperatures that are 10 degrees F above normal during fetal development cause adverse effects (Edwards, 1986). Therefore, the above results seen at 50 and 250 ppm cannot be considered to be genuine adverse effects.

F1b males and females of the RTI (1987) study were randomly mated on postnatal day 70 and their offspring (F2a and F2b) were evaluated through postnatal day 21. This phase included teratological evaluations of F2b fetuses. Evaluation of the data indicated that the 500 ppm dose caused significant body weight depression of both mothers and pups, and increased neonatal mortality during the postnatal development period. The intermediate dose, 250 ppm nickel, produced transient depression of maternal weight gain and water intake during gestation of the F2b litters. The 50 ppm nickel exposure caused a significant increase in short ribs (11%). However, since this effect was not seen in both the higher dose groups, the reported incidence of short ribs in the 50 ppm group is not considered to be biologically significant.

Schroeder and Mitchener (1971) conducted a 3-generation study in which 5 mating pairs of rats were provided drinking water containing 5 mg Ni/L (estimated as 0.43 mg/kg bw). Results of this study indicated significant increases in neonatal mortality and in the number of runts born to exposed rats compared with controls. The major weakness of this study, however, is that the end result is based on a total of five matings. The matings were not randomized and the males were not rotated. The Schroeder and Mitchener (1971) study was conducted in an environmentally controlled facility where rats had access to food and water containing minimal levels of essential trace metals. Because of the interactions of nickel with other trace metals, the restricted exposure to trace metals (chromium was estimated as inadequate) may have contributed to the toxicity of nickel.

Smith et al. (1990) also studied the reproductive and fetotoxic effects of nickel. Four groups of 34 female Long-Evans rats were given drinking water containing nickel chloride in the following concentrations of nickel: 0, 10, 50 or 250 ppm (0, 1.3, 6.8 or 31.6 mg/kg/day) for 11 weeks prior to mating and during two successive gestation periods (G1, G2) and lactation periods (L1, L2). Maternal body weight gain was reduced during G1 in mid- and high-dose females. The reproductive performance of the exposed rats was not affected. Pup birth weight was unaltered by treatment, and weight gain was reduced only in male pups exposed to 50 ppm nickel during L1. The most significant toxicological finding was the increased incidence of perinatal mortality. The proportion of dead pups per litter was elevated at the high dose in L1 and at 10 and 250 ppm in L2. While the perinatal mortality reported in this study is consistent with other reproductive studies on nickel, it is hard to define a NOAEL and LOAEL because of the absence of a clear dose-response trend at the lower doses.

Many studies have been published regarding nickel sensitivity in humans. Of the general population, approximately 8-10% of women and 1-2% of men demonstrate a sensitivity to nickel as determined by a patch test (North American Contact Dermatitis Group, 1973; Prystowsky et al., 1979). Initial sensitization to nickel is believed to result from dermal contact, but recurring flares of eczema, particularly of the hands, may be triggered by

ingestion.

The human studies described below are difficult to interpret for several reasons: very small numbers of subjects (mostly women already determined to be sensitive to nickel by a patch test) were used in the studies; many investigators reported a placebo effect; many studies were not conducted in a double-blind manner, thereby introducing investigator bias; and it was often not specified whether subjects had been fasted overnight or whether there were other dietary restrictions. It is important to note that the way in which nickel is consumed may greatly affect its bioavailability. Sunderman et al. (1989) demonstrated that 27+/-17% of the nickel in drinking water was absorbed by healthy humans whereas only 0.7+/-0.4% of the same dose of nickel ingested in food was absorbed (a 40-fold difference). One final point to bear in ind n interpreting these studies is that the subjects were generally given a bolus dose of nickel. The absorption and biokinetics following such an exposure may be quite different from an exposure which is given incrementally throughout the day.

Following an overnight fast, groups of 5 nickel-sensitive women were given 100 mL of water along with one oral dose of nickel sulfate containing 0.6, 1.25 or 2.5 mg nickel (Cronin et al., 1980). The clinical response was observed for the next 24 hours. Worsening of hand eczema was reported in 2/5 female subjects that received 0.6 mg, 3/5 at 1.25 mg and 5/5 at 2.5 mg. Erythema was observed in 1/5 (0.6 mg), 4/5 (1.25 mg) and 4/5 (2.5 mg) women. While there appears to be a good dose-response relationship, this study did not report controls. The response observed at the lowest dose may well be within background levels.

Numerous other studies have been conducted to attempt to establish the relationships between nickel exposure and dermal irritation. Kaaber et al. (1978, 1979) reported worsening of eczema following an oral challenge with 2.5 mg nickel. In the 1978 study, 17/28 subjects experienced aggravation of dermatitis following nickel ingestion. Nine of the 17 that experienced adverse effects from the nickel found that their condition improved when they adopted a low nickel diet. In the 1979 study 9/14 subjects responded negatively to nickel treatment.

Studies conducted by Gawrodger et al. (1986), Burrows et al. (1981) and Jordan and King (1979) offer different results. Jordan and King's double blind, placebo controlled investigation suggested that 0.5 mg supplement to a normal diet was safe with the possible exception of extremely sensitive individuals. Gawrodger et al. (1986) reported that 5/10 women responded to both the 0.4 and 2.5 mg doses of nickel, but 10/26 also reacted to a placebo. They determined the LOAEL of their experiment to be 5.6 mg of nickel, a dose at which 100% of the women responded. Burrows et al. (1981) administered 0.5 mg nickel twice a day on two consecutive days to 22 patients, each of whom served as her own control. There was no significant difference between the number of individuals responding to a placebo as compared to nickel. However, the placebo response was high (12/22). The authors concluded that there is probably no connection between nickel in an ordinary diet and exacerbation of dermatitis but that a higher level may aggravate dermatitis in some individuals.

Nielsen (1989) describes a study in which 12 nickel-sensitive women were challenged for a 4-day period with a diet providing 490 ug Ni/day. No changes were observed before the start of the nickel challenge to day 0 (start of challenge). On day 4, the eczema of 6 patients was considered to be worse according to both the patients' impressions and a dermatologist's evaluation. The delayed reaction in this study may be attributed to the fact that the dose of nickel was ingested in the diet throughout the day as opposed to studies which employed a bolus dose. This difference may greatly affect the pharmacokinetics of ingested nickel.

While the previous studies on humans with a hypersensitivity to nickel

were considered in developing the RfD, none of them were adequate to serve as the basis for the quantitative risk assessment. The RfD is believed to be set at a level which would not cause individuals to become sensitized to nickel; however, those who have already developed a hypersensitivity (e.g., from a dermal exposure) may not be fully protected.

One final point to bear in mind in establishing an RfD for nickel is that nickel has been shown to be an essential trace element for several animal species. Rats deprived of nickel exhibit retarded growth and low hemoglobin levels (Schnegg and Kirchgessner, 1977). A requirement for nickel has not been conclusively demonstrated in humans, but nickel is considered to be a normal constituent of the diet. Typical daily intake of nickel ranges from 100-300 ug/day.

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o ORAL RFD CONFIDENCE :

Study: Low
Data Base: Medium
RfD: Medium

The chronic study (Ambrose et al., 1976) was properly designed and provided adequate toxicological endpoints; however, high mortality occurred in the controls (44/50). Therefore, a low confidence is recommended for the study. The data base provided adequate supporting subchronic studies, one by gavage and the other in drinking water (Po animals of the RTI subchronic study, 1986). A medium confidence level in the data base is recommended since there are inadequacies in the remaining reproduction data.

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o ORAL RFD SOURCE DOCUMENT :

U.S. EPA. 1986. Health Assessment Document for Nickel. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. (Final Report). EPA/600/8-83/012FF.

U.S. EPA. 1991. Quantification of Toxicologic Effects for Nickel. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water, Office of Science and Technology, Washington, DC.

The information contained in this assessment was reviewed by the Science Advisory Board in August 1990.

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o REVIEW DATES : 04/16/87, 05/20/87, 07/16/87, 05/17/90, 08/14/91
o VERIFICATION DATE : 07/16/87
o EPA CONTACTS :

Sue Velazquez / ORD -- (513)569-7571 / FTS 684-7571

Jennifer Orme / OW -- (202)260-7586 / FTS 260-7586

RDI -
o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

CAREV- NO DATA
CARO - NO DATA

CARI - NO DATA
CARDR- NO DATA

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE-
o ACUTE TOXICITY :

Numerous cases of dermatitis have been reported (Clayton and Clayton, 1981-82).

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o SIGNS AND SYMPTOMS :

Symptoms include nausea, vomiting, diarrhea, central nervous system depression (Weiss, 1980, p. 1105), coughing, shortness of breath, chest pain, fever and weakness upon inhalation (Rumack, 1975 to Present).

BCF - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption: 1.34E+1 ug/L

Fish Consumption Only: 1.0E+2 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 1.34E+1 ug/L is based on consumption of contaminated aquatic organisms and water. A WQC of 1.0E+2 ug/L has also been established based on consumption of contaminated aquatic organisms alone.

Reference -- 51 FR 43665 (12/03/86)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute -- 1.4E+3 ug/L
Chronic -- 1.6E+2 ug/L

Marine:

Acute -- 7.5E+1 ug/L
Chronic -- 8.3E+0 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- Criteria were derived from a minimum data base consisting of acute and chronic tests on a variety of species. The freshwater criteria are hardness dependent. Values given here are calculated at a hardness of 100 mg/L CaCO3. A complete discussion can be found in the referenced notice.

Reference -- 51 FR 43665 (12/03/86)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value -- 0.1 mg/L (nickel) (Proposed, 1990)

Considers technological or economic feasibility? -- NO

Discussion -- EPA is proposing to regulate nickel based on its potential adverse effects (reduced body and liver weights) reported in a two-year dietary study in rats. The MCLG is based upon a DWEL of 0.58 mg/L and an assumed drinking water contribution of 20 percent.

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 0.1 mg/L (nickel) (Proposed, 1990)

Considers technological or economic feasibility? -- YES

Discussion -- EPA is proposing an MCL equal to the proposed MCLG of 0.1 mg/L.

Monitoring requirements -- Ground water systems every 3 years; surface water systems annually; will allow monitoring at up to 10-year intervals after the system completes 3 rounds of sampling at <50% of the MCL.

Analytical methodology -- Atomic absorption (EPA 249.2; SM 304); inductively-coupled plasma (EPA 200.7; SM 305); ICP mass spectrometry (EPA 200.8): PQL= 0.050 mg/L.

Best available technology -- Ion exchange; reverse osmosis; lime softening.

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

Status -- Listed (nickel) (Final, 1991)

Discussion -- "Unregulated" contaminants are those contaminants for which EPA establishes a monitoring requirement but which do not have an associated final MCLG, MCL, or treatment technique. EPA may regulate these contaminants in the future.

Monitoring requirement -- All systems to be monitored unless a vulnerability assessment determines the system is not vulnerable.

Analytical methodology -- Atomic absorption (EPA 249.2; SM 304); inductively coupled plasma (EPA 200.7; SM 305).

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value -- 100 pounds (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed RQ for soluble nickel salts is 100 pounds, based on potential carcinogenicity. The available data indicate a hazard ranking of low and a weight-of-evidence classification of C, which corresponds to an RQ of 100 pounds.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline (800) 424-9346 / (202) 260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed (total nickel)

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline (800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - Ambrose, A.M., P.S. Larson, J.R. Borzelleca and G.R. Hennigar, Jr. 1976. Long-term toxicologic assessment of nickel in rats and dogs. J. Food Sci. Technol. 13: 181-187.

OREF - ABC (American Biogenics Corp.). 1986. Ninety-day gavage study in albino rats using nickel. Draft Final Report submitted to Research Triangle Institute, P.O. Box 12194, Research Triangle Park, NC 27709.

OREF - Burrows, D., S. Creswell and J.D. Merrett. 1981. Nickel, hands and hip prostheses. Br. J. Dermatol. 105: 437-444.

OREF - Cronin, E., A. Di Michiel and S.S. Brown. 1980. Oral nickel challenge in nickel-sensitive women with hand eczema. In: Nickel Toxicology, S.S. Brown and F.W. Sunderman Jr., Ed. Academic Press, New York. p. 149-152.

OREF - Edwards, M.J. 1986. Hyperthermia as a teratogen: A review of experimental studies and their clinical significance. Terat. Carcin. Mutagen. 6: 563-582.

OREF - Gawkrodger, D.J., S.W. Cook, G.S. Fell and J.A.A. Hunter. 1986. Nickel dermatitis: The reaction to oral nickel challenge. Br. J. Dermatol. 115: 33-38.

OREF - Jordan, W.P. and S.E. King. 1979. Nickel feeding in nickel-sensitive patients with hand eczema. J. Am. Acad. Dermatol. 1(6): 506-508.

OREF - Kaaber, K., N.K. Veien and J.C. Tjell. 1978. Low nickel diet in the treatment of patients with chronic nickel dermatitis. Br. J. Derm. 98: 197-201.

OREF - Kaaber, K., T. Menne, J.C. Tjell and N. Veien. 1979. Antabuse treatment of nickel dermatitis. Chelation - a new principle in the treatment of nickel dermatitis. Contact Derm. 5: 221-228.

OREF - Nielsen, G.D. 1989. Oral challenge of nickel-allergic patients with hand eczema. In: Nickel and Human Health: Current Perspectives. Advances in Environmental Science and Technology, E. Nieboer and A. Aitio, Ed. John Wiley and Sons, Inc., New York, NY. Chapter 16: 1.

OREF - North American Contact Dermatitis Group. 1973. Epidemiology of contact dermatitis in North America: 1972. Arch. Dermatol. 108: 537-540.

OREF - Prystowsky, S.D., A.M. Allen, R.W. Smith, J.H. Nonomura, R.B. Odom and W.A. Akers. 1979. Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine and benzocaine. Relationships between age, sex, history, exposure and reactivity to standard patch tests and use tests in a general population. Arch. Dermatol. 115(8): 959-962.

OREF - RTI (Research Triangle Institute). 1987. Two generation reproduction and fertility study of nickel chloride administered to CD rats in drinking water: Fertility and reproductive performance of the Po generation (Part II of III) and F1 generation (Part III of III). Final study report. Report submitted to Office of Solid Waste Management, U.S. EPA, Washington, DC.

OREF - Schnegg, A. and M. Kirchgessner. 1977. Ni deficiency and its effect on metabolism. In: Trace Element Metabolism in Man and Animals, Vol. 3, M. Kirchgessner, Ed. Freising-Weihenstephan: Tech. Univ. Munich West Germany. p. 236-243.

OREF - Schroeder, H.A. and M. Mitchener. 1971. Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health. 23: 102-106.

OREF - Schroeder, H.A., J.J. Balassa and I.H. Tipton. 1962. Abnormal trace elements in man - nickel. J. Chronic Dis. 15: 51.

OREF - Smith, M.K., J.A. George, H.F. Stober and G.L. Kimmel. 1990. Perinatal toxicity associated with nickel chloride exposure. Fund. Appl. Toxicol. Preliminary unpublished draft.

OREF - Sunderman Jr., F.W., S.M. Hopfer, K.R. Sweeney, A.H. Marcus, B.M. Most and J. Creason. 1989. Nickel absorption and kinetics in human volunteers. Proc. Soc. Exp. Biol. Med. 191: 5-11.
OREF - U.S. EPA. 1986. Health Assessment Document for Nickel. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. (Final Report). EPA/600/8- 83/012FF.
OREF - U.S. EPA. 1991. Quantification of Toxicologic Effects for Nickel. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water, Office of Science and Technology, Washington, DC.
IREF - None
CREF - None
HAREF- None

1 - IRIS
NAME - Nitrate
RN - 14797-55-8
IRSN - 73
DATE - 920120
UPDT - 01/20/92, 52 fields
STAT - Oral RfD Assessment (RDO) on-line 10/01/91
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) pending
STAT - Drinking Water Health Advisories (DWHA) on-line 06/01/91
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 03/31/87 RDO Documentation corrected
IRH - 09/30/87 EXSR Regulatory Action section on-line
IRH - 03/01/88 HADV Health Advisory added
IRH - 07/01/90 RDO Oral RfD summary noted as pending change
IRH - 09/01/90 RDO Withdrawn; new Oral RfD verified (in preparation)
IRH - 05/01/91 RDO Oral RfD summary replaced (RfD changed)
IRH - 05/01/91 REFS Bibliography on-line
IRH - 06/01/91 HADV Health Advisory noted as being revised
IRH - 10/01/91 RDO Uncertainty factor text clarified
IRH - 01/01/92 EXSR Regulatory actions updated
RLEN - 29296
SY - Nitrate
SY - Nitric acid, ion(1-)

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Early clinical signs of methemoglobinemia in excess of 10% (0-3 months old infants formula) Human Epidemiological Surveys Bosch et al., 1950; Walton, 1951	NOAEL: 10 mg nitrate-nitrogen/L (1.6 mg/kg/day) LOAEL: 11-20 mg nitrate-nitrogen/L (1.8-3.2 mg/kg/day)	1	1	1.6E+0 mg/kg/day

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*Conversion Factor: Expressed as the amount of nitrogen within the nitrite molecule commonly shown as mg nitrate-nitrogen/L (1 mg nitrate-nitrogen = 4.4 mg nitrate). Doses based on ingestion of drinking water used to prepare infants' formula: 0.64 L/day by a 4 kg infant (0.16 L/kg/day) (Davidson et al., 1975). 10 mg/L x 0.64 L/day divided by 4 kg = 1.6 mg/kg/day.

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o ORAL RFD STUDIES :

Bosch, H.M., A.B. Rosefield, R. Huston, H.R. Shipman and F.L. Woodward. 1950. Methemoglobinemia and Minnesota well supplies. J. Am. Water Works Assoc. 42: 161-170.

Walton, G. 1951. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am. J. Public Health. 41: 986-996.

Most cases of infant methemoglobinemia are associated with exposure to nitrate in drinking water used to prepare infants' formula at levels >20 mg/L of nitrate-nitrogen (Bosch et al., 1950; Walton, 1951; Sattelmacher, 1962; Simon et al., 1964; ECETOC, 1988). Cases reported at levels of 11-20 mg/L nitrate-nitrogen are usually associated with concomitant exposure to bacteriologically contaminated water or excess intake of nitrate from other sources.

Bosch et al. (1950) evaluated 139 cases of cyanosis due to methemoglobinemia reported by physicians in Minnesota. All of the cases were in young children (ages 8 days to 5 months), with 90% occurring in infants <2 months of age. A study of the nitrate concentration of the wells (a total of 129) used to supply water to the children with methemoglobinemia was performed. None of the wells contained <10 mg/L nitrate-nitrogen. Two wells (1.5%) contained 10-20 mg/L, although the diagnosis of methemoglobinemia was considered questionable in both these cases. There were 25 wells (19%) that contained 21-50 mg/L, 53 (41%) that contained 51-100 mg/L, and 49 (38%) that contained >100 mg/L nitrate-nitrogen. Nearly all the wells were shallow with inadequate protection from surface contamination. Coliform organisms were detected in 45 of 51 samples (88%) tested for bacterial contamination.

Walton (1951) described a survey performed by the American Public Health Association to identify clinical cases of infantile methemoglobinemia that were associated with ingestion of nitrate-contaminated water. A total of 278 cases of methemoglobinemia were reported. Of 214 cases for which data were available on nitrate levels in water, none occurred in infants consuming water containing <10 mg nitrate-nitrogen/L (1.6 mg nitrate-nitrogen/kg/day). There were 5 cases (2%) in infants exposed to 11-20 mg nitrate-nitrogen/L (1.8-3.2 mg/kg/day), 36 cases (17%) in infants exposed to 21-50 mg/L (3.4-8.0 mg/kg/day), and 173 (81%) in infants exposed to >50 mg/L (>8 mg/kg/day). Data on the ages of the infants were not provided.

Cornblath and Hartmann (1948) supplied nitrate-containing water to eight healthy infants (ages 2 days to 11 months) at doses of 50 or 100 mg NO3/kg/day (11 or 23 mg nitrate-nitrogen/kg/day). Assuming average consumption of about 0.16 L/kg/day, this corresponds to concentrations of 70 or 140 mg nitrate-nitrogen/L. No cyanosis was evident in any infant, and the highest concentration of methemoglobin was 7.5%. These authors also administered doses of 100 mg/kg of nitrate to four healthy infants (age 2 days to 6 months) and to two infants (age 6 and 7 weeks) who had been admitted to the hospital for cyanosis. No cyanosis was produced in the healthy infants, but cyanosis did occur in the individuals with a prior history of cyanosis. Examination of the saliva, gastric juice and stools of these infants revealed the presence of bacteria that readily reduced nitrate to nitrite. The gastric pH of these infants was >4 in both cases.

Donahoe (1949) reported five cases of moderate to severe cyanosis in infants (age 1-7 weeks) in South Dakota. In four of the five cases, the water used to feed the infants was from shallow wells and was shown to be heavily contaminated with bacteria. Nitrate levels were measured in two cases, with values of 50 and 177 mg/L (12 and 41 mg nitrate-nitrogen/L), respectively. This corresponds to doses of 8 and 28 mg nitrate- nitrogen/kg/day.

Simon et al. (1964) measured methemoglobin levels in 89 healthy infants who received nitrate-free water, 38 infants who received water containing 11-23 mg nitrate-nitrogen/L (1.8-3.7 mg nitrate-nitrogen/kg/day), and 25 infants receiving water containing >23 mg nitrate-nitrogen/L (>3.7 mg nitrate-nitrogen/kg/day). For infants age 1-3 months, mean methemoglobin levels in these three groups were 1.0, 1.3 and 2.9%, respectively. For infants age 3-6 months, values were 0.8, 0.8 and 0.7%, respectively. No clinical signs of methemoglobinemia were detected in any of the infants.

Toussaint and Selenka (1970) supplied 34 healthy infants (age 1-3 months) with formula prepared with water containing 150 mg nitrate/L (34.5 mg nitrate-nitrogen/L, corresponding to 5.5 mg nitrate-nitrogen/kg/day). Average methemoglobin levels rose from about 1% to about 2-3% within 1-2 days, and then tended to stay steady for up to 10 days. No clinical signs of methemoglobinemia were reported.

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o ORAL RFD UNCERTAINTY :

UF = 1. An uncertainty factor of 1 was employed because available data define the no-observed-adverse-effect level for the critical toxic effect in the most sensitive human subpopulation.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

Nitrate toxicity is due primarily to its conversion to nitrite, which oxidizes the Fe(+2) form of iron in hemoglobin to the Fe(+3) state. This compound (methemoglobin) does not bind oxygen, resulting in reduced oxygen transport from lungs to tissues. Low levels of methemoglobin occur in normal individuals, with typical values usually ranging from 0.5 to 2.0% (NAS, 1981). However, due to the large excess capacity of blood to carry oxygen, levels of methemoglobin up to around 10% are not associated with any significant clinical signs (Walton, 1951; ECETOC, 1988). Concentrations above 10% may cause a bluish color to skin and lips (cyanosis), while values above 25% lead to weakness, rapid pulse and tachypnea (Jones et al., 1973). Death may occur if methemoglobin values exceed 50-60%.

Conversion of nitrate to nitrite is mostly mediated by bacteria in the gastrointestinal system. Consequently, the risk of methemoglobinemia from ingestion of nitrate depends not only on the dose of nitrate, but also on the number and type of enteric bacteria. In healthy adults, available data suggest about 5% of a dose of nitrate is reduced to nitrite by bacteria in the mouth (NAS, 1981). Conversion of nitrate to nitrite may also occur in the stomach if the pH of the gastric fluid is sufficiently high (above pH 5) to permit bacterial growth. This is of concern in adults with diseases such as achlorhydria or atrophic gastritis. It is also of concern in infants, since the infant gastrointestinal system normally has a high pH that favors the growth of nitrate-reducing bacteria. For this reason, infants (especially age 0-3 months) are generally recognized as being the subpopulation most susceptible to nitrate-induced methemoglobinemia. Risk is especially high in infants who are exposed to water that is contaminated with bacteria, since this tends to promote high concentrations of bacteria in the stomach and intestines.

Nitrate is a normal component of the human diet. A typical daily intake by an adult in the United States is about 75 mg/day (about 0.2-0.3 mg nitrate-nitrogen/kg/day) (NAS, 1981). Of this, over 85% comes from the natural nitrate content of vegetables such as beets, celery, lettuce and spinach. Daily intakes of nitrate by vegetarians may exceed 250 mg/day (0.8 mg nitrate-nitrogen/kg/day) (NAS, 1981). The contribution from drinking water is usually quite small (about 2-3% of the total) (NAS 1981), but could reach 85 mg/day (0.29 mg nitrate-nitrogen/kg/day) if water containing 10 mg nitrate-nitrogen/L was consumed. Thus, some adults consuming high levels of vegetables along with water containing high levels of nitrate (up to 10 mg nitrate-nitrogen/L) could receive total doses of nitrate approaching the RfD of 1.6 mg nitrate-nitrogen/kg/day.

Two epidemiological studies have been performed on the adverse effects of nitrate exposure, but the results are internally inconsistent or inconclusive. Dorsch et al. (1984) found a statistically significant increase in risk of birth defects in children of women consuming groundwater (which contained 5-15 mg/L of nitrate) compared with women consuming rainwater (which contained <5 mg/L nitrate). These authors emphasized that their results are limited by a number of factors, and stated that "it would be premature to interpret our case-control findings exclusively in terms of water nitrate exposure." Arbuckle et al. (1988) reported nonstatistically significant increase in the odds ratio for birth defects in children of women exposed to well-water (26 mg/L nitrate, equivalent to 0.2 mg nitrate- nitrogen/kg/day) compared with rain water (0.1 mg/L nitrate, equivalent to 0.0008 mg nitrate-

nitrogen/kg/day). However, decreased odds ratios (also not statistically significant) were noted for exposure to nitrate in spring water (17 mg/L, equivalent to 0.13 mg nitrate-nitrogen/kg/day) or public water (26 mg/L).

Craun et al. (1981) conducted an epidemiologic study of 102 children aged 1-8 years in Washington County, Illinois. Sixty-four children were selected from families consuming high-nitrate water (22-111 mg/L nitrate-nitrogen) and 38 children (controls) were from families consuming water containing <10 mg/L nitrate-nitrogen. Ingestion of high-nitrate water was not found to result in above-normal methemoglobin levels in exposed children. Assuming ingestion of 0.1 L/kg/day by older children, these concentrations correspond to doses of 2.2-11 mg nitrate-nitrogen/kg/day. This study indicates that older children are much less susceptible to nitrate-induced methemoglobinemia than are infants.

The Food and Drug Administration sponsored extensive tests of the reproductive and developmental effects of $NaNO_3$ and KNO_3 in mice, rats, hamsters and rabbits (FDA, 1972a,b). Groups of 20-26 mice, rats or hamsters and 10-13 rabbits were treated by gavage on days 6-15 (mice, rats), days 6-10 (hamster) or days 6-18 (rabbits) of gestation. Fetuses were delivered by Cesarean section and examined for visceral and skeletal malformations. Dose levels (expressed as mg nitrate-nitrogen) ranged from 0.6-66 mg/kg/day for mice, from 0.3-41 mg/kg/day for rats, from 0.4-66 mg/kg/day for hamsters and from 0.3-41 mg/kg/day for rabbits. No significant effects were detected regarding maternal reproductive parameters (percent pregnant, abortion frequency, number of litters), fetotoxicity (percent fetal resportions, live fetuses per dam, average fetal weight) or fetal malformations up to the maximum doses administered to each species. These studies identify a reproductive/developmental NOAEL of 66 mg nitrate-nitrogen/kg/day for mice and hamsters and 41 mg nitrate-nitrogen/kg/day for rats and rabbits.

Sleight and Atallah (1968) studied the effects of nitrate on reproduction and development in guinea pigs. Groups of 3-6 females were exposed to drinking water containing 0, 300, 2500, 10,000 or 30,000 ppm KNO_3 for 143-204 days. This resulted in average doses of 0, 12, 102, 507 or 1130 mg nitrate-nitrogen/kg/day. Normal conception occurred at all dose levels. No significant effect on reproductive performance was detected except in the high-dose group, where there was a decrease in number of live births. The authors attributed the fetotoxic effects to hypoxia due to maternal methemoglobinemia, although data on this were not provided. No fetal malformations were observed at any dose. This study identifies a reproductive NOAEL of 507 and a LOAEL of 1130 mg nitrate-nitrogen/kg/day.

No multi-generation studies were located on the reproductive effects of nitrate. In the absence of such data, observations from animals exposed to nitrite may be used as a conservative estimate of nitrate toxicity.

Hugot et al. (1980) performed a three-generation study in rats. Female animals were administered sodium nitrite in the diet at doses of 90 or 160 mg nitrite-nitrogen/kg/day. There were no effects on a number of reproductive parameters. Some pups showed small decreases in birth weight and growth rate during lactation, and changes in organ weights at weaning. This study identifies a LOAEL of 90 mg nitrite-nitrogen/kg/day. Assuming that a maximum of 10% of a dose of nitrate is converted to nitrite by an adult human, this would correspond to a LOAEL of 900 mg nitrate-nitrogen/kg/day.

Druckrey et al. (1963) supplied rats with $NaNO_2$ in drinking water for three generations at a dose level of 100 mg/kg/day (20 mg nitrite-nitrogen/kg/day). No teratogenic effects or adverse effects on reproduction were detected in any generation. Assuming that a maximum of 10% of a dose of nitrate is converted to nitrite by an adult human, this would correspond to a NOAEL of 200 mg nitrate-nitrogen/kg/day.

No studies were located on systemic effects of nitrate in humans or

animals. In the absence of such data, observations from animals exposed to nitrite may be used as a conservative estimate of nitrate toxicity. Druckrey et al. (1963) exposed rats for their lifetime to $NaNO_2$ in drinking water at a dose of 100 mg/kg/day (20 mg nitrite-nitrogen/kg/day). No treatment-related histologic or hematologic effects were noted except for elevated methemoglobin levels in the treated animals.

Til et al. (1988) supplied rats with drinking water containing up to 3000 mg/L of KNO_2 (500 mg nitrite-nitrogen/L, equivalent to 50 mg nitrite-nitrogen/kg/day) for 13 weeks. No histological effects were detected except for a very slight to slight hypertrophy of the zona glomerulosa. This was probably due to reduced water intake, and is not judged to constitute an adverse health effect. This study identifies a NOAEL of 17 and a LOAEL of 50 mg nitrite-nitrogen/kg/day (based on methemoglobin levels). Assuming that a maximum of 10% of a dose of nitrate is converted to nitrite by an adult human, this would correspond to a NOAEL of 170 and a LOAEL of 500 mg nitrate-nitrogen/kg/day.

Shuval and Gruener (1972) exposed rats for 24 months to water containing 0, 100, 1000, 2000 or 3000 ppm of sodium nitrite (0, 2, 20, 40 or 60 mg nitrite-nitrogen/kg/day). Histological examination of the lungs revealed dilated bronchi, fibrosis and emphysema at 1000 ppm or above. Histological examination of the heart revealed an increased percentage of coronary arteries that were characterized as "thin and dilated." This effect appears to be at least partly due to the absence of coronary artery thickening and narrowing that normally occurs in aged rats, so it is not certain that these changes are inherently adverse. Based on effects on the lung, this study identifies a NOAEL of 2 and a LOAEL of 20 mg nitrite-nitrogen/kg/day. Assuming that a maximum of 10% of a dose of nitrate is converted to nitrite by an adult human, this would correspond to a NOAEL of 20 and a LOAEL of 200 mg nitrate-nitrogen/kg/day.

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o ORAL RFD CONFIDENCE :

Study: High
Data Base: High
RfD: High

The studies of Bosch et al. (1950) and Walton (1951) provide convincing evidence that infantile methemoglobinemia does not occur at drinking water levels of 10 mg nitrate-nitrogen/L or less. This is supported by a large number of additional epidemiological and case studies in humans (e.g., Cornblath and Hartmann, 1948; Simon et al., 1964; Toussaint and Selenka, 1970; Craun et al., 1981; see U.S. EPA, 1990 for descriptions of additional studies).

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o ORAL RFD SOURCE DOCUMENT :

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1990

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o REVIEW DATES : 11/21/85, 02/05/86, 02/26/86, 06/20/90, 07/25/90, 08/22/90
o VERIFICATION DATE : 08/22/90
o EPA CONTACTS :

Susan Griffin / OSW -- (202)260-6392 / FTS 260-6392

Ken Bailey / OW -- (202)260-5535 / FTS 260-5535

RDI - NO DATA
CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

HAONE-

NOTE: The Health Advisory for nitrate will be revised by the Office of Water.

Appropriate data for calculating a One-day HA are not available. It is recommended that the Ten-day HA values (calculated below) be used as the One-day HA values.

HATEN-

NOTE: The Health Advisory for nitrate will be revised by the Office of Water.

In developing the nitrate/nitrite HA it was determined that the 4-kg infant is the most sensitive member of the population with respect to both nitrate and nitrite. This determination was based on studies by Walton (1951) and Craun, et al. (1981). Walton (1951) reported over 278 cases of cyanosis and, in some cases, mortality in infants associated with the consumption of water containing greater than 10 mg/L nitrate-nitrogen. In relation to populations other than the 4-kg infant, Craun et al. (1981) reported that ingestion of water containing 22 to 111 mg/L nitrate-nitrogen by children aged 1 to 8 years did not result in abnormal mean methemoglobin levels and was not related to increased methemoglobin levels in comparison to controls.

Therefore, while the Ten-day HA is usually derived for the 10-kg child, in this case this value was derived for the most sensitive members of the population (4-kg infants), as well as for other populations.

Ten-day HA for 4-kg infant -- 1E+1 mg/L nitrate-nitrogen

NOAEL -- 10 mg/L
UF -- 1 (used for human study in sensitive subpopulations)
Assumptions -- none

Principal study -- Walton, 1951

More than 278 cases of cyanosis, and in some cases, mortality were associated with consumption of nitrate-contaminated water by the infant. No cases associated with water containing 10 mg/L or less of nitrate-nitrogen were found.

Ten-day HA for a 10-kg child -- 1E+2 mg/L nitrate-nitrogen

NOAEL -- 111 mg/L
UF -- 1 (used for human study in sensitive subpopulations)
Assumptions -- none

Principal Study -- Craun et al., 1981

In an epidemiologic study of 102 children aged 1 to 8 years, 64 of the study subjects consumed water with high nitrate levels (22 to 111 mg/L nitrate-nitrogen) and 38 consumed water with low nitrate levels (<10 mg/L nitrate-nitrogen). Ingestion of water containing 22 to 111 mg/L nitrate-nitrogen did not result in abnormal mean methemoglobin levels and was not related to increased methemoglobin levels in comparison to controls. In the

entire study group of 102 children, only five had methemoglobin levels >2% (maximum of 3.1% in a child from the low exposure group).

HALTC-

NOTE: The Health Advisory for nitrate will be revised by the Office of Water.

Appropriate data for calculating Longer-term HAs are not available. However, as previously discussed, the 4-kg infant is the most sensitive member of the population with respect to the formation of methemoglobin induced by either nitrite directly or by the in vivo reduction of nitrate to nitrite. In addition, as the 4-kg infant ages (e.g., to a 10-kg child), sensitivity to the effects of methemoglobin as well as the amount of nitrate reduced to nitrite decreases, thus rendering the older child and adult less sensitive to the effects of both nitrate and nitrite. Thus, it has been concluded that the Ten-day HA for the 4-kg infant for nitrate-nitrogen (10 mg/L) will offer adequate protection against methemoglobin formation in all other age groups as well.

HALTA-

NOTE: The Health Advisory for nitrate will be revised by the Office of Water.

Appropriate data for calculating Longer-term HAs are not available. See explanation in HALTC.

HALIF-

NOTE: The Health Advisory for nitrate will be revised by the Office of Water.

Appropriate data for calculating a DWEL or a Lifetime HA are not available.

OLEP -

No data available

ALAB -

Determination of nitrite alone, or nitrite and nitrate combined, is by colorimetry or spectrophotometry.

TREAT-

Treatment techniques which are capable of removing nitrates from drinking water include ion exchange and reverse osmosis.

HADR -
o HEALTH ADVISORY SOURCE :

U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Nitrates/Nitrites. Office of Drinking Water, Washington, DC.
DOCUMENT

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o HEALTH ADVISORY REVIEW :

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

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o EPA DRINKING WATER CONTACT :

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CAA - NO DATA

WQCHU-

No data available

WQCAQ-

Freshwater:

Acute -- none
Chronic -- none

Marine:

Acute -- none
Chronic -- none

Considers technological or economic feasibility? -- NO

Discussion -- Recognizing that concentrations of nitrate/nitrite that would exhibit toxic effects on fish could rarely occur in nature, restrictive criteria were not recommended.

Reference -- Quality Criteria for Water, EPA 440/9-76-023 (7/76), PB-263943.

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 10.0 mg/L [as nitrogen] (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- Nitrate has been classed a Category III contaminant with methemoglobinemia in infants identified as the most sensitive endpoint. A level of 10 mg of nitrate will protect infants, and all other groups against the non-oncogenic effects presented by nitrate in drinking water. In reaching this conclusion, the agency examined a large body of studies concerning chronic toxicity, developmental and reproductive toxicity, and methemoglobinemia (among other endpoints). Both human and animal experimental data were included in this analysis. The MCLG is based upon a DWEL for

nitrate/nitrogen of 10 mg/L with an uncertainty factor of 1.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST / (202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value (status) -- 10 mg/L [as nitrogen] (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- The EPA has promulgated an MCL equal to the MCLG of 10.0 mg/L.

Monitoring requirements -- Ground water systems monitored every three years; surface water systems monitored annually; systems out of compliance must begin monitoring quarterly until system is reliably and consistently below MCL.

Analytical methodology -- Manual cadmium reduction (EPA 353.3; SM 418C; ASTM D-3867-79B); automated hydrazine reduction (EPA 353.1); automated cadmium reduction (EPA 353.2; SM 418F; ASTM D-3867-79A); ion selective electrode; ion chromatography (EPA 300; SM 429; ASTM D-4327-88): PQL= 0.4 mg/L.

Best available technology -- Ion exchange; reverse osmosis; electrodialysis.

Reference -- 56 FR 3256 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC - NO DATA

SARA - NO DATA

RCRA - NO DATA

TSCA -

No data available

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OREF - Bosch, H.M., A.B. Rosefield, R. Huston, H.R. Shipman and F.L. Woodward. 1950. Methemoglobinemia and Minnesota well supplies. J. Am. Water Works Assoc. 42: 161-170.
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Drinking Water, Washington, DC.
OREF - Walton, G. 1951. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am. J. Public Health. 41: 986-996.
IREF - None
CREF - None
HAREF- Craun, G.F., D.G. Greathouse and D.H. Gunderson. 1981. Methemoglobin levels in young children consuming high nitrate well water in the United States. Int. J. Epidemiol. 10: 309-317.
HAREF- U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Nitrates/Nitrites. Office of Drinking Water, Washington, DC.
HAREF- Walton, G. 1951. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am. J. Pub. Health. 41: 986-996.

2 - IRIS
NAME - Thallium nitrate
RN - 10102-45-1
IRSN - 111
DATE - 920122
UPDT - NO DATA
STAT - Oral RfD Assessment (RDO) on-line 09/01/90
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 09/01/90
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 03/31/87 RDO Documentation corrected
IRH - 06/30/88 RDO RfD withdrawn
IRH - 09/07/88 RDO Revised oral RfD summary added
IRH - 06/01/89 RDO Work group review dates revised
IRH - 09/01/90 RDO Text edited
IRH - 09/01/90 RDO Secondary contact changed
IRH - 09/01/90 CAR Carcinogen assessment on-line
IRH - 09/01/90 RCRA EPA contact changed
IRH - 09/01/90 REFS Bibliography on-line
IRH - 08/01/91 CREF Kada et al. citation corrected
IRH - 01/01/92 EXSR Regulatory actions updated
RLEN - 16392
SY - RCRA WASTE NUMBER U217
SY - THALLIUM(1+) SALT NITRIC ACID
SY - THALLIUM MONONITRATE
SY - Thallium nitrate
SY - THALLOUS NITRATE
SY - UN 2727

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased levels of SGOT and LDH	NOAEL: 0.25 mg/kg/day (Tl2SO4) (converted to 0.26 mg/kg/day TlNO3)	3000	1	9E-5 mg/kg/day
Rat Oral Subchronic Study	LOAEL: None			
U.S. EPA, 1986				

*Conversion Factors: 0.25 mg/kg/day Tl2SO4 = 0.20 mg/kg/day Tl; 0.20 mg/kg/day Tl x [molecular weight of TlNO3 (266) divided by molecular weight of Tl (204.4)] = 0.26 mg/kg/day TlNO3

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o ORAL RFD STUDIES :

U.S. EPA. 1986. Subchronic (90-day) toxicity of thallium sulfate in Sprague-Dawley rats. Office of Solid Waste, Washington, DC.

In a 90-day subchronic study, Sprague-Dawley rats (20/sex/group) were treated by gavage with 0, 0.01, 0.05, or 0.25 mg/kg/day of an aqueous solution of thallium sulfate (approximately 0, 0.008, 0.04, or 0.20 mg Tl/kg/day). Data generated from this study included body and organ weights, food consumption, hematology and clinical chemistry parameters, neurotoxicologic examinations, ophthalmologic examinations, and histopathology and neuropathology. No mortality was observed, but apparent dose-related increases in the incidence of alopecia, lacrimation, and exophthalmos were observed throughout the study. No differences between the control groups and groups receiving thallium nitrate were observed in body weights, body weight gains, food consumption, or absolute and relative organ weights. Moderate dose-related changes were observed in some blood chemistry parameters: increased SGOT, LDH, and sodium levels, and decreased blood sugar levels. The only grossly observed finding at necropsy thought to be treatment-related was alopecia, especially in female rats; however, microscopic evaluations did not reveal any histopathologic alterations. Based on the results of this study the highest dose, 0.25 mg/kg/day thallium sulfate (0.20 mg/kg/day Tl), is considered a NOAEL. Using the molecular weight of TlNO3 to Tl (266/204.4) for conversion, this NOAEL was converted to 0.26 mg/kg/day TlNO3.

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o ORAL RFD UNCERTAINTY :

UF = 3000. The UF of 3000 includes factors of 10 to extrapolate from subchronic to chronic data, 10 for intraspecies extrapolation and 10 to account for interspecies variability, and a factor of 3 to account for lack of reproductive and chronic toxicity data.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

Groups of rats (5/sex/dose) were fed diets containing nominal concentrations of thallium acetate of 0, 5, 15, or 50 ppm (Downs et al., 1960). An additional group (30 ppm) was added after the study had been initiated (time not specified). Animals were allowed ad lib access to these diets for 15 weeks. The 50 ppm level resulted in 100% mortality by week 5. The 30 ppm level resulted in 100% mortality by week 9. By week 15, 4/10 control animals died (2/sex), making interpretation of survival in remaining dose groups difficult (15 ppm, 3/5 males and 1/5 females died; 5 ppm, 2/6 males and 0/4 females died). At termination, the only gross finding was alopecia in the 15 and 30 ppm groups. The authors stated that there was a slight increase in kidney weight (doses not specified, data not shown). The authors reported that histopathologic evaluations did not indicate treatment-related pathology.

Male Wistar rats (10/group) were administered drinking water containing 10 ppm Tl_2SO_4 (approximately 0.7 mg Tl/kg/day based on reported thallium consumptions [270 ug Tl/rat] and body weights [350-370 g] for 30 or 60 days; controls were pair fed. After 60 days of treatment, the following testicular effects were observed: disarrangement of the tubular epithelium, cytoplasmic vacuolation and distention of the smooth endoplasmic reticulum of the Sertoli cells, reduced testicular beta-glucuronidase activities, high concentrations of thallium in the testes, and reduced sperm motility (Formigli et al., 1986).

Eighty female Sprague-Dawley rats were administered drinking water containing thallium sulfate at a concentration of 10 mg Tl/L (approximately equivalent to a dose of 1.4 mg Tl/kg/day based on reported Tl intakes and an assumption that the rats weighed 200 g). Mortality was 15 and 21% after 40 and 240 days of treatment, respectively. Functional and histopathological changes were observed in the peripheral nerves including changes in motor and

sensory action potentials and histopathological changes in the sciatic myelin sheath and axonal destruction characterized by Wallerian degeneration, mitochondrial degeneration, neurofilamentous clustering, and elevated lysozomal activity (Manzo et al., 1983).

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o ORAL RFD CONFIDENCE :

Study: Low
Data Base: Low
RfD: Low

Confidence in the critical study is rated low because of uncertainties in the results (i.e., vehicle vs. control differences) and because supporting studies show adverse health effects at doses slightly higher than the NOAEL. The data base provided only one subchronic study and some anecdotal human data, thus, a low confidence was assigned. Until additional chronic and reproductive studies are available, confidence in the RfD is considered low.

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o ORAL RFD SOURCE DOCUMENT :

The only U.S. EPA documentation at present is on IRIS.

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o REVIEW DATES : 08/05/87, 04/21/88
o VERIFICATION DATE : 04/21/88
o EPA CONTACTS :

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

Robert Cantilli / ODW -- (202)260-5546 / FTS 260-5546

RDI - NO DATA
CAREV-
o CLASSIFICATION : D; not classifiable as to human carcinogenicity
o BASIS FOR CLASSIFICATION : Based on the lack of carcinogenicity data in animals and humans.

o HUMAN CARCINOGENICITY DATA :

Inadequate. Medical records for 86 workers (sex and length of employment not reported) occupationally exposed to thallium at a magnesium seawater battery factory and 79 unexposed workers matched for age, length of employment, shift pattern, and type of work were examined (Marcus, 1985). No increase in incidence of benign neoplasms (site not specified) were observed. This study is limited by the examination of medical records only, lack of exposure quantitation, the small cohort, and unknown length of observation.

In another study, the health effects associated with exposure to thallium in 128 men (age 16 to 62 years) exposed for 1 to 42 years (average=19.5 years) in three cement manufacturing plants were reported (Schaller et al., 1980). Analyses of roasted pyrites and electro-filter dust confirmed the presence of thallium in various production areas in the plants. Urinary thallium was elevated in the workers. The health evaluation, consisting of a medical history and a physical exam, did not show any indication of thallium poisoning. However, this health evaluation was not adequate to detect any oncogenic response.

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o ANIMAL CARCINOGENICITY DATA :

None. Several subchronic and chronic animal studies on thallium and compounds are available; however, they were not designed to examine

carcinogenic endpoints (reviewed in U.S. EPA, 1988).

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o SUPPORTING DATA :

Thallium (I) salts were not mutagenic in reverse mutation assays using Salmonella typhimurium strains TA98, TA100, TA1535,and TA1538 and Escherichia coli strains B/r WP2 try and WP2 hcr try; use of hepatic homogenates was not specified (Kanematsu et al., 1980). Positive results were obtained at 0.001M for thallium nitrate in the Rec assay using Bacillus subtilis strains H17 and M45; use of hepatic homogenates was not specified (Kanematsu\et\al., 1980; Kada et al., 1980). Negative results were obtained in a screening of thallium nitrate for induction of mitotic gene coversion and reverse mutation in the yeast, Saccharomyces cerevisiae (Singh, 1983). Thallium nitrate produced negative effects on cell division in S. cerevisiae and E. coli. (Loveless et al., 1954). Cytotoxic levels (1000 ug/mL) of thallium acetate caused depressed DNA synthesis in Chinese hamster ovary cells (Garrett and Lewtas, 1983). Single-strand DNA breaks occurred in mouse and rat embryo fibroblasts exposed to thallium carbonate at E-6 to E-4M (Zasukhina et al., 1983). Thallium carbonate (0.5-0.005 ug/kg/day) was positive in a dominant lethal test in male white rats (Zasukhina et al., 1983).

CARO - NO DATA
CARI - NO DATA
CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1988. Health and Environmental Effects Document for Thallium and Compounds. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC.

The 1988 Health and Environmental Effects Document for Thallium and Compounds is a preliminary draft and has not received Agency review.
DOCUMENT

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o REVIEW DATES : 11/08/89
o VERIFICATION DATE : 11/08/89
o EPA CONTACTS :

William Pepelko / ORD -- (202)260-5904 / FTS 260-5904

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption: 13 ug/L [thallium]

Fish Consumption Only: 48 ug/L [thallium]

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 13 ug/L is based on consumption of contaminated aquatic organisms and water. A WQC of 48 ug/L has also been established based on consumption of contaminated aquatic organisms alone.

Reference -- 45 FR 79318 (11/28/80); NTIS No. PB81-117848.

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute LEC -- 1.4E+3 ug/L [thallium]
Chronic LEC -- 4.0E+1 ug/L [thallium]

Marine:

Acute LEC -- 2.13E+3 ug/L [thallium]
Chronic LEC -- None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria but are the lowest level effect levels found in the literature. LEC's are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80); NTIS No. PB81-117848.

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value -- 0.0005 mg/L (thallium) (Proposed, 1990)

Considers technological or economic feasibility? -- NO

Discussion -- EPA is proposing to regulate thallium based on its potential adverse effects (blood chemistry) reported in a subchronic rat study. The MCLG is based upon a DWEL of 0.0023 mg/L and an assumed drinking water contribution of 20 percent.

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Health and Ecological Criteria Division / OST / (202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 0.002 mg/L (thallium) (Proposed, 1990)

Considers technological or economic feasibility? -- YES

Discussion -- EPA is proposing alternate MCLs of 0.002 or 0.001 for thallium based on the proposed PQL.

Monitoring requirements -- Ground water systems every 3 years; surface water systems annually; will allow monitoring at up to 10-year intervals after the system completes 3 rounds of sampling at <50% of the MCL.

Analytical methodology -- Atomic absorption /furnace technique (EPA 279.2; SM 304); ICP mass spectrometry (EPA 200.8): PQL= 0.002/0.001 mg/L.

Best available technology -- Activated alumina; ion exchange.

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

Status -- Listed (thallium) (Final, 1991)

Discussion -- "Unregulated" contaminants are those contaminants for which EPA establishes a monitoring requirement but which do not have an associated final MCLG, MCL, or treatment technique. EPA may regulate these contaminants in the future.

Monitoring requirement -- All systems to be monitored unless a vulnerability assessment determines the system is not vulnerable.

Analytical methodology -- Atomic absorption/furnace technique (279.2; SM 304).

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 100 pounds (Final, 1986)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on chronic toxicity. RQ assignments based on chronic toxicity reflect two primary attributes of the hazardous substance, the minimum effective dose (MED) levels for chronic exposure (mg/day for a 70-kg person) and the type of effect (liver necrosis, teratogenicity, etc). A composite score is determined from an evaluation of these two attributes. Thallium nitrate was determined to have a composite score of between 21 and 40, corresponding to a chronic toxicity RQ of 100 pounds.

Reference -- 51 FR 34534 (09/29/86); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed (total thallium)

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

OREF - Downs, W.L., J.K. Scott, L.T. Steadman and E.A. Maynard. 1960. Acute and subacute toxicity studies of thallium compounds. Am. Ind. Hyg. Assoc. 21: 399-406.

OREF - Formigli, L., R. Schelsi, P. Poggi, et al. 1986. Thallium-induced testicular toxicity in the rat. Environ. Res. 40(2): 531-539.

OREF - Manzo, L., R. Scelsi, A. Moglia, et al. 1983. Long-term toxicity of thallium in the rat. Proceed. 2nd Int. Conf., Chem. Toxicol. Clin. Chem. Met. p. 401- 405.

OREF - U.S. EPA. 1986. Subchronic (90-day) toxicity of thallium sulfate in Sprague-Dawley rats. Office of Solid Waste, Washington, DC.

IREF - None

CREF - Garrett, N.E. and J. Lewtas. 1983. Cellular toxicity in Chinese hamster ovary cell cultures. I. Analysis of cytotoxicity endpoints for twenty-nine priority pollutants. Environ. Res. 32: 455-465.

CREF - Kada, T., K. Hirano and Y. Shirasu. 1980. Screening of environmental chemical mutagens by the Rec-assay system with Bacillus subtilis. In: Chemical Mutagens: Principles and Methods for Their Detection, F. deSerrres and A. Hollaender, Ed. 6: 149-173.

CREF - Kanematsu, N., M. Hara and T. Kada. 1980. Rec assay and mutagenicity

studies on metal compounds. Mutat. Res. 77: 109-116.
CREF - Loveless, L.E., E. Spoerl and T.H. Weisman. 1954. A survey of effects of chemicals on division and growth of yeast and Escherichia coli. J. Bacteriol. 68: 637-644.
CREF - Marcus, R.L. 1985. Investigation of a working population exposed to thallium. J. Soc. Occup. Med. 35(1): 4-9.
CREF - Schaller, K.H., G. Manke, H.J. Raithel, G. Buhlmeyer, M. Schmidt and H. Valentin. 1980. Investigations of thallium-exposed workers in cement factories. Int. Arch. Occup. Environ. Health. 47(3): 223-231.
CREF - Singh, I. 1983. Induction of reverse mutation and mitotic gene conversion by some metal compounds in Saccharomyces cerevisiae. Mutat. Res. 117: 149-152.
CREF - U.S. EPA. 1988. Health and Environmental Effects Document for Thallium and Compounds. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC.
CREF - Zasukhina, G.D., I.M. Vasilyeva, N.I. Sdirkova, et al. 1983. Mutagenic effect of thallium and mercury salts on rodent cells with different repair activities. Mutat. Res. 124(2): 163-173.
HAREF- None

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USER:
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[IRIS] SS 6 /cf?
USER:

??

[IRIS] SS 6 /cf?
USER:
find 75-35-4

Search in progress

SS (6) PSTG (1)

[IRIS] SS 7 /cf?
USER:

1 - IRIS
NAME - Nitrite
RN - 14797-65-0
IRSN - 75
DATE - 920807
UPDT - 08/07/92, 52 fields
STAT - Oral RfD Assessment (RDO) on-line 08/01/92
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) pending 08/01/92
STAT - Drinking Water Health Advisories (DWHA) on-line 03/01/88
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 03/31/87 RDO Documentation corrected
IRH - 09/30/87 EXSR Regulatory Action section on-line
IRH - 03/01/88 RDO Text added
IRH - 03/01/88 HADV Health Advisory added
IRH - 08/01/91 RDO Oral RfD summary noted as pending change
IRH - 08/01/91 REFS Bibliography on-line
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 08/01/92 RDO Work group review date added
RLEN - 13570
SY - Nitrite
SY - Nitrous acid, ion(1-)

RDO -
o ORAL RFD SUMMARY :

NOTE: The oral RfD for nitrite may change in the near future pending the outcome of a further review now being conducted by the RfD/RfC Work Group.

Critical Effect	Experimental Doses*	UF	MF	RfD
Methemoglobinemia Infant Chronic Exposure to Drinking Water	NOEL: 10 ppm of drinking water or 10 mg/L converted to 1.0 mg/kg/day	1	10	1E-1 mg/kg/day
Walton, 1951	LOAEL: 11-20 ppm			

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*Conversion Factor: 1 L drinking water/day 10 kg child; thus, 10 mg/L x 1 L/day / 10 kg = 1.0 mg/kg/day

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o ORAL RFD STUDIES :

Walton, G. 1951. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am. J. Public Health. 41: 986-996.

This is an epidemiologic study on the incidence of methemoglobinemia in infants routinely fed formula prepared from nitrate-contaminated water. This study analyzed all known cases of infant methemoglobinemia occurring in 37 U.S. states irrespective of date or type of water supply. Nitrate (nitrogen) content ranged from 10 ppm to over 100 ppm. No incidences of methemoglobinemia were found to occur in drinking water containing greater than 10 ppm (10 mg/L) nitrate (nitrogen). A NOEL of 10 mg/L was derived from these studies.

Exposure of hemoglobin to nitrite results in the oxidation of the hemoglobin to methemoglobin. Animals do not provide a good model for methemoglobin formation because many species lack nitrate-reducing bacteria. Infants are, however, particularly susceptible due to their high gut content of nitrate-reducing bacteria, their lower enzymatic capacity to reduce methemoglobin to hemoglobin, and to the the presence of hemoglobin F, which is more susceptible to oxidation.

Several more recent studies support Walton's (1951) 10 mg/L NOAEL for infant methemoglobinemia (NAS, 1977; Winton, 1971; Calabrese, 1978).

Using the NOAEL from the Walton study and a modifying factor of 10, the RfD for nitrite was calculated (U.S. EPA, 1985) for a 10-kg child drinking 1 L of water/day as 0.1 mg/kg/day or 1 mg/day.

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o ORAL RFD UNCERTAINTY :

UF -- No uncertainty factor was used in the derivation of the RfD because the NOEL was of the critical toxic effect (i.e., methemoglobinemia) in the sensitive human population (i.e., infants). The length of exposure encompassed both the critical effect and the sensitive population.

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o ORAL RFD MODIFYING FACTOR :

MF -- 10. A modifying factor of 10 was applied because of the direct toxicity of nitrite.

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o ORAL RFD COMMENTS :

An RfD of 0.2 mg/kg/day could be calculated from the Walton (1951) study using the body weight of 4 kg and fluid consumption of 0.64 L/day for infants. The lower value of 0.1 mg/kg/day is maintained, however, because of the uncertainties in the changing fluid consumption and body weight as a neonate (4 kg) ages to a 2-year-old child (10 kg). While there are some data to the contrary, it is most likely that older children do not respond with increased methemoglobin to nitrate in drinking water. For example, Craun et al. (1981) reported that 64 children aged 1-8, consuming water with nitrate nitrogen concentrations of 22 to 111 mg/L, had an average methemoglobin concentration of 1.13%. This is not considered to be elevated and was in fact no different from the level (0.98%) observed in 38 children who drank water contaminated with less than 10 mg nitrate/L.

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o ORAL RFD CONFIDENCE :

Study -- High
Data Base -- High
RfD -- High

Confidence in the study is high because the NOEL is determined in the known sensitive human population. The data base contains several recent supporting epidemiologic studies for the critical effect in the sensitive population (infants); therefore, a high confidence rating is given to the data base. High confidence in the RfD follows.

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o ORAL RFD SOURCE DOCUMENT :

The only U.S. EPA documentation at present is on IRIS.

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o REVIEW DATES : 11/21/85, 02/05/86, 02/26/86, 06/24/92
o VERIFICATION DATE : 02/26/86
o EPA CONTACTS :

Kenneth L. Bailey / OST -- (202)260-5535

Rita S. Schoeny / OHEA -- (513)569-7814

RDI - NO DATA
CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA

CARDR- NO DATA

HAONE-

Appropriate data for calculating a One-day HA are not available. It is recommended that the Ten-day HA values (calculated below) be used as the One-day HA values.

HATEN-

NOTE: In developing the nitrate/nitrite HA it was determined that the 4-kg infant is the most sensitive member of the population with respect to both nitrate and nitrite. This determination was based on studies by Walton (1951) and Craun, et al. (1981). Walton (1951) reported over 278 cases of cyanosis and, in some cases, mortality in infants associated with the consumption of water containing greater than 10 mg/L nitrate-nitrogen. In relation to populations other than the 4-kg infant, Craun et al. (1981) reported that ingestion of water containing 22 to 111 mg/L nitrate-nitrogen by children aged 1 to 8 years did not result in abnormal mean methemoglobin levels and was not related to increased methemoglobin levels in comparison with controls. Therefore, while the Ten-day HA is usually derived for the 10-kg child, in this case this value was derived for the most sensitive members of the population (4-kg infants), as well as for other populations.

Ten-day HA for 4-kg infant -- 1E+0 mg/L nitrite-nitrogen

NOAEL -- 10 mg/L
UF -- 1 (used for human study in sensitive subpopulations)
Assumptions -- 10% conversion of nitrate to nitrite by 4-kg infant

Principal study -- Walton, 1951

More than 278 cases of cyanosis, and in some cases, mortality were associated with consumption of nitrate-contaminated water by the infant. No cases associated with water containing 10 mg/L or less of nitrate-nitrogen were found.

Ten-day HA for a 10-kg child -- 1E+1 mg/L nitrite-nitrogen

NOAEL -- 111 mg/L
UF -- 1 (used for human study in sensitive subpopulation)
Assumptions -- 10% conversion of nitrate to nitrite by 10-kg child

Principal Study -- Craun et al., 1981

In an epidemiologic study of 102 children aged 1 to 8 years, 64 of the study subjects consumed water with high nitrate levels (22 to 111 mg/L nitrate-nitrogen) and 38 consumed water with low nitrate levels (<10 mg/L nitrate-nitrogen). Ingestion of water containing 22 to 111 mg/L nitrate-nitrogen did not result in abnormal mean methemoglobin levels and was not related to increased methemoglobin levels in comparison to controls. In the entire study group of 102 children, only five had methemoglobin levels greater than 2% (maximum of 3.1% in a child from the low exposure group).

HALTC-

Appropriate data for calculating Longer-term HAs are not available. However, as previously discussed, the 4-kg infant is the most sensitive member of the population with respect to the formation of methemoglobin induced by either nitrite directly or by the in vivo reduction of nitrate to nitrite. In addition, as the 4-kg infant ages (e.g., to a 10-kg child), sensitivity to the effects of methemoglobin as well as the amount of nitrate reduced to nitrite

decreases, thus rendering the older child and adult less sensitive to the effects of both nitrate and nitrite. Thus, it has been concluded that the Ten-day HA for the 4-kg infant for nitrite-nitrogen (1 mg/L) will offer adequate protection against methemoglobin formation in all other age groups as well.

HALTA-

Appropriate data for calculating Longer-term HAs are not available. See explanation in HALTC

HALIF-

Appropriate data for calculating a DWEL or a Lifetime HA are not available. See explanation in HALTC

OLEP -

No data available

ALAB -

Determination of nitrite alone, or nitrite and nitrate combined, is by colorimetry or spectrophotometry.

TREAT-

Treatment techniques which are capable of removing nitrates from drinking water include ion exchange and reverse osmosis.

HADR -

o HEALTH ADVISORY SOURCE :

Walton, G. 1951. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am. J. Pub. Health. 41: 986-996.
DOCUMENT

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o HEALTH ADVISORY REVIEW :

Craun, G.F., D.G. Greathouse and D.H. Gunderson. 1981. Methemoglobin levels in young children consuming high nitrate well water in the United States. Int. J. Epidemiol. 10: 309-317.

U.S. EPA. 1985. Final Draft of the Drinking Water Criteria Document on Nitrates/Nitrites. Office of Drinking Water, Washington, DC.

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

---

o EPA DRINKING WATER CONTACT :

Kenneth Bailey / OST -- (202)260-5535

Edward V. Ohanian / OST -- (202)260-7571

CAA - NO DATA

WQCHU-

No data available

WQCAQ-

Freshwater:

Acute -- none
Chronic -- none

Marine:

Acute -- none
Chronic -- none

Considers technological or economic feasibility? -- NO

Discussion -- Recognizing that concentrations of nitrate/nitrite that would exhibit toxic effects on fish could rarely occur in nature, restrictive criteria were not recommended.

Reference -- Quality Criteria for Water, EPA 440/9-76-023 (7/76), PB-263943.

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 1 mg/L [as nitrogen] (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- Nitrite has been classed a Category III contaminant with methemoglobinemia in infants identified as the most sensitive endpoint. The MCLG of 1.0 mg/L for nitrite/nitrogen is based on a review of all available data that demonstrates that 1 mg/L is adequate to protect infants and all other groups against the non/oncogenic effects of nitrite in drinking water. The MCLG is based upon a DWEL for nitrite/nitrogen of 1 mg/L.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 1.0 mg/L [as nitrogen] (Final, 1991)

Considers technological or economic feasibility? -- YES

Discussion -- The EPA has promulgated an MCL equal to the MCLG of 1.0 mg/L.

Monitoring requirements -- All systems must take one sample between 1993-1995.

Analytical methodology -- Spectrophotometric (EPA 354.1; SM 419); automated cadmium reduction (EPA 353.2; SM 418F; ASTM D-3867-79A); manual cadmium reduction (EPA 353.3: SM 418C; ASTM D-3867-79B0; ion chromatography (EPA 300; SM 429: ASTM D-4327-88): PQL= 0.4 mg/L.

Best available technology -- Ion exchange; reverse osmosis.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC - NO DATA

SARA - NO DATA

RCRA - NO DATA

TSCA -

___IV.E.1. TSCA, SECTION 6

Status -- Advance Notice of Proposed Rulemaking (ANPR) (1984)

Discussion -- EPA is proposing to investigate potential occupational risk for machinists from the formulation of nitrosamines when water-based metalworking fluids are combined with nitrite.

Reference: 49 FR 2767 (01/23/84); 40 CFR 747

EPA Contact -- Chemical Control Division / OTS (202)260-3749 / FTS 260-3749

OREF - Calabrese, E.J. 1978. Drinking Water Standards. In: Methodological

Approaches to Deriving Environmental and Occupational Health Standards. John Wiley and Sons, Inc., New York, NY. p. 165-169.
OREF - Craun, G.F., D.G. Greathouse and D.H. Gunderson. 1981. Methemoglobin levels in young children consuming high nitrate well water in the United States. Int. J. Epidemiol. 10: 309-317.
OREF - NAS (National Academy of Sciences). 1977. Drinking Water and Health. Washington, DC.
OREF - U.S. EPA. 1985. Drinking Water Criteria Document for Nitrates/Nitrites. Office of Drinking Water, Washington, DC.
OREF - Walton, G. 1951. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am. J. Public Health. 41: 986-996.
OREF - Winton, E.F., R.G. Tardiff and L.J. McCabe. 1971. Nitrate in drinking water. J. Am. Water Works Assoc. 63: 95-98.
IREF - None
CREF - None
HAREF- Craun, G.F., D.G. Greathouse and D.H. Gunderson. 1981. Methemoglobin levels in young children consuming high nitrate well water in the United States. Int. J. Epidemiol. 10: 309-317.
HAREF- Walton, G. 1951. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am. J. Pub. Health. 41: 986-996.
HAREF- U.S. EPA. 1985. Drinking Water Criteria Document for Nitrates/Nitrites. Office of Drinking Water, Washington, DC.

[IRIS] SS 4 /cf?
USER:
find 7757-79-1

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NP (7757-79-1 (IRIS))
*NONE-

[IRIS] SS 4 /cf?
USER:
find nitrate

Search in progress

NITRATE APPEARS IN THE FOLLOWING CATEGORIES IN IRIS:

#	CATEGORY		POSTINGS
1	ID	**	2
2	NCAR	**	9
3	CAR	**	8
4	DWHA	**	3
5	EXSR	**	3
6	REFS	**	6

SPECIFY NUMBERS, EXPAND, ALL OR NONE-
USER:
1

SS (4) PSTG (2)

[IRIS] SS 5 /cf?
USER:

6 - IRIS
NAME - Nitrogen dioxide
RN - 10102-44-0
IRSN - 77
DATE - 930201
UPDT - 02/01/93, 1 field
STAT - Oral RfD Assessment (RDO) on-line 07/01/92
STAT - Inhalation RfC Assessment (RDI) message 02/01/93
STAT - Carcinogenicity Assessment (CAR) pending 10/01/91
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 03/31/87 RDO Documentation corrected
IRH - 10/01/89 RDI Inhalation RfD now under review
IRH - 08/01/91 RDO Oral RfD summary noted as pending change
IRH - 10/01/91 CAR Carcinogenicity assessment now under review
IRH - 01/01/92 RDO Primary contact changed
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 07/01/92 RDO Last paragraph deleted
IRH - 07/01/92 OREF Oral RfD references on-line
IRH - 02/01/93 RDI No RfC in lieu of regulatory standard
RLEN - 8806
SY - Nitrito
SY - Nitro
SY - Nitrogen Dioxide
SY - Nitrogen Oxide
SY - Nitrogen Peroxide
SY - Nitrogen Tetroxide
MF - NO2
USE - It is used in bleaching flour; in initiation of organic compounds and explosives; in the manufacture of oxidized cellulose for acrylates (Hawley, 1977); as a chemical intermediate (captive) for nitric acid; and as a catalyst for sulfuric acid (SRI, 1983).
COFO - Colorless solid, yellow liquid (Weast, 1979). Reddish-brown gas, liquid below 21.15C, has an irritating odor (Merck, 1976).
ODOR - Colorless solid, yellow liquid (Weast, 1979). Reddish-brown gas, liquid below 21.15C, has an irritating odor (Merck, 1976).
BP - 70.07F, 21.15C
MP - 15.3F, -9.3C
MW - 46.01
DEN - 1.448 at 20C/4C
VAP - 720 at 20C
VAPD - 1.58
EVAP - Not Found
SOLW - Soluble; decomposes
FLPT - Not Found
FLMT - Does not burn
AVOI - Avoid moisture and physical damage to storage container (NFPA, 1978). Nitrogen dioxide is incompatible with combustible matter, chlorinated hydrocarbons, ammonia, carbon disulfide (NIOSH/OSHA, 1978, p. 171). It reacts with alkalies to form nitrates and nitrites (Merck, 1976) and reacts violently with cyclohexane, fluorine, formaldehyde, alcohols, nitrobenzene, petroleum, and toluene (Sax, 1984, p. 2023).
DCMP - Nitrogen dioxide decomposes in water, forming nitric acid and nitric oxide (Merck, 1976)

RDO -
o ORAL RFD SUMMARY :

NOTE: The oral RfD for nitrogen dioxide may change in the near future pending the outcome of a further review now being conducted by the RfD/RfC Work Group.

Critical Effect	Experimental Doses*	UF	MF	RfD
Methemoglobinemia	NOEL: 10 ppm of drinking	1	1	1E+0

Infant Chronic Exposure, Drinking Water	water or 10 mg/L converted to 1.0 mg/kg/day	mg/kg/day
Walton, 1951	LOAEL: 11-20 ppm	

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*Dose Conversion Factors & Assumptions: 1 L water consumed/day 10 kg child; thus, 10 mg/L x 1 L/day / 10 kg = 1.0 mg/kg/day

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o ORAL RFD STUDIES :

Walton, G. 1951. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am. J. Public Health. 41: 986-996.

This is an epidemiologic study on the formation of methemoglobinemia in infants who routinely consumed milk prepared from water containing various levels of nitrate. The study analyzed all cases of infant methemoglobinemia occurring in 37 U.S. states irrespective of date of occurrence or type of water supply. Nitrate (nitrogen) content ranged from 10 ppm to >100 ppm. No incidences of methemoglobinemia were found to occur in drinking water containing <10 ppm (10 mg/L) nitrate (nitrogen). Therefore, a NOEL of 10 ppm (10 mg/L) was derived.

Several more recent epidemiologic studies support Walton's (1951) threshold for infant methemoglobinemia (NAS, 1977; Winton, 1971; Calabrese, 1978).

Nitrogen dioxide in water dissociates to form nitrates and nitrite. Nitrate toxicity appears to be due to its conversion to nitrites, which results in the oxidation of hemoglobin to methemoglobin in humans. Animals are not a good model for methemoglobin formation because of interspecies variations in the response. Infants are, however, particularly susceptible due to their high nitrate-reducing bacteria content, their lower enzymatic capacity to reduce methemoglobin to hemoglobin, and finally to the presence of hemoglobin F, which is more susceptible to oxidation.

---

o ORAL RFD UNCERTAINTY :

UF -- No uncertainty factor was used in the derivation of the RfD because the NOEL was of the critical toxic effect (i.e., methemoglobinemia) in the sensitive human population (i.e., infants). The length of exposure encompassed both the critical effect and the sensitive population.

---

o ORAL RFD MODIFYING FACTOR :

MF -- None

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o ORAL RFD COMMENTS :

A RfD of 2 mg/kg/day could be calculated using the body weight of 4 kg and fluid consumption of 0.64 L/day from the Walton (1951) study. The lower value of 1 mg/kg/day is maintained, however, due to the uncertainties in the changing fluid consumption and body weight as a neonate (4 kg) ages to a 2-year-old child (10 kg). While there are some data to the contrary, it is most likely that older children do not respond with increased methemoglobin to nitrate in drinking water. For example, Craun et al. (1981) reported that 64 children, aged 1-8, consuming water with nitrate nitrogen concentrations of 22-111 mg/L, had an average methemoglobin concentration of 1.13%. This is not considered to be elevated and was, in fact, no different from the level (0.98%) observed in 38 children who drank water with <10 mg nitrate/L.

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o ORAL RFD CONFIDENCE :

Study -- High

Data Base -- High
RfD -- High

Confidence in the study is high because the NOEL is determined in the known sensitive human population. The data base contains several recent supporting epidemiologic studies for the critical effect in the sensitive population (infants); therefore, a high confidence rating is given to the data base. High confidence in the RfD follows.

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o ORAL RFD SOURCE DOCUMENT :

The only U.S. EPA documentation at present is on IRIS.

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o REVIEW DATES : 08/19/85, 02/26/86
o VERIFICATION DATE : 02/26/86
o EPA CONTACTS :

Harlal Choudhury / OHEA -- (513)569-7553

Michael L. Dourson / OHEA -- (513)569-7533

RDI -
o INHALATION RFD SUMMARY :

An inhalation RfC will not be derived for nitrogen dioxide because a National Ambient Air Quality Standard (NAAQS) is available.

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o REVIEW DATES : 09/19/89
CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE-
o ACUTE TOXICITY :

Severe exposures to nitrogen dioxide may be fatal (DASE, 1980, p. 685). It can cause death by asphyxiation. Contact may cause burns to skin and eyes. Contact with liquid may cause frostbite (DOT, 1984, Guide 20). This compound was reported to react with blood to form methemoglobin (Gosselin et al., 1978). The lowest lethal human inhalation dose has been reported at 200 ppm/1 minute (NIOSH/RTECS, 1985).

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o SIGNS AND SYMPTOMS :

Symptoms include coughing, frothy thick sputum, shortness of breath, labored breathing, chest pain, bluing of lips and nail beds, rapid breathing, rapid heart beat, abdominal pain, fatigue, restlessness, mental confusion and pulmonary edema (NIOSH/OSHA, 1978, p. 141, Weiss, 1980, p. 664, DASE, 1980, p. 685).

BCF - NO DATA

CAA -

Value -- 0.053 ppm (annual average)

Considers technological or economic feasibility? -- NO

Discussion -- Retention of the current primary annual standard of 0.053 ppm is necessary to protect public health against chronic effects with an adequate margin of safety, and provides some measure of protection against possible short-term health effects. Sensitive populations (young children and asthmatics) were considered in this decision.

Reference -- 50 FR 25532; 40 CFR Part 50.11 (06/19/85)

EPA Contact -- Emissions Standards Division, OAQPS
(917)541-5571 / FTS 629-5571

WQCHU- NO DATA

WQCAQ- NO DATA

MCLG - NO DATA

MCL - NO DATA

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 10 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on reactivity. Nitrogen oxide is a strong oxidizer, may cause other materials to ignite, and will sustain their combustion.

Reference -- 50 FR 13456 (04/04/85); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA - NO DATA

TSCA -

No data available

OREF - Calabrese, E.J. 1978. Drinking water standards. In: Methodological Approaches to Deriving Environmental and Occupational Health Standards, John Wiley and Sons, Inc., New York, NY. p. 165-169.
OREF - Craun, G.F., D.G. Greathouse and D.H. Gunderson. 1981. Methaemoglobin levels in young children consuming high nitrate well water in the United States. Int. J. Epidemiol. 10(4): 309-317.
OREF - NAS (National Academy of Sciences). 1977. Drinking Water and Health. Safe Drinking Water Committee, Advisory Center on Toxicology, Assembly of Life Sciences, National Research Council, Washington, DC.
OREF - Walton, G. 1951. Survey of literature relating to infant methmogloginemia due to nitrate-contaminated water. Am. J. Public Health. 41: 986-996.
OREF - Winton, E.F., R.G. Tardiff and L.J. McCabe. 1971. Nitrate in drinking water. Am. J. Water Works Assoc. 63: 95-98.
IREF - None
CREF - None
HAREF- None

print all

1 - IRIS
NAME - Merphos oxide
RN - 78-48-8
IRSN - 366
DATE - 921102
UPDT - 11/02/92, 2 fields
STAT - Oral RfD Assessment (RDO) on-line 04/01/91
STAT - Inhalation RfC Assessment (RDI) message 11/01/92
STAT - Carcinogenicity Assessment (CAR) no data
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) no data
IRH - 09/07/88 RDO Oral RfD summary on-line
IRH - 04/01/91 RDO Text edited
IRH - 04/01/91 RDO Citations added
IRH - 04/01/91 REFS Bibliography on-line
IRH - 08/01/92 RDI Inhalation RfC now under review
IRH - 11/01/92 RDI Not verified; data inadequate
IRH - 11/01/92 IREF No references available
CONTINUE PRINTING? (YES/NO/CONT)
USER:
y

RLEN - 5809
SY - B-1,776
SY - butifos
SY - butiphos
SY - butyl phosphorotrithioate
SY - Chemagro 1,776
SY - DEF defoliant
SY - DE-green
SY - E-Z-Off D
SY - Fos-Fall
SY - Merphos Oxide
SY - Ortho phosphate defoliant
SY - phosphorotrithioic acid, S,S,S-tributyl ester
SY - S,S,S-tributyl phosphorotrithioate
SY - S,S,S-tributyltrithiofosfat
SY - S,S,S-tributyl trithiophosphate

RDO -
o ORAL RFD SUMMARY :

CONTINUE PRINTING? (YES/NO/CONT)
USER:
cont

Critical Effect	Experimental Doses*	UF	MF	RfD
Ataxia, delayed neurotoxicity and weight loss	NOEL: 0.1 mg/kg/day LOAEL: 0.5 mg/kg/day	3000	1	3E-5 mg/kg/day

90-Day Hen Delayed Neurotoxicity Study

Abou-Donia et al., 1979

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*Conversion Factors: None

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o ORAL RFD STUDIES :

Abou-Donia, M.B., D.G. Graham, K.M. Abdo and A.A. Komeil. 1979. Delayed neurotoxic, late acute and cholinergic effects of S,S,S-tributylphosphorotrithioate (DEF): Subchronic (90 days) administration in hens. Toxicology. 14: 229-243.

Groups of mixed breed hens (5/group) were given a daily oral dose of either 0.1, 0.5, 1.0, 2.5, 5.0, 10, 20, 40 or 80 mg/kg of merphos oxide in gelatin capsules for 3 months. Hens at the highest two doses were given 10 to 30 mg/kg/day atropine sulfate (4 to 7 days) as protection against cholinergic effects. Controls consisted of four groups of five hens treated orally with either empty gelatin capsules; 10 mg/kg/day tri-o-cresyl phosphate (positive control); or 1 mg/kg/day parathion (negative control) for 3 months. Another group of three hens was given a daily oral dose of 30 mg/kg of atropine sulfate for 34 to 90 days as an atropine sulfate control. At the end of the treatment period, the birds were observed for 1 month then sacrificed and tissues were taken from the central and peripheral nervous systems for histological examination. Hens receiving 20-80 mg/kg/day lost weight and developed severe ataxia and delayed neurotoxicity that progressed to paralysis. Mortality also occurred at these dose levels. Hens receiving doses of 0.5 to 10 mg/kg/day lost weight, but regained it by the end of the observation period. These hens also showed mild to gross ataxia, and equivocal or negative histopathological changes in the spinal cord and peripheral nerves.

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o ORAL RFD UNCERTAINTY :

UF = 3000. An uncertainty factor of 3000 was used for inter- and intraspecies extrapolation, subchronic to chronic duration and an incomplete data base.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

Data Considered for Establishing the RfD

1) 90-Day Oral - hen: Principal study, see previous description; no core grade (Abou-Donia et al., 1979)

2) 2-Year Feeding - rat: NOEL=0.25 mg/kg/day; LEL=1.25 mg/kg/day (brain ChE inhibition); (Mobay Chemical Corp., 1969)

3) 2-Year Feeding - dog: ChE NOEL=0.12 mg/kg/day; Systemic NOEL=1.25 mg/kg/day (Mobay Chemical Corp., 1967a)

4) 2-Year Feeding - rat: ChE NOEL=0.25 mg/kg/day; Systemic NOEL=1.25 mg/kg/day; LEL=5 mg/kg/day (fatty change in liver) (Mobay Chemical Corp., 1967b)

5) 16-Week Feeding - rat: ChE NOEL=0.5 mg/kg/day; Systemic NOEL=0.5

mg/kg/day; LEL = 2.5 mg/kg/day (liver and kidney changes) (Mobay Chemical Corp., 1965a)

6) 12-Week Feeding - dog: ChE NOEL=none; ChE LEL=0.12 mg/kg/day; Systemic NOEL=0.12 mg/kg/day; Systemic LEL=0.62 mg/kg/day (oversensitive to stimuli) (Mobay Chemical Corp., 1965b)

7) 3-Generation Reproduction - mouse: Reproductive NOEL=100 ppm (13 mg/kg/day) (Mobay Chemical Corp., 1967c)

Data Gaps: None

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o ORAL RFD CONFIDENCE :

Study: Low
Data Base: Low
RfD: Low

Low confidence rating to the critical study is due to design deficiencies. Supporting data are too limited to merit a confidence greater than low. Low confidence in the RfD follows.

-

o ORAL RFD SOURCE DOCUMENT :

Pesticide Registration Files.

-

o REVIEW DATES : 11/21/85, 08/13/87
o VERIFICATION DATE : 08/13/87
o EPA CONTACTS :

William Burnam / OPP -- (703)557-7491

George Ghali / OPP -- (703)557-7490

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RDI -
o INHALATION RFD SUMMARY :

The health effects data for Merphos Oxide (orthophosphate defoliant) have been reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for derivation of an inhalation RfC. The verification status of this chemical is currently not verifiable. This assessment is not presented in any existing EPA document.

-

o REVIEW DATES : 06/25/92
CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

-

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

CAA - NO DATA

WQCHU- NO DATA

WQCAQ- NO DATA

MCLG - NO DATA

MCL - NO DATA

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC - NO DATA

SARA - NO DATA

RCRA - NO DATA

TSCA - NO DATA

OREF - Abou-Donia, M.B., D.G. Graham, K.M. Abdo and A.A. Komeil. 1979. Delayed neurotoxic, late acute and cholinergic effects of S,S,S-tributyl phosphoro- trithioate (DEF): Subchronic (90 days) administration in

hens. Toxicology. 14: 229-243.
OREF - Mobay Chemical Corporation. 1965a. MRID No. 00087423. Available from EPA. Write to FOI, EPA, Washington, DC 20460.
OREF - Mobay Chemical Corporation. 1965b. MRID No. 00087421. Available from EPA. Write to FOI, EPA, Washington, DC 20460.
OREF - Mobay Chemical Corporation. 1967a. MRID No. 00087428. Available from EPA. Write to FOI, EPA, Washington, DC 20460.
OREF - Mobay Chemical Corporation. 1967b. MRID No. 00145268, 00145868. Available from EPA. Write to FOI, EPA, Washington, DC 20460.
OREF - Mobay Chemical Corporation. 1967c. MRID No. 00087427, 00144939. Available from EPA. Write to FOI, EPA, Washington, DC 20460.
OREF - Mobay Chemical Corporation. 1969. MRID No. 00087426. Available from EPA. Write to FOI, EPA, Washington, DC 20460.
IREF - None available
CREF - None
HAREF- None

2 - IRIS
NAME - Merphos
RN - 150-50-5
IRSN - 365
DATE - 921102
UPDT - 11/02/92, 2 fields
STAT - Oral RfD Assessment (RDO) on-line 04/01/91
STAT - Inhalation RfC Assessment (RDI) message 11/01/92
STAT - Carcinogenicity Assessment (CAR) no data
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 09/07/88 RDO Oral RfD summary on-line
IRH - 04/01/91 RDO Text edited
IRH - 04/01/91 RDO Citations added
IRH - 04/01/91 REFS Bibliography on-line
IRH - 01/01/92 EXSR Regulatory Action section on-line
IRH - 08/01/92 RDI Inhalation RfC now under review
IRH - 11/01/92 RDI Not verified; data inadequate
IRH - 11/01/92 IREF No references available
RLEN - 6398
SY - chemagro B-1776
SY - deleaf defoliant
SY - Easy Off-D
SY - folex
SY - Merphos
SY - phosphorotrithious acid, tributyl ester
SY - phosphorotrithious acid, s,s,s-tributyl ester
SY - S,S,S-tributyl phosphorotrithioite
SY - S,S,S-tributyl trithiophosphite
SY - tributyl phosphorotrithioite
SY - tributylthiofosfin

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Ataxia, delayed neurotoxicity and weight loss	NOEL: 0.1 mg/kg/day LOAEL: 0.5 mg/kg/day	3000	1	3E-5 mg/kg/day

90-Day Hen Delayed Neurotoxicity Study

Abou-Donia et al.,

1980

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*Conversion Factors: None

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o ORAL RFD STUDIES :

Abou-Donia, M.B., D.G. Graham, P.R. Timmons and B.L. Reichert. 1980. Late acute, delayed neurotoxic and cholinergic effects of S,S,S-tributylphosphorotrithioite (merphos) in hens. Toxicol. Appl. Pharmacol. 53: 439-457.

Groups of mixed breed hens (5/group) were given a daily oral dose of 0.1, 0.5, 1.0, 2.5, 5.0, 10, 20, 40, or 80 mg/kg of merphos in gelatin capsules for 3 months. Hens at the highest two doses were given 10 to 30 mg/kg/day atropine sulfate (4 to 7 days) as protection against cholinergic effects. Controls consisted of four groups of five hens treated orally with either empty gelatin capsules; 10 mg/kg/day tri-o-cresyl phosphate (positive control); or 1 mg/kg/day parathion (negative control) for 3 months. Another group of three hens was given a daily oral dose of 30 mg/kg of atropine sulfate for 34 to 90 days as an atropine sulfate control. At the end of the treatment period, the birds were observed for 1 month then sacrificed and tissues from the central and peripheral nervous systems were taken for histological examination. Hens receiving 20-80 mg/kg/day lost weight and developed severe ataxia and delayed neurotoxicity that progressed to paralysis. Mortality also occurred at these dose levels. Hens receiving doses of 0.5-10 mg/kg/day lost weight, but regained it by the end of the observation period. These hens also showed mild to gross ataxia, and equivocal or negative histopathological changes in the spinal cord and peripheral nerves.

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o ORAL RFD UNCERTAINTY :

UF = 3000. The uncertainty factor of 3000 includes uncertainties in extrapolation from laboratory animals to humans (10A), subchronic to chronic exposure (10S), sensitive human subpopulations (10H) and an incomplete data base.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

Data Considered for Establishing the RfD

1) 90-Day Oral - hen: Principal study - see previous description; no core grade (Abou-Donia et al., 1980)

2) 90-Day Feeding - rat: NOEL=20 ppm (1.8 mg/kg/day); LEL=35.2 ppm ([3.8 mg/kg/day] reduced brain ChE activity]; no core grade (Virginia Carolina Chemical Corp., 1960a)

3) 90-Day Feeding - rat: ChE NOEL=0.5 mg/kg/day; Systemic NOEL=0.5 mg/kg/day; LEL=2.5 mg/kg/day (increased liver weight); no core grade (Virginia Carolina

Chemical Corp., 1960b)

4) 90-Day Feeding - rat: ChE and systemic NOEL=25 mg/kg/day; no core grade (Virginia Carolina Chemical Corp., 1958a)

5) 90-Day Feeding - dog: ChE NOEL=0.75 mg/kg/day; LEL=2.5 mg/kg/day (plasma ChE inhibition); no core grade (Virginia Carolina Chemical Corp., 1957)

6) 112-Day Feeding - rat: ChE NOEL=0.1 mg/kg/day; LEL=0.25 mg/kg/day (RBC ChE inhibition in females); no core grade Virginia Carolina Chemical Corp., 1958b)

7) 40-Day Feeding - rat: ChE and Systemic NOEL=1 mg/kg/day; no core grade (Virginia Carolina Chemical Corp., 1958c)

Data Gaps: None

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o ORAL RFD CONFIDENCE :

Study: Low
Data Base: Low
RfD: Low

The low confidence assigned to the critical study is due to design deficiencies. Supporting data are too limited to merit a confidence greater than low. Low confidence in the RfD follows.

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o ORAL RFD SOURCE DOCUMENT :

Pesticide Registration Files

---

o REVIEW DATES : 11/21/85, 08/13/87
o VERIFICATION DATE : 08/13/87
o EPA CONTACTS :

William Burnam / OPP -- (703)557-7491

George Ghali / OPP -- (703)557-7490

RDI -
o INHALATION RFD SUMMARY :

The health effects data for Merphos (orthophosphate defoliant) have been reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for derivation of an inhalation RfC. The verification status of this chemical is currently not verifiable. This assessment is not presented in any existing EPA document.

-
o REVIEW DATES : 06/25/92
CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

-
HAONE- NO DATA

-
HATEN- NO DATA

-
HALTC- NO DATA

-
HALTA- NO DATA

-
HALIF- NO DATA

-
OLEP - NO DATA

-
ALAB - NO DATA

-
TREAT- NO DATA

-
HADR - NO DATA

-
CAA - NO DATA

-
WQCHU- NO DATA

-
WQCAQ- NO DATA

-
MCLG - NO DATA

-
MCL - NO DATA

-
SMCL - NO DATA

-
FISTD-

Status -- Removed from list "B" pesticides/Registration canceled (1990)

Reference -- 55 FR 31166 (07/31/90)

EPA Contact -- Registration Branch / OPP
(703)557-7760 / FTS 557-7760

-

-
FIREV-

No data available

-

-
CERC - NO DATA

-
SARA - NO DATA

-
RCRA - NO DATA

-
TSCA -

No data available

-
OREF - Abou-Donia, M.B., D.G. Graham, P.R. Timmons and B.L. Reichert. 1980.
Late acute, delayed neurotoxic and cholinergic effects of
S,S,S-tributyl phosphoro- trithioite (merphos) in hens. Toxicol. Appl.
Pharmacol. 53: 439-457.
OREF - Virginia Carolina Chemical Corporation. 1957. MRID No. 00089576.
Available from EPA. Write to FOI, EPA, Washington, DC 20460.
OREF - Virginia Carolina Chemical Corporation. 1958a. MRID No. 00089576.
Available from EPA. Write to FOI, EPA, Washington, DC 20460.
OREF - Virginia Carolina Chemical Corporation. 1958b. MRID No. 00089578.
Available from EPA. Write to FOI, EPA, Washington, DC 20460.
OREF - Virginia Carolina Chemical Corporation. 1958c. MRID No. 00108720.
Available from EPA. Write to FOI, EPA, Washington, DC 20460.
OREF - Virginia Carolina Chemical Corporation. 1960a. MRID No. 00089580.
Available from EPA. Write to FOI, EPA, Washington, DC 20460.
OREF - Virginia Carolina Chemical Corporation. 1960b. MRID No. 00089572.
Available from EPA. Write to FOI, EPA, Washington, DC 20460.
IREF - None available
CREF - None
HAREF- None

[IRIS] SS 2 /cf?
USER:
find 16065-83-1

Search in progress

SS (2) PSTG (1)

[IRIS] SS 3 /cf?
USER:

1 - IRIS
NAME - Tetrachloroethylene
RN - 127-18-4
IRSN - 103
DATE - 920406
UPDT - 04/06/92, 3 fields
STAT - Oral RfD Assessment (RDO) on-line 03/01/88
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) pending
STAT - Drinking Water Health Advisories (DWHA) on-line 03/01/88
STAT - U.S. EPA Regulatory Actions (EXSR) withdrawn 04/01/92
IRH - 12/23/87 RDO RfD withdrawn pending further review
IRH - 03/01/88 RDO Revised Oral RfD sumary added - RfD changed
IRH - 03/01/88 HADV Health Advisory added
IRH - 07/01/89 REFS Bibliography on-line
IRH - 05/01/90 CAR Carcinogen assessment now under review
IRH - 06/01/90 CAA Area code for EPA contact corrected
IRH - 06/01/90 RCRA EPA contact changed
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 04/01/92 EXSR Regulatory action section withdrawn
RLEN - 12623
SY - Ankilostin
SY - Antisal 1
SY - Antisol 1
SY - Carbon bichloride
SY - Carbon dichloride
SY - Czterochloroetylen
SY - Dee-Solv
SY - Didakene
SY - Didokene
SY - Dowclene EC
SY - Dow-Per
SY - ENT 1,860
SY - Ethene, tetrachloro-
SY - Ethylene tetrachloride
SY - Ethylene, tetrachloro-
SY - Fedal-Un
SY - NCI-C04580
SY - Nema
SY - PCE
SY - PER
SY - Perawin
SY - PERC
SY - Perchloorethyleen, per
SY - Perchlor
SY - Perchloraethylen, per
SY - Perchlorethylene
SY - Perchlorethylene, per
SY - Perchloroethylene
SY - Perclene
SY - Percloroetilene
SY - Percosolv
SY - Percosolve
SY - PERK
SY - Perklone
SY - Persec
SY - Tetlen
SY - Tetracap
SY - Tetrachlooretheen
SY - Tetrachloraethen
SY - Tetrachlorethylene
SY - Tetrachloroethene
SY - Tetrachloroethylene
SY - 1,1,2,2-Tetrachloroethylene.

SY - Tetracloroetene
SY - Tetraguer
SY - Tetraleno
SY - Tetralex
SY - Tetravec
SY - Tetroguer
SY - Tetropil
SY - WLN: GYGUYGG

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Hepatotoxicity in mice, weight gain in rats	NOAEL: 20 mg/kg/day (converted to 14 mg/kg/day)	1000	1	1E-2 mg/kg/day
6-Week Mouse Gavage Study Buben and O'Flaherty, 1985	LOAEL: 100 mg/kg/day (converted to 71 mg/kg/day)			

*Conversion Factors: Doses have been adjusted for treatment schedule (5 days/week)

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o ORAL RFD STUDIES :

Buben, J.A. and E.J. O'Flaherty. 1985. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: a dose-effect study. Toxicol. Appl. Pharmacol. 78: 105-122.

Buben and O'Flaherty (1985) exposed Swiss-Cox mice to tetrachloroethylene in corn oil by gavage at doses of 0, 20, 100, 200, 500, 1500, and 2000 mg/kg, 5 days/ week for 6 weeks. Liver toxicity was evaluated by several parameters including liver weight/body weight ratio, hepatic triglyceride concentration, DNA content, histopathological evaluation, and serum enzyme levels. Increased liver triglycerides were first observed in mice treated with 100 mg/kg. Liver weight/body weight ratios were significantly higher than controls for animals treated with 100 mg/kg. At higher doses, hepatotoxic effects included decreased DNA content, increased SGPT, decreased levels of G6P and hepatocellular necrosis, degeneration and polyploidy.

A NOEL of 14 mg/kg/day was established in a second study, as well (Hayes et al., 1986). Groups of 20 Sprague-Dawley rats of both sexes were administered doses of 14, 400, or 1400 mg/kg/day in drinking water. Males in the high-dose group and females in the two highest groups exhibited depressed body weights. Equivocal evidence of hepatotoxicity (increased liver and kidney weight/body weight ratios) were also observed at the higher doses.

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o ORAL RFD UNCERTAINTY :

UF = 1000. The uncertainty factor of 1000 results from multiplying factors of

10 to account for intraspecies variability, interspecies variability and extrapolation of a subchronic effect level to its chronic equivalent.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

Other data support the findings of the principal studies. Exposure of mice and rats to tetrachloroethylene by gavage for 11 days caused hepatotoxicity (centrilobular swelling) at doses as low as 100 mg/kg/day in mice (Schumann et al., 1980). Mice were more sensitive to the effects of tetrachloroethylene exposure than rats. Increased liver weight was observed in mice at 250 mg/kg, while rats did not exhibit these effects until doses of 1000 mg/kg/day were reached. Relative sensitivity to man cannot be readily established but the RfD of 1E-2 mg/kg/day is protective of the most mild effects observed in humans [diminished odor perception/modified Romberg test scores in volunteers exposed to 100 ppm for 7 hours; roughly equivalent to 20 mg/kg/day (Stewart et al., 1961)].

The principal studies are of short duration. Inhalation studies have been performed which indicate that the uncertainty factor of 10 is sufficient for extrapolation of the subchronic effect to its chronic equivalent. Liver enlargement and vacuolation of hepatocytes were found to be reversible lesions for mice exposed to low concentrations of tetrachloroethylene (Kjellstrand et al., 1984). In addition, elevated liver weight/body weight ratios observed in animals exposed to tetrachloroethylene for 30 days were similar to those in animals exposed for 120 days. Several chronic inhalation studies have also been performed (Carpenter, 1937; NTP, 1985; Rowe et al., 1952). None are inconsistent with a NOAEL of 14 mg/kg/day for tetrachloroethylene observed by Buben and O'Flaherty (1985) and Hayes et al. (1986).

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o ORAL RFD CONFIDENCE :

Study: Low
Data Base: Medium
RfD: Medium

No one study combines the features desired for deriving an RfD: oral exposure, large number of animals, multiple dose groups, testing in both sexes and chronic exposure. Confidence in the principal studies is low mainly because of the lack of complete histopathological examination at the NOAEL in the mouse study. The data base is relatively complete but lacks studies of reproductive and teratology endpoints subsequent to oral exposure; thus, it receives a medium confidence rating. Medium confidence in the RfD follows.

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o ORAL RFD SOURCE DOCUMENT :

U.S. EPA. 1985. Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC for the Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA 600/8-82/005F.

U.S. EPA. 1987. Quantification of Toxicological Effects for Tetrachloroethylene. Prepared from the Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Office of Drinking Water, Washington, DC.

-

o REVIEW DATES : 05/20/85, 08/05/86, 09/17/87
o VERIFICATION DATE : 09/17/87
o EPA CONTACTS :

Krishan Khanna / OST -- (202)260-7588 / FTS 260-7588

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

-

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RDI - NO DATA
CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

-

HAONE-

The available studies were not considered sufficient for calculation of a One-day HA. It is recommended that the value for the Ten-day HA, 2 mg/L, be use for the One-day HA.

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HATEN-

Ten-day HA -- 2E+0 mg/L

NOAEL -- 20 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Buben and O'Flaherty, 1985

Male Swiss-Cox mice were administered tetrachloroethylene by gavage at doses of 0, 20, 100, 200, 500, 1000, 1500, and 2000 mg/kg, 5 days/week for 6 weeks. Liver toxicity was evaluated by several parameters including liver weight-to-body weight ratio, hepatic triglyceride concentrations, DNA content, histopathological evaluation and serum enzyme levels. Increased liver triglycerides were first observed in mice treated with 100 mg/kg. Liver weight/body weight ratios were significantly higher than controls for the 100

mg/kg group, and slightly higher than controls in the 20 mg/kg group. A NOAEL of 20 mg/kg/day was identified based on the absence of hepatotoxic effects. After 5 days of exposure, a NOAEL of 20 mg/kg/day was identified.

HALTC-

Longer-term (Child) HA -- 1.4E+0 mg/L

NOAEL -- 14 mg/kg/day (adjusted for dosing schedule of 5 days/week)
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Buben and O'Flaherty, 1985 (study described in HATEN)

HALTA-

Longer-term (Adult) HA -- 5.0E+0 mg/L

NOAEL -- 14 mg/kg/day (adjusted for dosing schedule of 5 days/week)
Assumptions -- 2 L/day water consumption for a 70-kg adult
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)

Principal Study -- Buben and O'Flaherty, 1985 (study described in HATEN)

HALIF-

Drinking Water Equivalent Level (DWEL) -- 5E-1 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date -- 05/20/85 (see RDO)

NOTE: The classification of this substance is currently under review. A final decision on whether this substance should be classified B2 or C has not yet been made. If this substance is classified as C, the lifetime HA calculated below is recommended. If the classification is B2, no lifetime HA is recommended.

Lifetime HA -- 1E-2 mg/L

Assumptions -- 20% exposure by drinking water

Principal Study -- Buben and O'Flaherty, 1985 (This study was used in the derivation of the chronic oral RfD; see RDO)

NOTE: A safety factor of 10 was used in the derivation of this HA, in addition to the UF of 1000 for the RfD, to account for the possible carcinogenicity of this substance.

OLEP -

Ordor perception threshold -- 300 ug/L.

ALAB -

Analysis of tetrachloroethylene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water.

TREAT-

Treatment techniques which will remove tetrachloroethylene from water include granular activated carbon adsorption, air stripping, and boiling.

HADR -

o HEALTH ADVISORY SOURCE :

U.S. EPA. 1985. Health Effects Criteria Document for Tetrachloroethylene. Office of Drinking Water, Washington, DC.
DOCUMENT

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o HEALTH ADVISORY REVIEW :

EPA review of HAs in 1986.

Public review of HAs is currently in progress (1987).

Science Advisory Board review to be determined.

---

o EPA DRINKING WATER CONTACT :

Krishan Khanna / ODW -- (202)260-7588 / FTS 260-7588

Edward V. Ohanian / ODW -- (202)260-7571 / FTS 260-7571

-

-

CAA - NO DATA

-

WQCHU- NO DATA

-

WQCAQ- NO DATA

-

MCLG - NO DATA

-

MCL - NO DATA

-

SMCL - NO DATA

-

FISTD- NO DATA

-

FIREV- NO DATA

-

CERC - NO DATA

-

SARA - NO DATA

-

RCRA - NO DATA

-

TSCA - NO DATA

OREF - Buben, J.A. and E.J. O'Flaherty. 1985. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: A dose- effect study. Toxicol. Appl. Pharmacol. 78: 105-122.

OREF - Carpenter, C.P. 1937. The chronic toxicity of tetrachloroethylene. J. Ind. Hyg. Toxicol. 19(7): 323-336.

OREF - Hayes, J.R., L.W. Condie, Jr. and J.F. Borzelleca. 1986. The subchronic toxicity of tetrachloroethylene (perchloroethylene) administered in the drinking water of rats. Fund. Appl. Toxicol. 7: 119-125.

OREF - Kjellstrand, P., B. Holmquist, M. Kanje, et al. 1984. Perchloroethylene: Effects on body and organ weights and plasma butyrylcholinesterase activity in mice. Acta Pharmacol. Toxicol. 54(5): 414-424.

OREF - NTP (National Toxicology Program). 1985. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Tetrachloroethylene (perchloroethylene). U.S. Dept. Health and Human Services, NIH Publ. No. 85- 2567.

OREF - Rowe, V.K., D.D. McCollister, H.C. Spencer, E.M. Adams and D.D. Irish. 1952. Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. Arch. Ind. Hyg. Occup. Med. 5: 566-579.

OREF - Schumann, A.M., J.F. Quast and P.G. Watanabe. 1980. The pharmacokinetics and macromolecular interaction of perchloroethylene in mice and rats as related to oncogenicity. Toxicol. Appl. Pharmacol. 55: 207-219.

OREF - Stewart, R.D., H.H. Gay, D.S. Erley, C.L. Hake and A.W. Schaffer. 1961. Human exposure to tetrachloroethylene vapor. Arch. Environ. Health. 2: 40-46.

OREF - U.S. EPA. 1985. Health Assessment Document for Tetrachloroethylene (perchloroethylene). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC for the Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA 600/8-82-005F. Office of Drinking Water, Washington, DC.
OREF - U.S. EPA. 1987. Quantification of Toxicological Effects for Tetrachloroethylene. Prepared from the Health Assessment Document for Tetrachloroethylene (perchloroethylene). Office of Drinking Water, Washington, DC.
IREF - None
CREF - None
HAREF- Buben, J.A. and E.J. O'Flaherty. 1985. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: A dose- effect study. Toxicol. Appl. Pharmacol. 78: 105-122.
HAREF- U.S. EPA. 1985. Health Effects Criteria Document for Tetrachloroethylene. Office of Drinking Water, Washington, DC.

[IRIS] SS 6 /cf?
USER:
find 79-01-6

Search in progress

SS (6) PSTG (1)

[IRIS] SS 7 /cf?
USER:

1 - IRIS
NAME - White phosphorus
RN - 7723-14-0
IRSN - 413
DATE - 931101
UPDT - 11/01/93, 1 field
STAT - Oral RfD Assessment (RDO) on-line 02/01/93
STAT - Inhalation RfC Assessment (RDI) pending 11/01/93
STAT - Carcinogenicity Assessment (CAR) on-line 02/01/93
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 08/01/90 RDO Oral RfD summary on-line
IRH - 08/01/90 REFS Bibliography on-line
IRH - 12/01/90 CAR Carcinogen assessment on-line
IRH - 12/01/90 CREF Carcinogen assessment references added
IRH - 01/01/92 EXSR Regulatory Action section on-line
IRH - 02/01/93 RDO Primary contact changed
IRH - 02/01/93 CARDR Primary contact changed
IRH - 07/01/93 CREF References alphabetized correctly
IRH - 11/01/93 RDI Inhalation RfC now under review
RLEN - 19110
SY - BONIDE BLUE DEATH RAT KILLER
SY - CASWELL NO. 663
SY - COMMON SENSE COCKROACH AND RAT PREPARATIONS
SY - EPA PESTICIDE CHEMICAL CODE 066502
SY - EXOLIT LPKN 275
SY - EXOLIT VPK-N 361
SY - FOSFORO BIANCO [ITALIAN]
SY - FOSFORO BLANCO [SPANISH]
SY - FOSFORO [SPANISH]
SY - GELBER PHOSPHOR [GERMAN]
SY - HSDB 1169
SY - PHOSPHORE BLANC [FRENCH]
SY - PHOSPHORE BLANC [FRENCH]
SY - PHOSPHORE [FRENCH]
SY - PHOSPHOROUS (WHITE)
SY - PHOSPHORUS
SY - PHOSPHORUS-31
SY - PHOSPHORUS (RED)
SY - PHOSPHORUS, RED
SY - PHOSPHORUS WHITE
SY - PHOSPHORUS, WHITE
SY - RAT-NIP
SY - RED PHOSPHORUS
SY - TETRAFOSFOR [DUTCH]
SY - TETRAPHOSPHOR [GERMAN]
SY - UN 1338
SY - UN 1381
SY - UN 2447
SY - WEISS PHOSPHOR [GERMAN]
SY - WHITE PHOSPHORUS
SY - YELLOW PHOSPHORUS

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Parturition mortality; forelimb hair loss	NOAEL: 0.015 mg/kg/day LOAEL: 0.075 mg/kg/day	1000	1	2E-5 mg/kg/day

Reproductive Rat Study

Condray, 1985

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*Conversion Factors: None

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o ORAL RFD STUDIES :

Condray, J.R. 1985. Elemental yellow phosphorus one-generation reproduction study in rats. IR-82-215; IRD No. 401-189. Monsanto Company, St. Louis, MO.

Elemental yellow (white) phosphorus in corn oil was administered orally by gavage to groups of 15 males and 30 female Sprague-Dawley rats at doses of 0, 0.005, 0.015, or 0.075 mg/kg/day beginning at 80 days prior to mating and continuing through weaning of two complete reproductive cycles. A mortality rate of 53%, reported in the high-dose females, was attributed to difficulty during parturition, with 13 of 16 deaths occurring on days 21 or 22 of gestation. No specific cause was determined but this finding is uncommon during rat reproduction studies and may be attributed to white phosphorus administration. Hair loss was evident on the forelimbs of this group. A slight but not significant decrease in mean number of viable pups in the F1a litter was reported with a concomitant increase in mean number of dead pups. A similar trend was observed in the F1b litter. All other findings were comparable to controls.

Mean body weight of the high dose males was lower than controls beginning at 15 weeks of treatment, while body weights of the males receiving the two remaining test doses were slightly, but not significantly, lower than controls throughout the study. The NOAEL was 0.015 mg/kg/day and the LOAEL was 0.075 mg/kg/day for effects of white phosphorus on parturition.

White phosphorus was incorporated into the diets of young female albino rats (6 to 10/group) and fed at median doses of 0.0032, 0.018, or 0.072 mg/kg/day for 22 weeks and to 10 older male rats at a median dose of 0.0027 mg/kg/day for 25 weeks (Sollmann, 1925). Half of the animals from each female rat group were removed from the test diet during the later part of the experiment and they were observed in the same manner as the animals that continued to receive the test diet. A zero dose concurrent control group was not included in the experiment; however, the results from this study were compared to "normal growth curves" determined by the author and others in 13 previous investigations using a total of 72 rats.

The 0.072 mg/kg/day group (i.e., the high-dose group) exhibited 30% (3/10) mortality and a marked and progressive weight loss. Upon termination of the experiment the final weight of the animals was 41% below normal. No recovery was evident when the test diet was removed from a part of the test group after 10 weeks, but the progressive weight loss was checked. There was 50% (3/6) mortality for the 0.018 mg/kg/day group and growth was below normal resulting in a final weight 15% less than normal. When the test diet was removed from several animals in this dose group their growth returned to normal. There was a check in growth at 15 weeks and an overall mortality of 33% (2/6) for the 0.0032 mg/kg/day animals. There was no definite growth effect prior to 15 weeks. When animals from this group were removed from the diet their weights increased to levels greater than normal.

The male rats that received 0.0027 mg/kg/day demonstrated greater weight gain than normal while remaining on the test diet. They had a 10% (1/10) mortality; however, no other treatment related effects or toxicity signs were reported. The median dose of 0.0027 was considered the NOAEL from this study based upon body weight gain.

White phosphorous was administered daily to young rabbits (15-17) by oral insertion of a tablet containing 0.6 mg white phosphorus (equivalent to approximately 0.3 mg/kg/day for a 2 kg rabbit) for a period of 13 to 117 days (Adams and Sarnat, 1940). Fourteen young rats received white phosphorus in cod liver oil in the diet at a concentration of 0.01% for 22 to 57 days (equivalent mg/kg/day doses could not be estimated from available data).

Treated rabbits exhibited a decrease in weight gain as well as in the average daily growth of the tibial diaphysis (0.27 mm vs 0.36 mm in controls). A retardation of the normal tubulation process was reported when white phosphorus was administered to rats for 4 weeks or longer. Histological examination of rabbit long bones revealed a narrowing of the epiphyseal cartilage plate, reduction in number of cartilage cells/column, increased density in metaphyseal zone along with a greater number of trabeculae containing increased amounts of calcified cartilage matrix. In some cases, the hemopoietic marrow of the bone was replaced with loose fibrous tissue. Examination of the teeth revealed zones of abnormal dentin corresponding to periods of white phosphorus ingestion, but changes were considered non-specific.

A solution of white phosphorus in peanut oil was incorporated into stock diets and fed to groups of domestic male and female rats (6/group) at doses of 0, 0.2, 0.4, 0.8, and 1.6 mg/kg/day over their lifetime (approximately 420 days average duration) (Fleming et al., 1942). While mortality decreased with decreasing dose of white phosphorus, background mortality of controls was reported to be higher than in groups receiving the lower doses of white phosphorus. Retardation of weight gain was reported and those animals fed the larger doses also exhibited a definite loss of appetite. All treated animals showed changes in the bone consisting of a thickening of the epiphyseal line and extension of the trabeculae into the shaft. No other changes related to ingestion of white phosphorus were seen. A NOAEL/LOAEL could not be determined.

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o ORAL RFD UNCERTAINTY :

UF -- This uncertainty factor includes a factor of 10 for interspecies diversity, 10 for intraspecies diversity, and 10 for incomplete reproductive/ developmental data and a less than adequate lifetime study.

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o ORAL RFD MODIFYING FACTOR :

MF -- None

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o ORAL RFD COMMENTS :

In humans, white phosphorus toxicity is associated with its use in matches during the 1830s and later in fireworks and rodent poisons. The reported acute effects of white phosphorus are conflicting; however, chronic effects of white phosphorus on the bone are widely known. Acute effects have been reported from cases of accidental or intentional (suicidal) ingestion sometimes in combination with other substances such as alcohol. The reports indicate that acute ingestion affects the liver, kidney, hematopoietic system, brain, intestines, circulatory system and the myocardium resulting in electrocardiographic changes (Davidson et al., 1987). Deaths usually occurred within the first 24 hours. A minimum lethal dose of 1 mg/kg has been reported, and in a child, death has occurred after the consumption of as little as 3 mg (Brewer and Haggerty, 1958; Dacre and Rosenblatt, 1974; Davidson et al., 1987). The white phosphorus doses reported in the acute poisoning cases were estimated, therefore exact dose-response relationships cannot be determined.

Chronic exposure to white phosphorus in man has been associated with a progressive necrotic disease of the jaw bones known as "phossy jaw" (Davidson et al., 1987). Cases of this disease have been observed among workers in the phosphorus match industry (white phosphorus is no longer used for this purpose), firecracker manufacture, and white phosphorus production. The disease often takes years to develop and its pathogenesis currently is uncertain. The most widely held theory is that the phosphorus enters the jaw directly, reacts with the mouth flora, and subsequent infection develops followed by the disease. Even though several investigators report the occurrence of this disease in workers, dose information either is lacking

entirely or a surrogate exposure measure, i.e., exposure time, is reported.

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o ORAL RFD CONFIDENCE :

Study -- Low
Data Base -- Low
RfD -- Low

On its merits an RfD based on the Condray (1985) study has low confidence. The study does not provide unequivocal evidence of an adverse effect from white phosphorus exposure at the doses tested. The mortality in female rats during parturition was considered by the author to be related to white phosphorus exposure. However, the exact nature of the deaths was not examined as to conclusively implicate white phosphorus. The study also lacked adequate assessment of developmental indices.

The supporting studies indicate significant white phosphorus-related body weight and/or bone changes, but they have design deficiencies that lower the confidence in the reported observations. The investigation by Sollmann (1925) did not use concurrent controls, treatment groups differed by sex, and judging from the initial weight at the beginning of the study, the test animals appeared to be from different age groups. The studies by Adams and Sarnat (1940) and Fleming et al. (1942) both suggest white phosphorus-induced bone growth retardation; however, the numbers of animals in the dose groups were small and in some cases the exact dose of the test compound administered could not be determined.

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o ORAL RFD SOURCE DOCUMENT :

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- None

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o REVIEW DATES : 05/17/90
o VERIFICATION DATE : 05/17/90
o EPA CONTACTS :

Brian J. Commons / OST -- (202)260-7589

Krishan Khanna / OST -- (202)260-7588

RDI -
o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

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o REVIEW DATES : 09/24/93
CAREV-
o CLASSIFICATION : D; not classifiable as to human carcinogenicity
o BASIS FOR CLASSIFICATION : Based on no data in humans or animals
o HUMAN CARCINOGENICITY DATA :

None.

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o ANIMAL CARCINOGENICITY DATA :

None.

o SUPPORTING DATA :

Groups of 6 to 10 male and female rats received subcutaneous injections of elemental phosphorus in vegetable oil solutions at 0.5-3.2 mg/kg/day in two injections/week for life. A control group received injections of oil alone (Fleming et al., 1942). The range of the average group survival was 3.2 to 610 days. No evidence of treatment-related lesions was noted. This study, however, was not designed as a carcinogenicity bioassay, and is further limited by the use of a small number of animals. In addition, the maximum tolerated dose was not achieved.

Mutagenicity testing with several strains of Salmonella typhimurium did not result in a significant increase in the number of revertant colonies with or without metabolic activation (Ellis et al., 1978).

CARO - NO DATA
CARI - NO DATA
CARDR-
o CARCINOGENICITY SOURCE :

Source Document -- U.S. EPA, 1990

The 1990 Health Advisory for White Phosphorus has received Agency review.
DOCUMENT

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o REVIEW DATES : 06/15/90
o VERIFICATION DATE : 06/15/90
o EPA CONTACTS :

Brian J. Commons / OST -- (202)260-7589

Krishan Khanna / OST -- (202)260-7588

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

CAA - NO DATA

WQCHU-

No data available

WQCAQ-

Freshwater:

Acute -- None
Chronic -- 1.0E-1 ug/L (elemental phosphorus)

Marine:

Acute -- None
Chronic -- 1.0E-1 ug/L (elemental phosphorus)

Considers technological or economic feasibility? -- NO

Discussion -- A criterion of 0.10 ug/L elemental phosphorus in water has been recommended based on lethality to important aquatic organisms and significant bioaccumulation.

Reference -- NTIS No. 81-117780

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG - NO DATA

MCL - NO DATA

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 1 pound (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for phosphorus is based on aquatic toxicity as established under CWA section 311 (40 CFR 117.3). The available data indicate that the aquatic 96-Hour Median Threshold Limit is <0.1 ppm, which corresponds to an RQ of 1 pound. This chemical is currently being assessed for chronic toxicity and is subject to change in future rulemaking.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA Superfund Hotline
(800) 424-9346 / (703) 920-9810 / FTS 260-3000

SARA - NO DATA

RCRA - NO DATA

TSCA -

No data available

OREF - Adams, C.O. and B.G. Sarnat. 1940. Effects of yellow phosphorus and arsenic trioxide on growing bones and growing teeth. Arch. Pathol. 30: 1192-1201.
OREF - Brewer, E. and R.J. Haggerty. 1958. Toxic Hazards * Rat Poisons. II - Phosphorus. N. Eng. J. Med. 258(3): 147-148.
OREF - Condray, J.R. 1985. Elemental yellow phosphorus one-generation reproduction study in rats. IR-82-215; IRD No. 401-189. Monsanto Company, St. Louis, MO.
OREF - Dacre, J.C. and D.H. Rosenblatt. 1974. Mammalian toxicology and toxicity to aquatic organisms of four important types of waterborne munitions pollutants - An extensive literature evaluation. Technical Report No. 7403. U.S. Army Medical Bioengineering Research and Development Laboratory, Aberdeen Proving Ground, Ft. Detrick, Frederick, MD. NTIS AD778-725.
OREF - Davidson, K.A., P.S. Hovatter and C.F. Sigmon. 1987. Water quality criteria for white phosphorus. Final Report ORNL - 6336. Oak Ridge National Laboratory. AD-A186613.
OREF - Fleming, R.B.L., J.W. Miller and V.R. Swayne, Jr. 1942. Some recent observations on phosphorus toxicology. J. Ind. Hyg. Toxicol. 24(6): 154-158.
OREF - Sollmann, T. 1925. Studies of chronic intoxications on albino rats. VIII. Yellow phosphorus. J. Pharmacol. Exp. Therap. 24: 119-122.
IREF - None
CREF - Ellis, H.V., III, J.R. Hodgson, S.W. Hwang, et al. 1978. Mammalian toxicity of munitions compounds Phase I: Acute oral toxicity, primary skin and eye irritation, dermal sensitization, disposition and metabolism, and Ames tests of additional compounds. Progress report No. 6, prepared by Midwest Research Institute and submitted to U.S. Army Medical Bioengineering Research and Development Laboratory, Environmental Protection Research Division, Fort Detrick, Frederick, MD. December 8, 1978.
CREF - Fleming, R.B.L., J.W. Miller and V.R. Swayne, Jr. 1942. Some recent observations on phosphorus toxicology. J. Ind. Hyg. Toxicol. 24(6): 154-158.
CREF - U.S. EPA. 1990. Health Advisory for White Phosphorus. Office of Drinking Water, Washington, DC. (Draft)
HAREF- None

[IRIS] SS 18 /cf?
USER:
find phospfhate

Search in progress

PHOSPHATE APPEARS IN THE FOLLOWING FIELDS IN IRIS:

#	FIELD	POSTINGS
1	IRH	1
2	RDO	7
3	RDI	1
4	CAREV	3
5	TREAT	1
6	CAA	1
7	IREF	1
8	CREF	1
9	NF	8

SPECIFY NUMBERS, ALL, OR NONE-
USER:
1

SS (18) PSTG (1)

[IRIS] SS 19 /cf?
USER:

PRINT DL

1 - IRIS
IRSN - 288
DATE - 920122
STAT - Oral RfD Assessment (RDO) no data
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 01/01/90
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 05/01/89 CAR Carcinogen summary on-line
IRH - 01/01/90 CAR Text edited
IRH - 01/01/90 REFS Bibliography on-line
IRH - 01/01/92 EXSR Regulatory Action section on-line
RLEN - 24507
NAME - Polychlorinated biphenyls (PCBs)
RN - 1336-36-3
SY - AROCLOR
SY - AROCLOR 1221
SY - AROCLOR 1232
SY - AROCLOR 1242
SY - AROCLOR 1248
SY - AROCLOR 1254
SY - AROCLOR 1260
SY - AROCLOR 1262
SY - AROCLOR 1268
SY - AROCLOR 2565
SY - AROCLOR 4465
SY - AROCLOR 5442
SY - BIPHENYL, POLYCHLORO-
SY - CHLOPHEN
SY - CHLOREXTOL
SY - CHLORINATED BIPHENYL
SY - CHLORINATED DIPHENYL
SY - CHLORINATED DIPHENYLENE
SY - CHLORO BIPHENYL
SY - CHLORO 1,1-BIPHENYL
SY - CLOPHEN
SY - DYKANOL
SY - FENCLOR
SY - INERTEEN
SY - KANECHLOR
SY - KANECHLOR 300
SY - KANECHLOR 400
SY - MONTAR
SY - NOFLAMOL
SY - PCB
SY - PCBs
SY - PHENOCHLOR
SY - PHENOCLOR
SY - POLYCHLORINATED BIPHENYL
SY - Polychlorinated Biphenyls
SY - POLYCHLOROBIPHENYL
SY - PYRALENE
SY - PYRANOL
SY - SANTOTHERM
SY - SANTOTHERM FR
SY - SOVOL
SY - THERMINOL FR-1
SY - UN 2315
CAREV-
o CLASSIFICATION : B2; probable human carcinogen

o BASIS FOR CLASSIFIION : hepatocellular carcinomas in three strains of rats and two strains of mice and inadequate yet suggestive evidence of excess risk of liver cancer in humans by ingestion and inhalation or dermal contact.

o HUMAN CARCINOGENICITY DATA :

Inadequate. Although there are many studies, the data are inadequate due to confounding exposures or lack of exposure quantification. The first documentation of carcinogenicity associated with PCB exposure was reported at a New Jersey petrochemical plant involving 31 research and development employees and 41 refinery workers (Bahn et al., 1976, 1977). Although a statistically significant increase in malignant melanomas was reported, the two studies failed to report a quantified exposure level and to account for the presence of other potential or known carcinogens. In an expanded report of these studies, NIOSH (1977) concurred with the Bahn et al. (1976) findings.

Brown and Jones (1981) reported a retrospective cohort mortality study on 2567 workers who had completed at least 3 months of employment at one or two capacitor manufacturing plants. Exposure levels were 24-393 mg/cu.m at plant A and 318-1260 mg/cu.m at plant B. No excess risk of cancer was observed. In a 7-year follow-up study, Brown (1987) reported a statistically significant excess risk of liver and biliary cancer, with four of the five liver cancers in female workers at plant B. A review of the pathology reports indicated that two of the liver tumors counted in the follow-up study were not primary liver tumors. When these tumors are excluded the elevation in incidence is not statistically significant. The results also may be confounded by population differences in alcohol consumption, dietary habits, and ethnic composition.

Bertazzi et al. (1987) conducted a mortality study of 544 male and 1556 female employees of a capacitor-making facility in Northern Italy. Aroclor 1254 and Pyralene 1476 were used in this plant until 1964. These were progressively replaced by Pyralenes 3010 and 3011 until 1970, after which lower chlorinated Pyralenes were used exclusively. In 1980 the use of PCBs was abandoned. Some employees also used trichloroethylene but, according to the authors, were presumed to be protected by efficient ventilation. Air samples were collected and analyzed for PCBs in 1954 and 1977 because of reports of chloracne in workers. Quantities of PCBs on workers' hands and workplace surfaces also were measured in 1977. In 18 samples, levels ranged from 0.2-159.0 ug/sq.m on workplace surfaces and 0.3-9.2 ug/sq.m on workers' hands.

The authors compared observed mortality with that expected between 1946 and 1982 based on national and local Italian mortality rates. With vital status ascertainment 99.5% complete, relatively few deaths were reported by 1982 [30 males (5.5%) and 34 females (2.2%)]. In cohort males, the number of deaths from malignant tumors was significantly higher than expected compared with local or national rates, as was the number of deaths from cancer of the GI tract (6 observed vs. 1.7 national expected and 2.2 local expected). Of the six GI cancer deaths, one was due to liver cancer and one to biliary tract cancer. Deaths from hematologic neoplasms in males were also higher than expected, but the excess was not statistically significant. Total cancer deaths in females were significantly elevated in comparison to local rates (12 observed vs. 5.3 expected). None of these were liver or biliary cancers. The number of deaths from hematologic neoplasms in females was higher than expected when compared with local rates (4 observed vs. 1.1 expected). This study is limited by several factors, particularly the small number of deaths

that occurred by the cut-off period. The power of the study is insufficient to detect an elevated risk of site-specific cancer. In addition, the authors stated, after an examination of the individual cases, that interpretation of the increase in GI tract cancer in males was limited, as it appeared likely that some of these individuals had only limited PCB exposure. Confounding factors may have included possible contamination of the PCBs by dibenzofurans and exposure of some of the workers to trichloroethylene, alkylbenzene, and epoxy resins.

Two occurrences of ingestion of PCB-contaminated rice oil have been reported: the Yusho incident of 1968 in Japan and the Yu-Cheng incident of 1979 in Taiwan. Amano et al. (1984) completed a 16-year retrospective cohort mortality study of 581 male and 505 female victims of the Yusho incident. A consistently high risk of liver cancer in females over the entire 16 years was observed; liver cancer in males was also significantly increased. Several serious limitations are evident in this study. There was a lack of information regarding job histories or the influence of alcoholism or smoking. The information concerning the diagnosis of liver cancer was obtained from the victims' families, and it is not clear whether this information was independently verified by health professionals. For some of the cancers described, the latency period is shorter than would be expected. Furthermore, the contaminated oils contained polychlorinated dibenzofurans and polychlorinated quinones as well as PCBs, and the study lacks data regarding exposure to the first two classes of compounds. There is strong evidence indicating that the health effects seen in Yusho victims were due to ingestion of polychlorinated dibenzofurans, rather than to PCBs themselves (reviewed in EPA, 1988). The results of the Amano et al. study can, therefore, be considered as no more than suggestive of carcinogenicity of PCBs.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. PCB mixtures assayed in the following studies were commercial preparations and may not be the same as mixtures of isomers found in the environment. Although animal feeding studies demonstrate the carcinogenicity of commercial PCB preparations, it is not known which of the PCB congeners in such preparations are responsible for these effects, or if decomposition products, contaminants or metabolites are involved in the toxic response. Early bioassays with rats (Kimura and Baba, 1973; Ito et al., 1974) were inadequate to assess carcinogenicity due to the small number of animals and short duration of exposure to PCB. A long-term bioassay of Aroclor 1260 reported by Kimbrough et al. (1975) produced hepatocellular carcinomas in female Sherman rats when 100 ppm was administered for 630 days to 200 animals. Hepatocellular carcinomas and neoplastic nodules were observed in 14 and 78%, respectively, of the dosed animals, compared with 0.58 and 0%, respectively, of the controls.

The NCI (1978) reported results for 24 male and 24 female Fischer 344 rats treated with Aroclor 1254 at 25, 50, or 100 ppm for 104 to 105 weeks. Although carcinomas of the gastrointestinal tract were observed among the treated animals only, the incidence was

elevated. An apparent dose-related incidence of hepatic nodular hyperplasia in both sexes as well as hepatocellular carcinomas among mid- to high-dose treated males was reported (4-12%, compared to 0% in controls).

Norback and Weltman (1985) fed 70 male and 70 female Sprague-Dawley rats a diet containing Aroclor 1260 in corn oil at 100 ppm for 16 months, followed by a 50 ppm diet for an additional 8 months, then a basal diet for 5 months. Control animals (63 rats/sex) received a diet containing corn oil for 18 months, then a basal diet alone for 5 months. Among animals that survived for at least 18 months, females exhibited a 91% incidence (43/47) of hepatocellular carcinoma. An additional 4% (2/47) had neoplastic nodules. In males corresponding incidences were 4% (2/46) for carcinoma and 11% (5/46) for neoplastic nodules. Concurrent liver morphology studies were carried out on tissue samples obtained by partial hepatectomies of three animals/group at eight time points. These studies showed the sequential progression of liver lesions to hepatocellular carcinomas.

Orally administered PCB resulted in increased incidences of hepatocellular carcinomas in two mouse strains. Ito et al. (1973) treated male dd mice (12/group) with Kanechlors 500, 400 and 300 each at dietary levels of 100, 250 or 500 ppm for 32 weeks. The group fed 500 ppm of Kanechlor 500 had a 41.7% incidence of hepatocellular carcinomas and a 58.3% incidence of nodular hyperplasia. Hepatocelluar carcinomas and nodular hyperplasia were not observed in mice fed 100 or 250 ppm of Kanechlor 500, nor among those fed Kanechlors 400 or 300 at any concentrations.

Schaeffer et al. (1984) fed male Wistar rats diets containing 100 ppm of the PCB mixtures Clophen A 30 (30% chlorine by weight) or Clophen A 60 (60% chlorine by weight) for 800 days. The PCB mixtures were reported to be free of furans. Clophen A 30 was administered to 152 rats, Clophen A 60 to 141 rats, and 139 rats received a standard diet. Mortality and histologic lesions were reported for animals necropsied during each 100-day interval for all three groups. Of the animals that survived the 800-day treatment period, 1/53 rats (2%) in the control group, 3/87 (3%) in the Clophen A 30 group and 52/85 (61%) in the Clophen A 60 group had developed hepatocellular carcinoma. The incidence in the Clophen A 60 group was significantly elevated in comparison to the control group. Neoplastic nodules were reported in 2/53 control, 35/87 Clophen A 30, and 34/85 Clophen A 60-treated animals. The incidence of nodules was significantly increased in both treatment groups in comparison to the control group. Neoplastic liver nodules and hepatocellular carcinomas appeared earlier and at higher incidence in the Clophen A 60 group relative to the Clophen A 30 group. The authors interpreted the results as indicative of a carcinogenic effect related to the degree of chlorination of the PCB mixture. The authors also suggested that these findings support those of others, including Ito et al. (1973) and Kimbrough et al. (1975), in which hepatocellular carcinomas were produced by more highly chlorinated mixtures.

Kimbrough and Linder (1974) dosed groups of 50 male BALB/cJ mice (a strain with a low spontaneous incidence of hepatoma) with Aroclor 1254 at 300 ppm in the diet for 11 months or 6 months, followed by a 5-month recovery period. Two groups of 50 mice were fed a control diet for 11 months. The incidence of hepatomas in survivors fed Aroclor 1254 for 11 months was 10/22. One hepatoma was observed in the 24 survivors fed Aroclor 1254 for 6 months.

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o SUPPORTING DATA :

Most genotoxicity assays of PCBs have been negative. The majority of microbial assays of PCB mixtures and various congeners showed no evidence of mutagenic effects (Schoeny et al., 1979; Schoeny, 1982; Wyndham et al., 1976).

Of various tests on the clastogenic effect of PCBs (Heddle and Bruce, 1977; Green et al., 1975), only Peakall et al. (1972) reported results indicative of a possible clastogenic action by PCBs in dove embryos.

Chlorinated dibenzofurans (CDFs), known contaminants of PCBs, and chlorinated dibenzodioxins (CDDs) are structurally related to and produce certain biologic effects similar to those of PCB congeners. While the CDDs are known to be carcinogenic, the carcinogenicity of CDFs is still under evaluation.

CARO -

o CLASSIFICATION : B2; probable human carcinogen
o BASIS FOR CLASSIFICATION : hepatocellular carcinomas in three strains of rats and two strains of mice and inadequate yet suggestive evidence of excess risk of liver cancer in humans by ingestion and inhalation or dermal contact.
o ORAL SLOPE FACTOR : 7.7/mg/kg/day
o DRINKING WATER UNIT RISK : 2.2E-4/ug/L
o DOSE EXTRAPOLATION METHOD : Linearized multistage procedure, extra risk
o RISK/WATER CONCENTRATIONS :

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Coentration
E-4 (1 in 10,000)	5E-1 ug/L
E-5 (1 in 100,000)	5E-2 ug/L
E-6 (1 in 1,000,000)	5E-3 ug/L

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o ORAL DOSE-RESPONSE DATA :

Tumor Type -- trabecular carcinoma/adenocarcinoma, neoplastic nodule
Test Animals -- Rat/Sprague-Dawley, female
Route -- oral, diet
Reference -- Norback and Weltman, 1985

Dose		Tumor
Administered (mg/kg/day) (TWA)	Human Equivalent (mg/kg/day)	Incidence
0	0	1/49
3.45	0.59	45/47

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o ADDITIONAL COMMENTS :

Human equivalent dosage assumes a TWA daily dose of 3.45 mg/kg/day. This reflects the dosing schedule of 5 mg/kg/day (assuming the rat consumes an amount equal to 5% of its bw/day) for the first 16 months, 2.5 mg/kg/day for the next 8 months, and no dose for the last 5 months.

A slope factor of 3.9/mg/kg/day was based on data from the Kimbrough et al. (1975) study of female Sherman rats fed Aroclor 1260. The estimate based on the data of Norback and Weltman (1985) is preferred because Sprague-Dawley rats are known to have low incidence of spontaneous hepatocellular neoplasms.

Moreover, the latter study spanned the natural life of the animal, and concurrent morphologic liver studies showed the sequential progression of liver lesions to hepatocellular carcinomas.

Although it is known that PCB congeners vary greatly as to their potency in producing biological effects, for purposes of this carcinogenicity assessment Aroclor 1260 is intended to be representative of all PCB mixtures.

There is some evidence that mixtures containing more highly chlorinated biphenyls are more potent inducers of hepatocellular carcinoma in rats than mixtures containing less chlorine by weight (reviewed in Kimbrough, 1987 and Schaeffer et al., 1984).

The unit risk should not be used if the water concentration exceeds 50 ug/L, since above this concentration the slope factor may differ from that stated.

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o DISCUSSION OF CONFIDENCE :

The Norback and Weltman study used an adequate number of animals, observed

for their normal lifespan. Only one non-zero test dose was used. A second risk estimate was also calculated based on the numbers of malignant tumors alone, as called for in the EPA's guidelines for carcinogen risk assessment. The slope factor thus derived is 5.7/mg/kg/day, which is 26% less than that derived using combined malignant tumors and neoplastic nodules. This risk estimate is supported by one based on data of Kimbrough et al. (1975).

PCB mixtures in drinking water may not be the same as the mixtures introduced or used for testing carcinogenicity in animals.

CARDR-

o CARCINOGENICITY SOURCE :

U.S. EPA. 1988. Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

The 1988 Drinking Water Criteria Document for PCBs has received OHEA review.

DOCUMENT

-
o REVIEW DATES : 04/22/87
o VERIFICATION DATE : 04/22/87
o EPA CONTACTS :

Charli Hiremath / ORD -- (202)260-5725/ FTS 260-5725

Debdas Mukerjee / ORD -- (513)569-7572/ FTS 684-7572

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WQCHU-

Water and Fish Consumption: 7.9E-5 ug/L

Fish Consumption Only: 7.9E-6 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. Since zero, however, may not be attainable at this time, the recommended criteria represents an E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)
EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

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-

WQCAQ-

Freshwater:

Acute -- 2.0E+0 ug/L
Chronic -- 1.4E-2 ug/L

Marine:

Acute -- 1.0E+1 ug/L
Chronic -- 3.0E-2 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- Criteria were derived from a minimum data base consisting of acute tests on a variety of species. Requirements and methods are covered in the reference to the Federal Register.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

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MCLG -

Value -- 0.0 mg/L (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- The MCLG for polychlorinated biphenyls is zero based on the evidence of carcinogenic potential (classification B2).

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST / (202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

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MCL -

Value -- 0.0005 mg/L (Final, 1991)

Considers technological or economic feasibility? -- YES

Discussion -- The MCL is based on a PQL of 0.0005 mg/L and is associated with a maximum lifetime individual risk of E-4.

Monitoring requirements -- All systems monitored initially for four consecutive quarters every three years; repeat monitoring dependent upon detection, vulnerability status and system size.

Analytical methodology -- Microextraction/gas chromatography (EPA 505); electron capture detector (EPA 508); perchlorination/gas chromatography (EPA 508A). PQL= 0.0005 mg/L.

Best available technology -- Granular activated carbon

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

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CERC -

1 - IRIS
NAME - Selenium and Compounds
RN - 7782-49-2
IRSN - 461
DATE - 930701
UPDT - 07/01/93, 2 fields
STAT - Oral RfD Assessment (RDO) on-line 09/01/91
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) on-line 07/01/93
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 03/01/91 CAR Carcinogenicity assessment on-line
IRH - 03/01/91 REFS Bibliography on-line
IRH - 06/01/91 CAREV Para 4: Correct Shamber&Willis to Shamberger&Willis
IRH - 06/01/91 RDO Oral RfD summary on-line
IRH - 06/01/91 OREF Oral RfD references added
IRH - 09/01/91 RDO Paragraph 2, line 2: number corrected to 5/349
IRH - 09/01/91 RDO Text revised
IRH - 09/01/91 RDO Confidence in RfD changed; text revised
IRH - 01/01/92 EXSR Regulatory Action section on-line
IRH - 07/01/93 CARDR Primary contact's phone number changed
RLEN - 52320
SY - Selenium
SY - C.I. 77805
SY - Caswell No. 732
SY - ELEMENTAL SELENIUM
SY - EPA Pesticide Chemical Code 072001
SY - HSDB 4493
SY - SELEN [Polish]
SY - Selenio [Spanish]
SY - Selenium
SY - SELENIUM ALLOY
SY - SELENIUM BASE
SY - SELENIUM DUST
SY - SELENIUM ELEMENTAL
SY - SELENIUM HOMOPOLYMER
SY - UN 2658
SY - 13410-01-0
SY - Selenic acid, disodium salt
SY - Caswell No. 791
SY - Disodium selenate
SY - EPA Pesticide Chemical Code 072002
SY - Natriumseleniat [German]
SY - NSC 378348
SY - Selenic acid, disodium salt
SY - Sodium selenate
SY - 10102-18-8
SY - Selenious acid, disodium salt
SY - DISODIUM SELENITE
SY - DISODIUM SELENIUM TRIOXIDE
SY - HSDB 768
SY - Natriumselenit [German]
SY - SELENIOUS ACID, DISODIUM SALT
SY - SODIUM SELENITE
SY - UN 2630
SY - 7783-00-8
SY - Selenious acid
SY - HSDB 6065
SY - MONOHYDRATED SELENIUM DIOXIDE
SY - Selenious Acid
SY - 7783-08-6
SY - Selenic acid
SY - Acide selenique [French]
SY - Acido selenico [Spanish]

SY - HSDB 675
SY - Selenic acid
SY - UN 1905
SY - 1313-85-5
SY - Sodium selenide [Na2Se]
SY - Disodium monoselenide
SY - Sodium selenide

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Clinical selenosis	NOAEL: 0.015 mg/kg/day	3	1	5E-3 mg/kg/day
Human Epidemiological Study	LOAEL: 0.023 mg/kg/day			

Yang et al., 1989b

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*Conversion Factors: NOAEL (0.853 mg/day) and LOAEL (1.261 mg/day) calculated from regression analysis (log Y = 0.767log X - 2.248, where Y = blood selenium and X = selenium intake) as detailed in Yang et al. (1989a) based upon the correlation (r = 0.962) between dietary selenium intake and blood selenium level for data showing incidence of clinical selenosis in adults based on an average adult body weight of 55 kg (Yang et al., 1989b).

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o ORAL RFD STUDIES :

Yang, G., S. Yin, R. Zhou, et al. 1989b. Studies of safe maximal daily dietary Se-intake in a seleniferous area in China. II. Relation between Se-intake and the manifestation of clinical signs and certain biochemical alterations in blood and urine. J. Trace Elem. Electrolytes Health Dis. 3(2): 123-130.

Yang et al. (1989b), in a follow-up to an earlier study (Yang et al., 1983), studied a population of approximately 400 individuals living in an area of China with unusually high environmental concentrations of selenium (Se). The subjects were evaluated for clinical and biochemical signs of Se intoxication. Three geographical areas with low, medium and high selenium levels in the soil and food supply were chosen for comparison in the studies. The earlier Yang et al. (1983) study was conducted in response to endemic selenium intoxication in two separate areas with sample sizes of only 6 and 3. Comparisons were then made to a selenium-adequate area (n=8) and low- selenium area (n=13). The Yang et al. (1989a,b) studies provide a much larger sample size and include additional analysis of tissue selenium levels. This allows a more accurate estimation of the dose-response relationship observed for selenium toxicity. Selenium levels in soil and approximately 30 typical food types commonly eaten by the exposed population showed a positive correlation with blood and tissue Se levels. The daily average Se intakes, based on lifetime exposure, 70, 195 and 1438 ug for adult males and 62, 198 and 1238 ug for adult females in the low-, medium- and high-selenium areas, respectively. Significant correlations demonstrated between Se concentrations of various tissues were used to estimate the minimal daily Se intake values that elicited various alterations in biochemical parameters indicative of possible Se-induced liver dysfunction (i.e., prolongation of clotting time and serum glutathione titer) and clinical signs of selenosis (i.e., hair or nail loss, morphological changes of the nails, etc.). In this manner, a marginal safe level of daily Se intake was estimated.

Analysis of the results indicated that perisistent clinical signs of selenosis were observed only in 5/349 adults, a potentially sensitive subpopulation. The blood selenium concentration in this group ranged from 1.054 to 1.854 mg/L with a mean of 1.346 mg/L. Clinical signs observed included the

characteristic "garlic odor" of excess selenium excretion in the breath and urine, thickened and brittle nails, hair and nail loss, lowered hemoglobin levels, mottled teeth, skin lesions and CNS abnormalities (peripheral anesthesia, acroparesthesia and pain in the extremities). Alterations in the measured biochemical parameters occurred at dietary intake levels of 750-850 ug/day. These alterations were described as a delay in prothrombin time, i.e., increase in blood coagulation time and reduction in blood glutathione concentration. However, these indicators were poorly characterized and are not typically used as an index for clinical selenosis resulting from chronic exposure to selenium (NAS, 1989). Based upon the blood selenium levels shown to reflect clinical signs of selenium intoxication, a whole blood selenium concentration of 1.35 mg/L corresponding to 1.261 mg of daily selenium intake is indicative of the lowest correlative selenium intake causing overt signs of selenosis. The next lowest whole blood selenium concentration of 1.0 mg/L, corresponding to 0.853 mg selenium/day, produces no clinical signs of selenosis. The NOAEL for this study is 0.85 mg Se/day and the LOAEL is 1.26 mg Se/day.

A group of 142 volunteers in South Dakota and Wyoming were recruited by Longnecker et al. (1991) at random from households listed in a telephone directory or from ranches with suspected high selenium intake based on previous cases of livestock selenosis. The geographical areas were chosen because of known seleniferous topsoil and high concentrations of selenium in plants and food. The subjects were followed for 1 year and completed health questionnaires, underwent physical examinations, provided blood samples for clinical assessment, and provided blood, urine, toenails and duplicate-plate food collections for selenium analysis. The average selenium intake was 239 ug/day, approximately 2-3 times higher than the national average. The concentration of selenium in whole blood, serum, urine and toenails and the amount in diet were highly correlated. Blood selenium concentration was highly correlated with selenium intake. The correlation was very similar to that reported by Yang et al. (1989a). Liver function (prothrombin time and alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase and alkaline phosphatase), hematologic functon (leukocyte count, hemoglobin and hematocrit) and clinical chemistry (sodium, potassium and chloride concentration) were not found to be altered as a result of selenium intake. High regression coefficient predictor variables for selenium toxicity (muscle twitching, paresthesia, nail loss, nail lines, hair loss and garlic breath) were not found in increased frequency for this population. No signs of selenium toxicity were found in this population, including individuals whose selenium intake was as high as 724 ug/day. This report corroborates that of Yang et al. (1989b), which showed that aselenium intake of up to 853 ug/day is not associated with characteristic nail or hair loss typical of selenium intoxication.

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o ORAL RFD UNCERTAINTY :

UF -- An uncertainty factor of 3 was applied to the NOAEL to account for sensitive individuals. A full factor of 10 was not deemed necessary since similar NOAELs were identified in two moderately-sized human populations exposed to selenium levels in excess of the RDA throughout a lifetime without apparent clinical signs of selenosis.

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o ORAL RFD MODIFYING FACTOR :

MF -- None

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o ORAL RFD COMMENTS :

The essentiality for selenium has been well-documented in livestock based upon the alleviation of specific deficiency conditions by selenium supplementation of the diet (Combs and Combs, 1986). Selenium has been clearly demonstrated to be a cofactor of glutathione peroxidase, a hydrogen and lipid peroxide reducing enzyme and is therefore essential (Rotruck et al., 1973). Human

requirements for selenium were not conclusively established until 1979 when an association was made between low selenium status and cardiomyopathy (Keshan disease) in China for young children and women of child-bearing age (Keshan Disease Research Group, 1979a,b). More recently, iatrogenic episodes of selenium deficiency have been reported in patients receiving intravenous total parenteral administration of feeding solutions devoid of selenium. Symptoms included low glutathione peroxidase activity and low selenium levels in erythrocytes (Levander and Burk, 1986), muscular weakness and discomfort (van Rij et al., 1979) and cardiomyopathy (Johnson et al., 1981). It is important to note that glutathione peroxidase activity is a valid indicator of human selenium status only in populations with relatively low selenium intakes, since the enzyme activity plateaus at adequate selenium intake levels (Whanger et al., 1988), thereby precluding the use of this biochemical indicator under excessive selenium intake situations.

The NAS (1989) has determined the recommended dietary allowance for selenium to be 0.87 ug/kg, or approximately 70 and 55 ug/day for the reference adult North American male and female, respectively. Requirements for selenium increase during pregnancy to 65 ug/day and for lactation to 75 ug/day. Selenium requirements for infants and children vary according to age. However, based on the reference weights of NHANES II, these populations demonstrate an increased requirement per unit weight relative to adults. For infants, the selenium requirement is 1.67 ug/kg and for children the requirement ranges from 1.07-1.53 ug/kg. It should be noted that the most recent RDA for selenium did not consider the 1989 results of Yang et al. (1989a,b) discussed above, but an earlier preliminary report by the same authors (Yang et al., 1983).

Yang et al. (1983) reported clinical signs of selenosis (i.e., loss of hair and nails) in approximately 50% of a population of 248 inhabitants living in Enshi County, Hubei Province of the People's Republic of China. Selenosis was reported in the highest selenium contaminated area where the average daily Se intake was 5.0 mg/day (range 3.2-6.7), but no selenosis occurred when the average intake was 0.750 mg/day (range 0.240-1.51). These estimates, however, were based upon estimates of intake from only 6 and 3 inhabitants in the high and low contaminated areas, respectively. Yang et al. (1989b) reported prolonged clotting time and serum glutathione and these biochemical changes were indicated as adverse effects of selenium exposure. Glutathione is a strong nucleophile that reacts well with soft electrophiles and is an important conjugate-forming compound for the detoxification and excretion of electrophilic metabolites and metabolically produced oxidizing agents. If glutathione is depleted or markedly reduced in the liver, the hepatotoxicity of these compounds would likewise be expected to be enhanced (Ketterer et al., 1983). However, the significance of decreased serum glutathione is not well characterized and should not be used in this context as a biochemical marker of selenium toxicity. Likewise, there is no indication that prothrombin activity is affected by excess selenium administration (Longnecker et al., 1991). Furthermore, the description of this effect in Yang et al. (1989b) was based on a population for which there is insufficient documentation of normal clotting times in the general Chinese population.

Selenium toxicity has been clinically described according to three types: acute selenosis, subacute selenosis and chronic selenosis. The acute condition is caused by consuming relatively high amounts of selenium over a short period of time. After the onset of this condition, walking becomes unsteady, cyanosis of the mucous membranes occurs and labored breathing is usually seen sometimes resulting in death. Pathological findings include congestion of the liver, endocarditis and myocarditis, degeneration of the sooth musculature of the gastrointestinal tract, gallbladder and bladder, and erosion of the long bones (Francke and Moxon, 1936).

Subacute selenosis occurs from exposure to large doses of Se over a longer period of time resulting in neurological dysfunction (impaired vision, ataxia, disorientation) and respiratory distress. It is typically seen most

frequently in grazing livestock feeding upon Se-accumulating plants and has been referred to as "blind staggers" (Rosenfeld and Beath, 1964).

Prolonged exposure to more moderate levels of selenium result in skin lesions involving alopecia, hoof necrosis and loss, emaciation and increased serum transaminases and alkaline phosphatase in animals. In man, the condition is characterized by chronic dermatitis, fatigue, anorexia, gastroenteritis, hepatic degeneration, enlarged spleen and increased concentrations of Se in the hair and nails (Harr and Muth, 1972).

Selenium exists naturally in a number of oxidation states, thereby accounting for the different forms of selenium important to living organisms by oral ingestion. In the -2 oxidation state, selenium can be found as hydrogen selenide (H_2Se), sodium selenide (Na_2Se), di-[$(CH_3)_2Se$] and trimethyl selenium [$(CH_3)_3Se$] and various selenoamino acids such as selenomethionine, selenocysteine, Se-methyl selenocysteine, selenocystathionine and selenotaurine. Elemental selenium and the dipeptide selenodiglutathione have an oxidation state of 0. In the +4 oxidation state, selenium can exist as selenium dioxide (SeO_2), selenious acid (H_2SeO_3) or as sodium selenite (Na_2SeO_3). Finally, in its most oxidized state (+6), selenium can be found as selenic acid (H_2SeO_4) or as sodium selenate (Na_2SeO_4).

The toxicity of selenium has been consistently well documented. However, some early studies reported that selenium may be a carcinogen. Nelson et al. (1943) showed that rats fed diets containing Se as seleniferous wheat developed hepatic tumors and low-grade carcinomas in 11/53 animals. This work has subsequently been criticized due to low-protein content and relatively high levels of Se in the diet (5, 7 or 10 ppm Se), a poorly characterized source of selenium, and in general poor experimental design. The authors reported no encapsulation or metastases and in fact noted their own difficulty in determining the difference between hyperplasia and tumor. Another early investigation by Seifter et al. (1946) reported several thyroid tumors and adenomatous hyperplasia in livers of rats fed 0.05% bis-4-acetylaminophenyl selenium dihydroxide for 105 days. This organic selenium compound was suspected of having goitrogenic properties but its carcinogenic effect has not been further confirmed to be attributable to the selenium in the molecule.

The first animal experiment which demonstrated anticarcinogenic effects of selenium was performed by Clayton and Baumann (1949). An approximate 50% reduction in dimethylaminoazobenzene-induced tumor incidence occurred in rats fed a diet supplemented with 5 ppm Se as selenite. Additional evidence subsequently reported, further illustrated the inhibitory effect of selenium on transplantable tumors in rats (Weisberger and Suhrland, 1956a) and leukemia in humans (Weisberger and Suhrland, 1956b). The National Cancer Institute sponsored an extensive study on selenium toxicity in rats in order to resolve the issue of selenium carcinogenicity. Diets containing up to 8 ppm selenium did not increase tumor incidence (Tinsley et al., 1967; Harr et al., 1967). Since 1970, there has been an increased interest in characterizing the anti-carcinogenic and anti-tumorigenic properties of selenium. The number of reports characterizing these properties are too numerous to discuss in detail here. The reader is referred to a review by Milner and Fico (1987) for a more comprehensive treatment of the data base.

The essentiality and toxicity of selenium varies according to the valence state of selenium when incorporated into biomolecules and the form in which selenium is fed or administered. This is especially true when comparing the LD50 value as an index of toxicity for the various selenium compounds. Although it is difficult to make an assessment for several selenium compounds by a similar mode of administration in a common species, there is general agreement that sodium selenite, sodium selenate, selenomethionine and selenoglutathione are among the more toxic species (Combs and Combs, 1986). The relative potency of systemic toxicity for selenium compounds is also similar in experiments examining potency of anti-tumorigenic activity. In

vitro examination of potency of effect of selenium compounds on incubated Ehrlich ascites tumor cells (EATC) showed that sodium selenite is more efficacious in significantly reducing EATC viability than an equivalent concentration of sodium selenate. Although selenium dioxide, selenomethionine and selenocystine ultimately decreased viability of the EATC, nearly 50% more incubation time was required for the same effect (Poirier and Milner, 1979). The same authors investigated the relative potency of various selenium compounds administered intraperitoneally on EATC growth in vivo. Sodium selenite and selenodiglutathione (an intermediate of selenium metabolism) were the most effective forms of selenium in preventing EATC propagation. Sodium selenide, dimethyl selenide and selenocystine were not effective in inhibiting EATC growth (Poirier and Milner, 1983). Similar relative potency results have been reported in in vitro systems for canine mammary cells (Fico et al., 1986) and human mammary cells (Watrach et al., 1984).

Since selenium has been reported to cause growth retardation, decreased fertility, embryotoxicity, fetotoxicity and teratogenic effects in animals, Yang et al. (1989b) made the following observations: Malformation in chickens hatched from locally produced eggs did occur; however, teratogeneic effects in human infants were never seen in this area although Se has been reported to be transmitted through the placenta to the fetus in animals. These findings confirm those reported by Yang et al. (1983) in which chicken eggs from this same area were reported to have very low hatchability and some deformed embryos in those that did hatch.

The developmental toxicity of selenomethionine was investigated by Tarantal et al. (1991) in non-human primates. Forty pregnant long-tailed macaques were dosed daily by nasogastric intubation with 0, 0.025, 0.150 or 0.3 mg selenium/kg as selenomethionine through gestational days 20-50. Dams were examined clinically and the pregnancies of two to three dams within each test group were followed to term (gestational day 165). All other dams were hysterectomized on gestational day 100. Neonates delivered at term were examined for morphometric, neurologic, behavioral and ophthalmologic effects on days 1, 8, 15, 22 and 30. Pregnancy loss among treated animals was not significantly different from concurrent or historical controls. No statistically significant treatment-related effects were observed at necropsy on gestational day 100. There were no significant maternal or fetal developmental effects or teratogenesis found up to 0.3 mg/kg selenium, the highest dose tested.

Halverson et al. (1966) fed 60-70 g male, post-weanling Sprague-Dawley rats selenium as selenite or seleniferous wheat ad libitum at 1.6, 3.2, 4.8, 6.4, 8.0, 9.6 or 11.2 ppm of selenium (13, 27, 40, 67, 81 or 94 ug/kg/day, respectively). Levels of selenium up to 4.8 ppm showed no effect. At 8.0 ppm selenium as seleniferous wheat, there was an observed decrease in liver weight, increase in spleen weight, and decrease in hemoglobin. Mortality was observed in the groups fed 8.0, 9.6 and 11.2 ppm selenium as seleniferous wheat at incidences of 1/8, 5/8 and 8/8, respectively. The incidences of mortality reported for groups fed 8.0 and 9.6 ppm selenium as selenite were 1/8 and 1/10, respectively. A significant growth reduction was reported for both selenium sources at 6.4 ppm and higher, although feed utilization was not decreased. No other effects were reported for the rats fed sodium selenite.

Schroeder and Mitchener (1971) administered 3 ppm selenium as selenate (390 ug/kg/day) to CD mice through four generations. Maternal effects were not observed. There was a significant increase in young deaths in the F1 generation and an increase in numbers of runts in generations F1 through F3. By the F3 generation there was also a decrease in breeding events.

Rosenfeld and Beath (1954) administered selenium as potassium selenate to sires and pregnant rats through five breeding cycles at 1.5, 2.5 or 7.5 ppm selenium (75, 125 or 375 ug/kg/day). No effect was observed on reproduction, the number of young reared or on the reproduction of two successive generations of dams and sires in groups receiving 1.5 ppm selenium. In the

group receiving 2.5 ppm selenium, the was a 50% reduction in the number of young reared. At 7.5 ppm there was a decrease in fertility of the females but not males, a decrease in the number of survivors and a reduction in the rate of growth in the young.

Nobunaga et al. (1979) administered 3 or 6 ppm selenium (390 or 780 ug/kg/day, respectively) as selenite to IVCS mice for 30 days prior to mating and throughout gestation. On day 18 of gestation, maternal mice were sacrificed and the embryos removed. Number of litters, total implants, total implants per dam, dead fetuses, dead embryos, resorptions, surviving fetuses (% to total implants), litter size, gross malformations and skeletal anomalies were not significantly different for either selenium-treated or control mice. The only significant effect noted was a decrease in the body weight of surviving fetuses in mice given 6 ppm selenium.

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o ORAL RFD CONFIDENCE :

Study -- Medium
Data Base -- High
RfD -- High

Confidence in the chosen principal study is medium. Although this is a human epidemiological study in which a sizable population with sensitive subpopulations was studied, there are still several possible interactions that were not fully accounted for, e.g., fluoride intake and protein status. Also, except for clinical signs of selenosis there are no other reliable indicators, biochemical or clinical, of selenium toxicity. Confidence in the data base is high because many animal studies and epidemiologic studies (reviewed by Combs and Combs, 1986) support the principal study. An additional human study with a freestanding NOAEL (Longnecker et al., 1991) strongly corroborates the NOAEL identified in the principal study. Therefore, high confidence in the RfD is selected based upon support of the critical study and the high level of confidence in the data base.

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o ORAL RFD SOURCE DOCUMENT :

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1985

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o REVIEW DATES : 01/20/88, 03/22/89, 09/21/89, 11/14/90, 03/27/91
o VERIFICATION DATE : 03/27/91
o EPA CONTACTS :

Kenneth A. Poirier / OHEA -- (513)569-7553

Gary L. Foureman / OHEA -- (919)541-1183

RDI - NO DATA
CAREV-
o CLASSIFICATION : D; not classifiable as to carcinogenicity in humans
o BASIS FOR CLASSIFICATION : Based on inadequate human data and inadequate evidence of carcinogenicity in animals. The evidence for various selenium compounds in animal and mutagenicity studies is conflicting and difficult to interpret; however, evidence for selenium sulfide is

sufficient for a B2 (probable human carcinogen) classification.

o HUMAN CARCINOGENICITY DATA :

Inadequate. Data on the potential carcinogenicity of selenium and various selenium compounds in humans are inadequate. Epidemiological studies have evaluated selenium in blood and cancer death rates in areas of high vs. low naturally-occurring selenium. However, these studies have limited value because they do not assess specific selenium compounds or correlate exposure with cancer risk.

Several investigators have studied the association between serum selenium and the risk of cancer through prospective, case-control and nested case-control studies. Analysis of blood serum levels indicated that patients with cancer, particularly gastrointestinal cancer, prostatic cancer, or Hodgkin's lymphoma, had significantly lower blood selenium levels in blood than healthy patients (Shamberger et al., 1973; Salonen et al., 1984; Kok et al., 1987; Willet et al., 1983; Willet and Stampfer, 1986). The risk of cancer for men (Kok et al., 1987) or for all subjects (Willet et al., 1983) in the lowest quintile of serum selenium was twice that of subjects with higher levels.

Geographic correlational studies have compared cancer mortality in areas of high vs. low levels of naturally-occurring selenium. In an ecological study Shamberger and Frost (1969) reported that an inverse relationship existed between cancer death rates and the selenium concentrations in foliage plants of several Canadian provinces. The human cancer death rate in provinces with selenium-containing plants was 122.2 +/- 7.8 (presumably per 100,000 population although this was not specified), while in the provinces devoid of these plants, the human death rate was 139.9 +/- 4.0.

In an ecological study Shamberger and Willis (1971) reported that there was a correlation between decreased cancer death rates in humans and an increase in the selenium in the forage crops in California. In high-selenium areas (selenium 0.11 ppm of forage crops) the cancer death rate per 100,000 was 141.2. In the medium-selenium areas (0.05-0.10 ppm) the cancer death rate was 190.1. In low-selenium areas (0.02-0.05 ppm) the cancer death rate was 233.0. Shamberger and Willis (1971) also investigated the ratio of observed to expected cancer death rates by anatomic site for men in 17 paired cities including high- and low-selenium areas. The anatomic sites that would come into contact with dietary selenium, such as pharynx, esophagus, stomach, bladder and intestine, showed a substantially lower rate ratio in the high-selenium cities than in the low-selenium cities. Other ecological and prospective studies have correlated an increased incidence of colon, breast and other forms of cancer in humans in geographic areas where selenium is deficient and a lowered cancer incidence with higher selenium concentrations (Schrauzer and Ishmael, 1974; Shamberger, 1976; Schrauzer et al., 1976; Jansson et al., 1978; Yang et al., 1983).

In a study of approximately 300 employees exposed to selenium (form not specified) in a rectifier (electronics) process over a 26-year period, only 17 deaths occurred, 6 of which were because of cancer (Glover, 1970). This number, however, is not statistically different from the 5.1 deaths expected based on national mortality rates. The source of the mortality rates was not specified. Several toxic effects including pulmonary irritation, epigastric pain and dermal irritation and dermatitis were associated with selenium exposure in men, but no carcinogenic effect was reported.

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o ANIMAL CARCINOGENICITY DATA :

Inadequate. The carcinogenicity of selenium compounds has been evaluated in several animal studies. However, the data are conflicting and difficult to interpret because of apparent anticarcinogenic activity and high toxicity of some selenium salts. In addition, comparison of the available data is difficult because several different salts with varying degrees of

FICHE # 5

bioavailability were used in the assays.

In a 2-year dietary study reported by Nelson et al. (1943), Osborne-Mendel rats (sex not specified) were fed selenium in the form of seleniferous corn or wheat or ammonium potassium selenide at 5-10 ppm. Survival was lower in the treated rats; 53/126 (42%) rats fed selenium survived 18 months or longer compared with 14/18 (78%) control rats. Of the 53 surviving selenium-treated rats, 43 (81%) developed liver cirrhosis and 11 (21%) developed hepatocellular adenoma or carcinoma. All 11 animals with tumors also had liver cirrhosis. None of the 14 control animals surviving 2 years developed liver tumors. Only pooled group data were reported and no statistical analysis was reported.

No tumors developed in a total of 1437 Wistar rats fed sodium selenite or sodium selenate in the diet at levels of 0.5-16 ppm for their lifetime (Harr et al., 1967; Tinsley et al., 1967). Nonneoplastic liver effects such as hyperemia, cellular degeneration, binucleation, and mild proliferation of hepatocytes were observed at concentrations of 4 ppm and higher.

Long-Evans rats (approximately 50/sex/group at study initiation) received 2 ppm (as selenium) sodium selenate or sodium selenite in drinking water for 1 year, then 3 ppm for the remainder of the study (Schroeder and Mitchener, 1971). The treatment of the control group was not discussed. The animals were observed for the duration of their natural lifespan, approximately 36 months, although one selenate-treated female lived for 5 years. Selenite produced 50% mortality in males by 58 days. At this time, 2 ppm selenate was substituted for selenite in the male group. The concentration of selenium was raised to 3 ppm in this group when the animals were 1 year old; however, the high mortality rendered the group size too small for further statistical analysis. Selenite produced 50% mortality in females by 348 days; selenite-treated females were sacrificed at 23 months due to high mortality. Selenate produced 50% mortality in females by 1014 days and in males by 962 days. In the control groups 50% mortality was achieved by 872 and 853 days in females and males, respectively. Survival of rats receiving selenate was comparable to controls and median lifespan was increased by >100 days. Body weights of treated males were comparable to controls throughout the study. Body weights of females fed selenate were significantly greater than controls at 24 and 36 months; body weights of females fed selenite were significantly less than controls at all times but 18 months.

Incidence of all tumors and of malignant tumors was significantly increased in the selenate-treated rats compared with the controls. Incidence of all tumors in controls, selenate- and selenite-treated rats was 20/65 (30.8%), 30/48 (62.5%) and 4/32 (12.5%), respectively. Incidence of malignant tumors in the same groups was 11/65 (16.9%), 20/48 (41.7%) and 4/32 (12.5%), respectively. The earliest tumor occurred on day 833 in the control males, on day 633 in the control females, on day 344 in selenate males and on day 633 in selenate females. The shortened survival time of the selenite groups was thought to be responsible for the small number of tumors. This study is considered inadequate because only the heart, lung, liver, kidney and spleen tissues from animals necropsied were examined histologically, and an increase in longevity was observed in selenate-treated female rats.

Schroeder and Mitchener (1972) administered 3 ppm sodium selenate or sodium selenite in drinking water to Swiss mice (50/sex/group). Body weights of selenate-treated animals were comparable to controls. Body weights of males fed selenite were significantly increased compared with controls, but body weights of females fed selenite were significantly decreased compared with controls. Longevity in males fed selenate was increased compared with controls. Longevity in females fed selenate increased, but longevity in females fed selenite decreased compared with controls. When compared to controls, there was no significant increase in total tumor incidence or malignant tumor incidence observed in selenium- (form not specified) treated mice. In the control group 23/119 (19%) had tumors (10/119 (8%) malignant tumors). Selenium-fed mice showed 13/88 (15%) tumors (all were malignant).

In selenium-treated group 8/13 malignancies were lymphoma or leukemia, 4/13 were papillary or alveologenic adenocarcinoma and 1/13 an osteosarcoma. In the control group there were two incidences of lymphoma or leukemia, 7 of lung carcinoma and 1 carcinoma of unknown origin. The 13 benign tumors included breast and ovary tumors.

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o SUPPORTING DATA :

Selenium is an essential micronutrient for several species, including humans, and is part of several enzymes such as glutathione peroxidase, an enzyme involved in cellular defense against oxidative damage, and heme oxidase. While low doses of selenium are essential, high doses of selenium or a deficiency of dietary selenium may cause a toxic response. Additionally, selenium may be protective against tumor development. The greatest daily exposure to selenium is via food. Bioavailability of selenium is dependent on numerous factors, including the intake levels, chemical form and nutritional status. Organic forms of selenium are more bioavailable than inorganic forms; selenates and selenites are the inorganic forms more readily absorbed. Sodium selenate and selenite are soluble in water, but the extent to which they are absorbed dermally or through the gastrointestinal tract has not been fully elucidated (U.S. EPA, 1989).

Shamberger (1985) reported that the oral administration of 0.1-6 ppm or dermal application of 0.005% of selenium reduced incidences of skin, liver, tracheal, intestinal and lung tumors induced by several carcinogens in rats, mice and hamsters. Shamberger theorized that selenium may reduce cellular damage caused by peroxidation of fat. In another study, natural killer (NK) cell activity was significantly increased in female rats administered 0.5 or 2.0 ppm selenium (sodium selenate) in the drinking water for 10 weeks (Koller et al., 1986), suggesting to the authors that NK-sensitive tumors may be prevented by using selenium therapy.

Data on the mutagenicity of selenium and its compounds are equivocal. Selenate and selenite (12 uM) were mutagenic in a reverse mutation assay using Salmonella typhimurium strains TA98, TA100 and TA1537 (Noda et al., 1979) in the absence of rat hepatic homogenates. In a second assay, sodium selenate, but not sodium selenite, was mutagenic; the S. typhimurium strains used were not reported (Lofroth and Ames, 1978). Selenite (selenious acid and sodium selenite) produced DNA damage in Bacillus subtilis strains 17A and 45T; however, selenate (selenic acid and sodium selenate) was negative in the Rec assay (Nakamuro et al., 1976).

Sodium selenide, sodium selenite, and sodium selenate (in order of decreasing activity) caused an increase in unscheduled DNA synthesis in the presence or absence of glutathione in Chinese hamster ovary cells at concentrations of 1.0E-4 M (Whiting et al., 1980). Increased chromosomal aberrations were also produced by sodium selenite at E-5 M in rat lymphocytes (Newton and Lilly, 1986) and by sodium selenite, selenious acid, selenic acid, and selenium oxide at 2.6E-6 M in human lymphocytes (Nakamuro et al., 1976). Sodium selenite produced an increase in chromosomal aberrations in the bone marrow of rats administered a total of 10-12 mg/kg intravenously (near-lethal doses) (Newton and Lilly, 1986). Selenium (elemental), selenium dioxide, sodium selenide, and sodium selenite (in order of decreasing activity) induced an increase in SCEs in human whole-blood cultures; sodium selenate was not mutagenic in this assay (Ray and Altenburg, 1980).

CARO - NO DATA
CARI - NO DATA
CARDR-
o CARCINOGENICITY SOURCE :

Source Document -- U.S. EPA, 1980, 1984, 1989

The 1989 Health and Environmental Effects Document on Selenium and Compounds has received OHEA review.
DOCUMENT

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o REVIEW DATES : 11/09/89, 03/07/90
o VERIFICATION DATE : 03/07/90
o EPA CONTACTS :

Jim Cogliano / OHEA -- (202)260-3814

William E. Pepelko / OHEA -- (202)260-3903

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption: See discussion

Fish Consumption Only: See discussion

Considers technological or economic feasibility? -- NO

Discussion -- The ambient water quality criterion for selenium is recommended to be identical to the existing water standard which is 10 ug/L.

Reference -- 45 FR 79318 (11/28/80); NTIS No. PB81-117814.

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute -- 2E+1 ug/L (1-hour average) [total selenium]
Chronic -- 5E+0 ug/L (4-hour average) [total selenium]

Marine:

Acute -- 3.0E+2 ug/L (1-hour average) [total selenium]
Chronic -- 7.1E+1 ug/L (4-hour average) [total selenium]

Considers technological or economic feasibility? -- NO

Discussion -- Criterion were derived from a minimum database consisting of acute tests on a variety of species. Requirements and methods are covered in the reference to the Federal Register. The agency recommends an exceedence frequency of no more than 3 years.

Reference -- 53 FR 177 (01/05/88)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value -- 0.05 mg/L [total selenium] (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- EPA has concluded that selenium should be placed in Category III and promulgates an MCLG of 0.05 mg/L based on a no-effect level obtained from a human study in China (Yang et al.,1989). Yang suggests that 0.400 mg of selenium/person/day is the maximum safe daily intake of selenium and assuming a a daily average consumption of 2 L drinking water per person containing 0.05 mg/L selenium, the resulting selenium ingestion would be 0.1 mg/person/day. The average daily dietary intake in this country is 0.125 mg selenium/person/day. A combined ingestion of water containing 0.05 mg/L and a typical U.S. diet would result in a total daily exposure of 0.225 mg selenium/person/day, well below the limit of 0.400 mg selenium that Yang et al. suggests is safe.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 0.05 mg/L [total selenium] (Final, 1991)

Considers technological or economic feasibility? -- YES

Discussion -- EPA has promulgated an MCL equal to The MCLG of 0.05 mg/L.

Monitoring requirements -- Ground water systems monitored every three years; surface water systems monitored annually; systems out of compliance must begin monitoring quarterly until system is reliably and consistently below MCL.

Analytical methodology -- Atomic absorption/furnace technique (EPA 270.2; SM 304): PQL= 0.01 mg/L.

Best available technology -- Activated alumina; ion exchange; lime softening; reverse osmosis; electrodialysis.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 100 pounds (Final, 1989) [Selenium metal]

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for selenium metal is based on acute toxicity. Selenium has an inhalation LDlo of 33 mg/cu. m. (8 hours). Assessment of chronic toxicity and potential carcinogenicity of selenium metal is complete and insufficient effects have been found to establish an RQ for these primary criterion.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA Superfund Hotline
(800) 424-9346 / (703) 920-9810 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed (total selenium)

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

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HAREF- None

1 - IRIS
NAME - Strontium
RN - 7440-24-6
IRSN - 540
DATE - 921007
UPDT - 10/07/92, 6 fields
STAT - Oral RfD Assessment (RDO) on-line 10/01/92
STAT - Inhalation RfC Assessment (RDI) no data
STAT - Carcinogenicity Assessment (CAR) no data
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) no data
IRH - 08/01/91 RDO Oral RfD now under review
IRH - 08/01/92 RDO Work group review dates added
IRH - 10/01/92 RDO Oral RfD summary on-line
IRH - 10/01/92 OREF Oral RfD references on-line
RLEN - 18587
SY - strontium
SY - stable strontium
SY - HSDB 2545

RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Rachitic bone	NOAEL: 0.19% Sr (as SrCO3) (190 mg Sr/kg/day)	300	1	6E-1 mg/kg/day
20-Day, 9-Week, and 3-Year Oral Studies in Young and Adult Rats	LOAEL: 0.38% Sr (as SrCO3) (380 mg/kg/day)			

Storey, 1961;
Marie et al., 1985;
Skoryna, 1981

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*Conversion Factors: 0.19% Sr = 1900 mg Sr/kg diet. Assuming young rats consume food equivalent to 10% of their body weight/day, the actual intake is calculated to be 190 mg Sr/kg bw/day.

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o ORAL RFD STUDIES :

Storey, E. 1961. Strontium "rickets": bone calcium and strontium changes. Austral. Ann. Med. 10: 213-222.

Marie, P.J., M.T. Garba, M. Hott and L. Miravet. 1985. Effect of low doses of stable Sr on bone metabolism in rats. Miner. Electrolyte Metab. 11: 5-13.

Skoryna, S.C. 1981. Effects of oral supplementation with stable strontium. Can. Med. Assoc. J. 125(7): 703-712.

Storey (1961) fed young (40-60 g) and adult (200-250 g) female rats (strain unspecified; 3/group) diets with adequate calcium (1.6%), phosphorous (0.9%) and vitamin D for 20 days. The dietary levels of strontium (as strontium carbonate) given to both adult and young rats were 0.19, 0.38, 0.75, 1.0 (young rats only), 1.5 and 3.0%. Assuming young rats consume 10% and adult rats consume 5% of their body weight in food per day, these doses correspond to 190, 380, 750, 1000, 1500 and 3000 mg/kg-day for young rats and 95, 190, 375, 750 and 1500 mg/kg-day for adult rats. Rats were examined for changes in bone mineralization and defects in cartilage. They were weighed at the onset and end of the experiment. Young rats were found to be affected more severely at lower dietary Sr levels than were adult rats. In young rats at 0.38% (380 mg/kg-day) the epiphyseal plate was irregular and slightly widened; however, at 0.75% (750 mg/kg-day) this plate was so irregular that

measurements were unreliable. Changes observed with the dose of 0.38% and higher were inhibition of calcification, as evidenced by increasing width of epiphyseal cartilage, presence of uncalcified bone matrix and decreased ash weight of bone. In adults, the first obvious bone change occurred at the 1.5% dietary strontium level (750 mg/kg-day) and included slightly wider than normal epiphyseal cartilage plate and metaphyseal osteoid seams, which were irregularly increased in extent and width. At the 3% strontium level in adult animals (1500 mg/kg-day), the cartilage plate was much larger. For young rats, the dietary level of 0.19% strontium (190 mg/kg-day) was a NOAEL and 0.38% strontium (380 mg/kg-day) was a LOAEL. For adult rats, the dietary level of 0.75% strontium (375 mg/kg-day) was a NOAEL and 1.5% strontium (750 mg/kg-day) was a LOAEL.

Marie et al. (1985) administered stable strontium to weanling male Spraque-Dawley rats. The purpose of this study was to determine the effect of low doses of stable strontium on mineral homeostasis and bone histology. Rats were divided into groups (8/group) receiving 0, 0.19, 0.27, 0.34 and 0.40% of SrCl2 in distilled water for 9 weeks. The diet contained 0.5% calcium. Based on body weight and water consumption data, the authors estimated average strontium intakes of 0, 316, 425, 525 and 633 mg/kg-day. The authors concluded that an oral dose lower than 0.40% (633 mg/kg-day) did not produce adverse effects on body growth or on bone mineralization. Rats in the 0.40% (633 mg/kg-day) dose group showed signs of increased mineralization lag time; excessive osteoid thickness associated with a decline in the rate of calcification, which resulted in slow growth rate; and a decreased double-labeled osteoid surface, which frequently resulted in defective long bone growth. This study identified a NOAEL of 525 mg/kg and a LOAEL of 633 mg/kg-day.

Skoryna (1981) investigated the oral toxicity of stable strontium in male adult RVH hooded rats. The rats (12/group, starting weight of 250 g) were fed ad libitum a standard laboratory diet and divided into four groups, which were administered 0.002, 900, 1900 or 3400 ppm strontium chloride (55% strontium) in their drinking water for 3 years. Assuming that an adult rat consumes water at a rate of 49 mL/day, the experimental doses correspond to 70, 147 and 263 mg/kg Sr/day. The control and experimental groups received adequate amounts of calcium (0.35 ppm) and magnesium (0.0682 ppm) in their drinking water. The animals were weighed and examined weekly. Histologic examinations of bone and observation of body weight changes in rats receiving strontium in drinking water revealed no abnormalities (Skoryna and Fuskova, 1981). The animal tissues from different organs (kidney, lungs, adrenal, brain, heart and muscle) were examined on gross and histologic levels. No evidence of changes in morphology was observed; organs were not weighed. The concentration of strontium in tissues was determined by heated graphite atomization. In addition, strontium levels in the animals' serum were analyzed by standard atomic absorption spectrophotometry. Except for bone, no organ predilection for strontium was observed in either group. A chronic NOAEL of 263 mg/kg-day was identified from this study.

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o ORAL RFD UNCERTAINTY :

UF -- The uncertainty factor of 300 includes 10 for species-to-species extrapolation and 10 for an incomplete data base (including a lack of developmental and reproductive data) and to account for uncertainties in using data for strontium carbonate to derive a risk estimate that may apply to other salts of strontium. An uncertainty factor of 3 was applied for sensitive subpopulations; a factor of 10 was not warranted because the critical study was performed in young animals, a recognized sensitive subpopulation.

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o ORAL RFD MODIFYING FACTOR :

MF -- 1.

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o ORAL RFD COMMENTS :

Pertinent data to derive an oral RfD based on the toxicity of stable strontium in humans were not located in the available literature. Estimates of dietary strontium intake range from 0.98-2.2 mg/day for adults, with milk providing about one-third of this (Snyder et al., 1975). Absorption of strontium from the gastrointestinal tract varies greatly, ranging from 9-63% (average of 38%) (Snyder et al., 1975). The bioavailability of strontium was estimated to be 20% in 6 healthy adult males administered 2.5 mmol of strontium chloride (Leeuwenkamp et al., 1990). Deficiency of dietary calcium leads to an increased absorption of strontium (Stokinger, 1981).

Use of strontium in the treatment of patients with osteoporosis has been reported. McCaslin and Janes (1959) reported treating 72 patients with daily doses of 1.7 g strontium (as strontium lactate) for periods ranging from 3 months to 3 years. Of the 32 patients who were available for follow-up, 84% experienced marked improvement. Assuming an average body weight of 70 kg, the supplementation to these patients was about 24 mg Sr/kg/day. Skoryna (1981) also reported subjective improvement in patients with osteoporosis receiving 274-1750 mg Sr/day as the gluconate, carbonate or lactate. No adverse side effects were reported in either study. Although these cases have been reported, strontium is not recognized as a standard therapy for osteoporosis (Krane, 1977).

Ingested strontium is distributed in the body in three compartments: plasma extracellular fluid; soft tissue and superficial zone of bone tissue; and bone itself (El Solh and Rousselet, 1981). The average adult is estimated to have a body burden of 320 mg strontium, 99% of which is in the bones (Snyder et al., 1975; Stokinger, 1981). The toxic effect of excessive strontium intakes is inhibition of calcification of epiphyseal cartilage and deformities of long bones at high doses. Strontium causes adverse effects on bone by substituting for calcium in the hydroxyapatite crystal during bone calcification or by displacing calcium from existing calcified matrix (Skoryna, 1984; Kshirsagar, 1985).

As opposed to calcium, which is under homostatic regulation, strontium appears to be passively absorbed (Comar and Wasserman, 1964). However, several factors may affect the bioavailability of ingested strontium, for example, age and species, the form of strontium, and the composition of the diet, especially with regard to phosphorus, vitamin D and calcium levels. These factors are reviewed in U.S. EPA (1990, 1992).

The adequacy of calcium nutrition is a critical factor regarding strontium toxicity; rachitic changes are exacerbated by inadequate calcium levels (El Solh and Rousselet, 1981). The effect of dietary calcium on strontium toxicity was also demonstrated by Engfeldt and Hjerquist (1969). Rachitic changes were observed in weanling Sprague-Dawley rats fed a diet containing 0.95% strontium (950 mg/kg-day) and "optimal" 0.69% calcium for 4 weeks. When dietary calcium was raised to 1.6%, no rachitic changes were seen at the same dose of strontium.

Because their bones are actively growing, young animals are more sensitive than adult animals to excessive strontium intakes. In addition to the information presented in the critical study (Storey, 1961), the greater sensitivity of young animals was also demonstrated by Storey (1962). Both young (50-70 g) and adult (200-250 g) rats of both sexes (strain not specified) were provided a diet containing 1.8% strontium as strontium carbonate. The exposure continued for up to 7 months with several interim sacrifices. After only 3 weeks of exposure, the young rats exhibited a "rachitic gait" with the most obvious changes occurring in the distal end of the femur and the proximal end of the tibia. The epiphyseal plate was reported to be "grossly widened" and the "metaphysis was a mass of soft white tissue." Conversely, it was 3 months before any change was observed in the adult rats, this being the appearance of fine traverse lines in the upper tibial metaphysis. The author goes on to portray significant differences in

the effects seen in young animals vs. adults provided the same dietary concentration of strontium. Because young rats consume more food per kg body weight, it is difficult to ascertain how much more sensitive young animals would be at a dose adjusted on a mg/kg bw/day basis.

Relatively little information is available regarding the potential for developmental toxicity resulting from exposure to strontium. Pregnant female Wistar rats (3/group) were administered subcutaneous doses of 0, 25, 50, 100 or 200 mg/kg of strontium nitrate (10.3, 20.7, 41.4 or 82.8 mg Sr/kg/day, respectively) during gestational days 9-19 (Lansdown et al., 1972). No effects were seen on the size or body weight of fetuses, litter sizes or the number of resorption sites. Skeletons and zones of calcification were normal and no histologic changes were seen in soft tissues. Although this study reported no teratogenic effects of strontium, the small number of dams exposed and fetuses examined preclude a definite evaluation of the results.

In addition to the information available in rats, Marie and Hott (1986) studied the effects of strontium on weanling mice. Eleven male C57BL/6J mice were provided with drinking water containing 0.27% strontium chloride from 21 to 50 days of age. Another group of 13 untreated mice served as controls. The dose of strontium was based on the earlier study by Marie et al. (1985), which determined this level of strontium to be effective in stimulating bone formation without affecting bone mineralization in rats. In mice, no significant effects were observed in bone formation parameters except an increase in the osteoid surface and a decrease in the number of osteoclasts involved in bone resorption. No effect was seen on total calcified bone volume.

Skeletal abnormalities have also been observed in dogs administered oral doses of strontium (1-3 g strontium phosphate/day) in conjunction with low levels of dietary calcium (Lehnerdt, 1910). substitute for calcium in

In addition to the effects exerted on bones, strontium can also physiologic processes such as heart and other skeletal muscle contraction, and ionic transport across red blood cell membranes and nerve cells (reviewed in U.S. EPA, 1990, 1992). However, these effects are reported following intravenous infusion of large doses of strontium, which is of questionable relevance to oral exposures.

Initially, the primary concern of most investigators was the retention and absorption of radioactive strontium from water and food sources. Radioactive strontium is generally used as a tracer element to evaluate toxicokinetic properties (absorption, distribution and excretion). The actual dose of radioactive strontium used for this purpose is frequently unreported. The kinetics of trace amounts of radioisotopes and of stable isotopes, which are usually administered in much higher quantities, may differ.

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o ORAL RFD CONFIDENCE :

Study -- Medium
Data Base -- Medium
RfD -- Medium

Confidence in the critical studies is rated as medium because together they determine the critical effect and suggest a sensitive population but have difficulties with incomplete reporting of experimental details (e.g., number of animals, experimental protocol). The data base is rated as medium to low because although several studies exist to support these critical studies, they are all in one species and little information is available on reproductive or developmental effects. Also, little is known about the speciation of strontium (e.g., how the toxicity of $SrCO_3$ relates to other strontium compounds). The confidence in the RfD is medium, reflecting the confidence in the study and the data base.

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o ORAL RFD SOURCE DOCUMENT :

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1990, 1992

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o REVIEW DATES : 07/18/91, 06/23/92
o VERIFICATION DATE : 06/23/92
o EPA CONTACTS :

Susan Velazquez / OHEA -- (513)569-7571

Eletha Brady-Roberts / OHEA -- (513)569-7662

RDI - NO DATA
CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

CAA - NO DATA

WQCHU- NO DATA

WQCAQ- NO DATA

MCLG - NO DATA

MCL - NO DATA

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC - NO DATA

SARA - NO DATA

RCRA - NO DATA

TSCA - NO DATA
OREF - Comar, C.L. and R.H. Wasserman. 1964. Strontium, Chapter 23. In: Mineral Metabolism, C.L. Comar and F. Bronner, Ed. Vol II, Part A. Academic Press, New York and London. p. 523-572.
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OREF - McCaslin, F.E. and J.M. Janes. 1959. The effect of strontium lactate in the treatment of osteoporosis. Proc. Mayo Clin. 34(13): 329-334.
OREF - Skoryna, S.C. 1981. Effects of oral supplementation with stable strontium. Can. Med. Assoc. J. 125(7): 703-712.
OREF - Skoryna, S.C. 1984. Metabolic aspects of the pharmacologic use of trace elements in human subjects with specific reference to stable strontium. In: Trace Substances in Environmental Health-XVIII, D.D. Hemphill, Ed. University of Missouri. p. 3-20.
OREF - Skoryna, S.C. and M. Fuskova. 1981. Effects of stable strontium supplementation. In: Handbook of Stable Strontium, S.C. Skoryna, Ed. Plenum Press. p. 593-613.
OREF - Snyder, W.S., M.J. Cook, E.S. Nasset, L.R. Karhausen, G.P. Howells and I.H. Tipton. 1975. International Commission on Radiological Protection (ICRP). Report of the Task Group on Reference Man, New York. ICRP Publ. 23.
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OREF - Storey, E. 1961. Strontium "rickets" bone calcium and strontium changes. Austral. Ann. Med. 10: 213-222.
OREF - Storey, E. 1962. Intermittent bone changes and multiple cartilage defects in chronic strontium rickets in rats. J. Bone Joint Surg. 44B(1): 194-208.
OREF - U.S. EPA. 1992. Health and Environmental Effects Document for Stable Strontium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.
OREF - U.S. EPA. 1990. Drinking Water Criteria Document for Stable Strontium.

Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.
IREF - None
CREF - None
HAREF- None

[IRIS] SS 15 /cf?
USER:
find 156-59-2

Search in progress

SS (15) PSTG (1)

[IRIS] SS 16 /cf?
USER:

7 - IRIS
NAME - Styrene
RN - 100-42-5
IRSN - 101
DATE - 930701
UPDT - 07/01/93, 6 fields
STAT - Oral RfD Assessment (RDO) on-line 09/01/90
STAT - Inhalation RfC Assessment (RDI) on-line 07/01/93
STAT - Carcinogenicity Assessment (CAR) pending
STAT - Drinking Water Health Advisories (DWHA) on-line 09/01/90
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 01/01/92
IRH - 06/30/88 RDO Contacts changed
IRH - 10/01/89 RDI Inhalation RfD now under review
IRH - 02/01/90 REFS Bibliography on-line
IRH - 05/01/90 RDO Oral RfD summary noted as pending change
IRH - 05/01/90 CAR Carcinogen assessment now under review
IRH - 09/01/90 RDO Text edited
IRH - 09/01/90 HADV Health Advisory on-line
IRH - 09/01/90 HAREF Health Advisory references added
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 11/01/92 RDI Inhalation RfC summary on-line
IRH - 11/01/92 IREF Inhalation RfC references on-line
IRH - 07/01/93 RDI 'E' notation added
RLEN - 69063
SY - BENZENE, VINYL-
SY - CINNAMENE
SY - CINNAMENOL
SY - CINNAMOL
SY - DIAREX HF 77
SY - ETHENYLBENZENE
SY - ETHYLENE, PHENYL-
SY - NCI-C02200
SY - PHENETHYLENE
SY - PHENYLETHENE
SY - PHENYLETHYLENE
SY - STIROLO
SY - STYREEN
SY - STYREN
SY - Styrene
SY - STYRENE, MONOMER
SY - STYROL
SY - STYROLE
SY - STYROLENE
SY - STYRON
SY - STYROPOL
SY - STYROPOR
SY - UN 2055
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA
VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

RDO -

o ORAL RFD SUMMARY :

NOTE: The Oral RfD for styrene may change in the near future pending the outcome of a further review now being conducted by the Oral RfD Work Group.

Critical Effect	Experimental Doses*	UF	MF	RfD
Red blood cell and liver effects Dog Subchronic Oral Study Quast et al., 1979	NOAEL: 200 mg/kg-day LOAEL: 400 mg/kg-day	1000	1	2E-1 mg/kg-day

*Conversion Factors: none

o ORAL RFD STUDIES :

Quast, J.F., C.G. Humiston, R.Y. Kalnins, et al. 1979. Results of a toxicity study of monomeric styrene administered to beagle dogs by oral intubation for 19 months. Toxicology Research Laboratory, Health and Environmental Sciences, DOW Chemical Co., Midland, MI. Final Report.

Four beagle dogs/sex were gavaged with doses of 0, 200, 400, or 600 mg styrene/kg bw/day in peanut oil for 560 days. No adverse effects were observed for dogs administered styrene at 200 mg/kg-day. In the higher dose groups, increased numbers of Heinz bodies in the RBCs, decreased packed cell volume, and sporadic decreases in hemoglobin and RBC counts were observed. In addition, increased iron deposits and elevated numbers of Heinz bodies were found in the livers. Marked individual variations in blood cell parameters were noted for animals at the same dose level. Other parameters examined were body weight, organ weights, urinalyses, and clinical chemistry. The NOAEL in this study is 200 mg/kg-day and the LOAEL is 400 mg/kg-day.

Long-term studies (120 weeks) in rats and mice (Ponomarkov and Tomatis, 1978) showed liver, kidney, and stomach lesions for rats (dosed weekly with styrene at 500 mg/kg) and no significant effects for mice (dosed weekly with 300 mg/kg). Rats receiving an average daily oral dose of 95 mg styrene/kg bw for 185 days showed no adverse effects, while those receiving 285 or 475 mg/kg-day showed reduced growth and increased liver and kidney weights (Wolf et al., 1956). Other subchronic rat feeding studies found LOAELs in the 350-500 mg/kg-day range and NOAELs in the range of 100-400 mg/kg-day.

The lifetime studies in rats and mice (Ponomarkov and Tomatis, 1978) are not appropriate for risk assessment of chronic toxicity because of the dosing schedule employed. The Wolf et al. (1956) study is of insufficient duration (185 days) to be considered chronic.

o ORAL RFD UNCERTAINTY :

UF -- The uncertainty factor of 1000 reflects 10 for both intraspecies and

interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of subchronic effects to chronic effects.

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o ORAL RFD MODIFYING FACTOR :

MF -- None

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o ORAL RFD COMMENTS :

None.

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o ORAL RFD CONFIDENCE :

Study -- Medium
Data Base -- Medium
RfD -- Medium

The principal study is well done and the effect levels seem reasonable, but the small number of animals/sex/dose prevents a higher confidence than medium at this time. The data base offers strong support, but lacks a bona fide full-term chronic study; thus, it is also considered to have medium confidence. Medium confidence in the RfD follows.

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o ORAL RFD SOURCE DOCUMENT :

U.S. EPA. 1984. Health and Environmental Effects Profile for Styrene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document for Styrene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

The ADI in the 1984 Health and Environmental Effects Profile document has received an Agency review with the help of two external scientists.

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o REVIEW DATES : 10/09/85, 11/06/85, 10/09/85
o VERIFICATION DATE : 10/09/85
o EPA CONTACTS :

Julie Du / OST -- (202)260-7583

Edward V. Ohanian / OST -- (202)260-7571

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RDI -
o INHALATION RFD SUMMARY :

Critical Effect	Exposures*	UF	MF	RfC
CNS effects Occupational Study Mutti et al. (1984)	NOAEL: 94 mg/cu.m (25 ppm = 150 mmole urinary styrene metabolites/mole creatinine adjusted to lower 95% confidence limit = 22 ppm) NOAEL(HEC): 34 mg/cu.m LOAEL: >94 mg/cu.m (>22 ppm derived as in NOAEL listing)	30	1	1E+0 mg/cu.m

*Conversion Factors: MW = 104.15. Assuming 25 C and 760 mmHg, NOAEL (mg/cu.m) = NOAEL (ppm) x MW/24.45 = 94 mg/cu.m. The NOAEL exposure level is based on a back extrapolation from worker urinary concentration of styrene metabolites reported in the principal study and adjusted to the lower 95% confidence limit listed in Guillemin et al. (1982), which was 88%, 25 ppm x 0.88 = 22 ppm. The NOAEL(HEC) is calculated using an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. NOAEL(HEC) = 94 mg/cu.m x MVho/MVh x 5 days/7 days = 34 mg/cu.m. The feasibility of applying the exposure model of Perbellini et al. (1988) for extrapolation of the values in the principal study is currently being investigated. Application of this model may result in changes in the NOAEL(HEC) value and, therefore, the RfC.

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o INHALATION RFD STUDIES :

Mutti, A., A. Mazzucchi, P. Rusticelli, G. Frigeri, G. Arfini, and I. Franchini. 1984. Exposure-effect and exposure-response relationships between occupational exposure to styrene and neuropsychological functions. Am. J. Ind. Med. 5: 275-286.

In a cross-sectional study, Mutti et al. (1984) examined the neuropsychological function in 50 workers whose mean duration of styrene exposure was 8.6 (SD of 4.5) years. Styrene exposure was assessed by the authors to correspond to air concentrations ranging from 10-300 ppm as a mean daily exposure. These concentrations were estimated from the summation of the principal urinary metabolites of styrene, mandelic acid (MA) and phenylglyoxylic acid (PGA). Urinary metabolite levels are considered as reliable biological indicators of styrene exposure (ACGIH, 1986; WHO, 1983), and several laboratories have determined collectively that the specific method used in this study, the summation of the principal metabolites collected in next-morning urine, is the most reliable and representative of actual air exposure concentrations (Guillemin et al., 1978, 1982; Ikeda et al., 1982; Franchini et al., 1983). Workers with absence of metabolic and neurologic disorders, smoking habits of <20 cigarettes/day, and an alcohol intake of <80 mL of ethanol/day were chosen. These same eligibility criteria were used to select a control group of 50 workers that was matched for age, sex, and educational level. The exposed workers were further segregated into four subgroups (n = 9-14) according to increasing levels of urinary styrene metabolites. A battery of neuropsychological tests was conducted on the same day as the urine collection and included exams evaluating visuo-motor speed, memory, and intellectual function. No other endpoints were considered. Correlation analysis of the test results and urinary metabolite levels showed a clear concentration response in at least three of eight tests, including block design (intellectual function), digit-symbol (memory), and reaction times (visuo-motor speed). Evidence of a concentration-response relationship was also present for short- and long-term logical memory and embedded figures (impaired visual perception). When the results were analyzed using duration of exposure as a covariate, increases in reaction times and a decrease in

digit symbol (memory, concentration) were apparent. The only test showing results in the lowest exposure group, short-term verbal memory loss, exhibited

no concentration-response relationship. The neuropsychological results from this study are from established tests for CNS dysfunction, are present when compared against a stringently matched control population, and show concentration-response relationships. Also, the deficiencies noted in the reaction-times corroborate the results presented by Moller et al. (1990) and others discussed below.

The concentration-response relationship between urinary metabolite concentration (mandelic acid and phenylglyoxylic acid levels normalized to creatinine in "morning-after" urine) and test results indicated a significant effect level in the subgroup whose urine contained 150-299 mmole urinary metabolites/mole creatinine. Workers with metabolite concentrations of up to 150 mmoles/mole appeared to have no significant effects, and this level is therefore designated as the NOAEL in this study. The authors state that this level of urinary metabolites corresponds to a mean daily 8-hour exposure to air
styrene of 25 ppm (106 mg/cu.m). Derivation of this air level is from the creatinine-normalized, combined concentration of the styrene metabolites, MA and PGA, in urine collected from the workers on Saturday mornings. Guillemin et al. (1982) demonstrated a logarithmic relationship (r = 0.871) between the summation of urinary metabolites (MA + PGA, next morning) and air concentrations of styrene (ppm x hours). Guillemin calculated the mean combined urinary metabolite concentration (next morning) for an 8-hour exposure
to 100 ppm. This relationship was used by both Mutti et al. (1984) and Guillemin and Berode (1988) in a proportional manner to obtain styrene air levels at lower urinary metabolite concentrations. The 95% confidence interval
was also calculated for an 8-hour exposure at 100 ppm, the lower limit of the confidence calculation being 88% of the mean styrene exposure. This factor was applied directly to the NOAEL of 25 ppm [25 ppm x 0.88 = 22 ppm (94 mg/cu.m)]. Due to the construction of the subgroups, designation of a LOAEL was the lower limit of the subgroup in which adverse effects were observed [i.e., greater than the NOAEL of 22 ppm (94 mg/cu.m)].

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o INHALATION RFD UNCERTAINTY :

UF -- A partial UF of 3 was used for data base inadequacy, including the lack of concentration-response information on respiratory tract effects. A partial

UF of 3 instead of 10 was used for intraspecies variability since the lower 95% confidence limit of the exposure extrapolation was used and because Perbellini et al. (1988) demonstrated that this biological exposure index (i.e., urinary metabolites) accounts for differences in pharmacokinetic/ physiologic parameters such as alveolar ventilation rate. A partial UF of 3 instead of 10 was also evoked for lack of information on chronic studies as the average exposure duration of the principal study of Mutti et al. (1984) was not long enough (8.6 years) to be considered chronic. The total uncertainty is therefore 30 (three times the one-half logarithm of 10).

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o INHALATION RFD MODIFYING :

MF -- None
FACTOR

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o INHALATION RFD COMMENTS :

Central nervous system effects caused by exposure to styrene have been reported by several investigators in studies since the early 1970s. Gotell et al. (1972) noted significantly increased reaction times in a group of six polyester plant workers exposed to >150 ppm styrene as compared with unexposed controls and another group exposed to <150 ppm. Gamberle et al. (1975) noted longer and more irregular reaction times in 106 exposed workers (estimated at 13-101 ppm styrene for an average of 2.7 years) as compared with a control population. Cherry et al. (1980) found no alteration in reaction times among 27 workers exposed to a mean of 92 ppm styrene (duration unspecified) and no difference in performance on four behavioral tests of memory and vigilance. However, a follow-up study conducted 21 months later by these authors on 8 of the same 27 individuals (Cherry et al., 1981) found that the three men with the highest urinary mandelic acid concentrations all improved reaction times significantly ($p < 0.05$) as compared with their earlier values. These alterations were correlated with those individuals having slow clearance of mandelic acid. Among 98 male laminating workers (mean styrene exposure of 5.1 years), Lindstrom et al. (1976) reported weak correlations of CNS-behavioral testing (poor psychomotor performance and visuomotor inaccuracy) with levels of styrene exposure estimated to be between 25 and 75 ppm based on urinary mandelic acid levels. The study of Mutti et al. (1984) is one of few in which extensive CNS-behavioral testing was carried out. The recent studies of Moller et al. (1990) and Flodin et al. (1989) couple functional decrements with adverse behavioral effects in a chronically exposed worker population. The effect of styrene on peripheral nerves has also been reported, although not to the extent of central effects. These studies are briefly described in the recent study of Murata et al. (1991) in which data on a small number of workers suggest that styrene may differentially affect sensory nerves.

The studies of Moller et al. (1990) and Flodin et al. (1989) both examined central effects of styrene in the same worker population. The Flodin et al. (1989) study on neuropsychiatric effects of styrene exposure provides documentation of the styrene levels to which these workers were exposed.

In a cross-sectional occupational study, Moller et al. (1990) studied 18 male Swedish boatbuilders exposed to styrene for an average of 10.8 years (range of 6-15 years). Personal sampling (8-hour TWA concentrations) available for 7/10 years showed that the workers had been exposed to 50-140 mg/cu.m styrene. The exposure data is discussed at length in the text of the Flodin et al. (1989) study below. These workers were not further subgrouped into high-and low-exposure groups as in the Flodin et al. (1989) study. Two reference groups were used for evaluation of the tests; both were unexposed to industrial solvents and matched to the exposure group with respect to smoking and alcohol consumption. These workers were subsequently given a thorough otoneurological examination, evaluating auditory, visual, and vestibular systems, as well as coordination of vestibular sensations with compensatory eye movements manifest in the vestibuloocular reflex (VOR). The test showing the greatest and most consistent deviation in performance between the exposed workers and the reference population was the visual suppression of the VOR. Execution of this test required the subjects to fixate on a target that moved with movement of the subjects' chair. The normal VOR functions to maintain steady gaze of the eyes despite movements of the head. However, when the target moves with the subject, this reflex must be suppressed in order to follow the target. Quantitation of a subject's capacity to suppress VOR is measured as the ratio between eye and target velocity (gain) and in the temporal relationship between eye and target velocity (phase). Abnormal functioning would be manifest by an increase in gain and a decrease in phase,

if the values exceeded the mean +/- 2 SD units of the corresponding measurement in a reference population. Abnormal phase shifts were recorded for 4/18 workers; in each of the four cases, the gain was also abnormal. These differences were reflected in the group values that showed a higher mean gain ($p < 0.001$) and a decrease in angle of phase lead ($p < 0.001$) in examinations carried out with predictable (sinusoidal frequency sweep) and unpredictable (pseudorandomized) conditions. The deficits shown in these tests suggest lesions in the brainstem or cerebellar regions, because these findings are in accordance with findings in patients with known brainstem or cerebellar disorders (Odkvist et al., 1982, 1987). Other tests reported in this study also gave indications of neurological deficits. The posturography test demonstrated increases in sway area of subjects with their eyes closed, which are consistent with vestibular deficits. The overall results of this test are, however, internally inconsistent as more of these workers showed abnormal scores with their eyes open than with their eyes closed. Although examination of saccadic eye movements (brief, fast movements occurring with change in fixation point) did reveal abnormal scores in latency for 7/18 subjects, none of the 18 were found to have abnormal velocity. This also is an internal inconsistency within the exam, making these results equivocal. A similar internal inconsistency was noted in the results of the smooth-pursuit eye movement during which the subject is asked to visually track a slowly moving stimulus. Seven of the 18 subjects had abnormal results in lag time (phase), whereas none of the 18 tested abnormal for gain. Disturbances were found in the central auditory pathways of seven workers but the significance of these effects were not evaluated (see discussion of Pryor et al., 1987). This study provides credible toxicological information on the possible long-term consequences of human exposure to styrene. No effect levels are assigned based on these data as the number of subjects is small and no indication is given of a dose-response relationship among these chronically exposed workers.

Twenty-one male Swedish workers were exposed to styrene for an average of 11.6 years (range of 6-21 years) as a consequence of their occupation, boatbuilding (Flodin et al., 1989). Personal sampling (8-hour average concentrations) had been carried out in 9 of the last 12 years, with the number of sampling days for each year ranging from 3 to 27; the data presented indicate an exposure range of around 40-140 mg/cu.m during this time. In one year, 30-minute sampling times were performed on most tasks and showed that peak exposures were exceptinal, with only about 1% of all measurements of styrene >300 mg/cu.m; about 44% of the samples were <25 mg/cu.m, and about 65% were <50 mg/cu.m. Based on these sampling data, the workers were classified into two groups: those exposed to about 50 mg/cu.m styrene for the past 7 years and those exposed to about 25 mg/cu.m. The higher exposed workers were primarily involved in lamination processes. Workers were examined by a clinical interview that included a detailed inquiry about neuropsychiatric symptoms; psychometrical tests and some clinical chemistry were also included.

The workers were examined twice, the first time (21 workers examined) occurring when they had not been exposed for 1 week. The second examination (17 workers examined;nie in the higher exposure group and eight in the lower exposure group) occurred after the workers had not been exposed for a minimum of 3 months because the factory had gone bankrupt. Two of the remaining four workers refused participation in the second interview, and results from two others were disallowed as one was diagnosed as having pulmonary thrombosis and the other psycho-organic syndrome (POS) (see discussion of Moller et al., 1989). No concurrent control group was used. According to the questionnaire, the symptoms at the first examination were distributed in a exposure-related manner, with the higher exposure group having an average of 10.4 symptoms/worker and the lower exposure group having an average of 5.3

symptoms/worker. On the second examination, the average symptoms/worker decreased to 1.9 in both exposure groups. The claim that the higher exposure group performed significantly worse in one psychometrical test (manual dexterity) is not interpretable due to lack of specifics in the text. Internal inconsistencies of the results and the lack of a concurrent matched control group cause the results from this study to be equivocal. No effect levels were designated in this study.

The levels of styrene reported in the study of Mutti et al. (1984) were estimated from levels of urinary styrene metabolites. As already discussed, this method is considered as a biological indicator of exposure and has been shown to reliably reflect the total concentration of styrene to which individuals have been exposed. The relationships between styrene exposure and urinary metabolite concentrations have been established by a number of studies including those of Guillemin et al. (1982) and Ikeda et al. (1982) and reviewed by the WHO (1983). The work of Perbellini et al. (1988) has shown that the variability of urinary metabolite levels observed in styrene-exposed worker populations may reflect physiologic and metabolic variability inherent in humans. These characteristics are not shared by the extensive studies on styrene levels reported by Lemasters et al. (1985a) and of Jensen et al. (1990), both of which are historical and are based on area and personal sampling procedures.

A diagnosis of psycho-organic syndrome has been used to describe the symptomatology observed in workers heavily exposed to a variety of organic solvents. Examples of specific effects include neurasthenia, personality alterations, unsteadiness, dizziness, and vertigo. Moller et al. (1989) examined nine men who had been diagnosed as having POS, subjecting them to a battery of audiological and vestibular-oculomotor tests, the latter of which measure the capacity to transform signals from the inner ear to compensatory eye movements for purposes such as maintenance of equilibrium. The men were described as having been exposed to various mixtures of alcoholic, aromatic, and aliphatic industrial solvents during their working careers of 8-30 years (mean = 21 years). Seven of them had been granted disability pensions at the time of the examinations. Abnormal static posture was noted in 4/9 members of the POS group ($p < 0.001$). Voluntary saccades (rapid intermittent movements of the eye) were abnormal (both prolonged latency and decreased maximum speed) in 5/9 of the POS group, but in only 2/9 matched controls. As these functions are considered to be controlled centrally in the area of the cerebellum, these findings indicate that cerebellar lesions may occur from chronic exposures to a variety of organic solvents. The results presented by Moller et al. (1990) for these tests in workers exposed to styrene indicate this chemical to be capable of eliciting this toxicity.

A duration-response between length of exposure to solvents and incidence of altered cerebellar functioning (as evidenced by effects on hearing and the vestibular-oculomotor system) is indicated in the study of Odkvist et al. (1987). This study examined 23 workers, all of whom had been extensively exposed to aliphatic and aromatic solvents. Sixteen of the 23 workers were diagnosed with POS. The average length of exposure of these 16 workers was 27 years (range 9-40 years), considerably more than the average of 21 years (range 5-30 years) for the remaining seven individuals. In the battery of 11 vestibular-oculomotor tests, five (including saccade, visual-suppression, Romberg's test, and electronystagmography) showed a dose-response relationship with the percentage incidences being higher in the group diagnosed with POS; the other six tests either were not conducted in one or the other group or

exhibited no change. Thus, both the number of workers diagnosed with POS and incidence of cerebellar dysfunctioning were correlated with duration of exposure to organic solvents.

The specific capacity of styrene to cause alterations in cerebellar function in humans under short-term acute exposure conditions was experimentally shown by Odkvist et al. (1982). Ten people (5/sex) were exposed to 370-591 mg/cu.m styrene for 80 minutes. A battery of six vestibular-oculomotor tests was administered before, during, and after the exposure. Visual suppression and saccade tests both showed statistically significant alterations in 8/10 subjects. Results between exposed subjects and controls did not differ for the optovestibular, optokinetic, and slow pursuit movement test or the sinusoidal swing test. These results indicate that acute exposures to high concentrations of styrene may affect processes within the cerebellum. It should be noted, however, that the results obtained by Moller et al. (1990) and Flodin et al. (1989) were obtained in workers that had not been exposed to styrene for a minimum of 3 months.

Larsby et al. (1978) investigated the relationship between vestibulo-oculomotor function and styrene levels in arterial blood and cerebrospinal fluid. Rabbits (n = 16) were cannulated and infused with a 10% solution of styrene introduced at 3.1-12.6 mg/minute. Vestibular function was evaluated using electronystagmography in response to rotary acceleration. Styrene concentration was monitored in both arterial (ear) and cerebrospinal fluid. During the exposure, positional nystagmus (i.e., involuntary eye movement response to rotary movement evident only when the animal is lying on one side or the other, not prone) was observed in 10/11 rabbits tested. In addition, a paradoxical rotary response was observed in 6/16 rabbits. This phenomenon is described as involuntary eye movement opposite to the direction of rotation (left-beating eye movements when rotated clockwise and vice versa). Both observations indicate that vestibular function was affected. Results also showed that, at an infusion rate of 4.9 mg/minute, arterial blood levels reached a constant level only after about 2 hours. Styrene concentrations in cerebrospinal fluid had the same shape as the arterial curve and was constantly 5-10% of the corresponding arterial concentration.

A number of other occupational studies investigating the effects of styrene on workers are available in the literature. Most of these reports examine either central or peripheral nervous function, although blood effects (Stengel et al., 1990), nephrotoxicity (Viau et al., 1987), and liver effects (Hotz et al., 1980) have also been examined. Nearly all of these reports suffer from one or more deficiencies, the most common being lack of exposure information. Almost all, however, indicate that styrene affects central processes in humans. An overview of several of these studies follows.

In addition to the auditory data listed in the Moller et al. (1990) study, two other studies have reported hearing loss, one in humans and the other in laboratory animals. Muijser et al. (1988) evaluated hearing thresholds up to 16 kHz in 59 workers exposed to airborne styrene. Air samples (4-hour mean averages, 6-16 samples/group work area) were taken in the breathing zone during 3 consecutive days in work areas where 31 workers were directly exposed to styrene (mean = 138 mg/cu.m) and 28 workers were indirectly exposed to styrene (mean = 61 mg/cu.m). The duration of employment for the combined group was 8.6 +/- 6.5 years. The control population consisted of 88 individuals not exposed to styrene or other chemicals but who were comparable in age and socio-economic status to the exposed workers. Audiometric analyses were corrected for age. Comparison of hearing thresholds between the controls

and both exposed groups revealed no differences in hearing thresholds at frequencies up to and including 16 kHz. Comparison between the experimental groups, however, did reveal that the directly exposed workers had higher thresholds for frequencies at 8-16 kHz than did the indirectly exposed workers (p value from multivariate analysis of covariance = 0.012). Quantitative and qualitative differences in the background noise between the control and study plants may have compromised the control population in this study. Although difficulties with the control population prevent definite assignment of effect levels, human exposure to 138 mg/cu.m styrene appears to have resulted in high-frequency hearing loss [LOAEL(HEC) = 69 mg/cu.m]. Pryor et al. (1987) exposed male Fisher 344/N rats (12/group) to 0 (clean air), 800, 1000, or 1200 ppm (0, 3408, 4260, or 5112 mg/cu.m, respectively) styrene for 14 hours/day, 7 days/week for 3 weeks. The duration-adjusted values are 0, 1988, 2485, or 2982 mg/cu.m, respectively. Auditory response thresholds were determined by both behavioral and electrophysiologic methods, apparently some weeks after the last exposure. Increases in auditory thresholds were recorded at 8-20 kHz with both methods at the lowest concentration used [LOAEL(HEC) = 1988 mg/cu.m].

Several occupational studies have reported adverse health effects on workers whose exposure was at or near 25 ppm (110 mg/cu.m) styrene. Lindstrom et al. (1976) reported that the visuomotor accuracy of styrene-exposed workers (n = 98, average exposure 4.9 years, range 0.5-14 years) was significantly poorer ($p < 0.05$) than that of the nonexposed workers. Moreover, this deficit was shown to be related to concentration in two subgroups whose exposures (estimated from urinary mandelic acid) were 25 and 75 ppm. Seppalainen and Harkonen (1976) conducted a cross-sectional study on 96 styrene workers, all of whom received EEG examinations 24 hours after termination of exposure. Mean exposure to styrene was estimated from urinary mandelic acid to be 808 mg/L, approximately 36 ppm in air. Twenty-three of 96 (24%) EEG's were abnormal in the exposed group as compared with a normal population (indicated as about 10% in the text), a difference that is statistically significant ($p < 0.05$).

Human irritation from styrene exposure has been characterized in a limited study by Stewart et al. (1968). Nine male volunteers were exposed to air concentrations of styrene of 50-375 ppm (213-1597 mg/cu.m) for periods of 1-7 hours. Urinalysis, hematology, and blood chemistry studies were conducted prior to exposure and at 16 and 72 hours postexposure; subjective symptoms were also recorded. Within 15 minutes following a 60-minute exposure to 375 ppm styrene, 4/5 volunteers complained of mild eye and nasal irritation. (Throughout the remainder of the exposure, all subjects noted a progressive loss of their ability to perceive the odor of styrene.) It is not clear from the text whether or not the irritation remained throughout the exposure. After 45 minutes of exposure, one of the subjects reported being nauseated and two others complained of feeling slightly inebriated. At 216 ppm styrene, 1/3 subjects noted nasal irritation 20 minutes into a 60-minute exposure. No adverse symptoms were reported by the three subjects exposed to 52 ppm styrene for 1 hour. Six subjects were then exposed to 99 ppm styrene for a total of 7 hours. Three of the six subjects complained of mild eye and throat irritation

20 minutes after the start of the exposure; in two of these subjects, the eye irritation persisted for 30 minutes before subsiding. At the end of the exposure, none of the subjects reported nausea, headache, or eye, nose, or throat irritation. The clinical studies were all normal. None of the six individuals exposed to 99 ppm (422 mg/cu.m) styrene for 7 hours or 216 ppm for 1 hour experienced any subjective symptoms of significant consequence. Although these results suggest no symptoms of consequence in humans exposed to styrene concentrations as high as 216 ppm (920 mg/cu.m), the population tested was small (only three subjects), and the duration was minimal.

Considerable success has been attained in modeling levels of inhaled styrene in biological systems. The physiologically based pharmacokinetic model for styrene of Ramsey and Andersen (1984) allows simulation over a wide range of concentrations on the time course of styrene distributed to four main tissue groups: (1) highly perfused organs, (2) moderately perfused organs (predominately muscle), (3) slowly perfused tissue (predominately fat), and (4) liver. When applied to actual rat data, this model accurately predicted blood styrene levels of 80-1200 ppm (340-5112 mg/cu.m). Then the behavior of inhaled styrene in humans was simulated successfully by substitution of human physiological parameters. These authors were able to demonstrate that blood concentrations of inhaled styrene in rats, mice, and humans were nearly identical at air concentrations of less than or equal to 200 ppm (852 mg/cu.m) but differed widely at higher concentrations. Perbellini et al. (1988) developed a physiologically based mathematical model for human exposure to airborne styrene that accounts for metabolism, subsequent synthesis, transfer, and urinary excretion of the principal metabolites MA and PGA. The model comprises eight compartments: (1) lung; (2) the richly perfused tissues of heart, brain, and kidney; (3) muscle; (4) fat; (5) liver tissue for catabolism of styrene; (6) liver tissue for transfer of metabolites; (7) body water in which the metabolites are distributed; and (8) urine in which the metabolites are excreted. Simulation results using this model were in agreement with reported urinary metabolite concentrations measured in various studies of worker populations, including that of Guillemin et al. (1982). Further simulations demonstrated that the use of urinary metabolites as a biological exposure index can accurately account for variability in pharmacokinetic/physiologic parameters such as the alveolar ventilation rate. Simulations using an alveolar ventilation rate of 6-12 L/minute resulted in less than a three-fold range in model output (urinary metabolite concentration).

Jersey et al. (1978) exposed Sprague-Dawley rats (96/sex/group) to 0, 600, or 1200 ppm (0, 2556, or 5112 mg/cu.m, respectively) of 99.5% styrene for 6 hours/day, 5 days/week for up to 20 months. The exposure concentration of the 1200 ppm exposure group was reduced to 1000 ppm (4260 mg/cu.m) after 2 months because the males showed signs of toxicity (narcosis leading to anesthesia and excessive weight loss) with death coming to three animals. Exposures were terminated when mortality reached 50% for one exposure group of each sex; this was at 18.3 months for males and 20.7 months for females. All surviving rats were euthanized at the end of 2 years with interim group samplings at 6 and 12 months. Hematology, clinical chemistry, body weights, gross anatomical and histopathological analysis, and cage-side observations were performed for evaluation of toxicity. The respiratory tract (including the lungs, trachea,

and nasal turbinates) was not examined in all animals; the nasal turbinates, for example, were examined only in a portion of the controls and high-exposure animals (14/28 animals, sexes combined). The number of sections examined in the nasal turbinates, trachea, or lungs is not indicated in the text. No exposure-related increase in mortality was noted in either sex. An inverse relationship between mortality and exposure was noted in male rats. A high incidence of murine pneumonia was associated with an increased mortality, but only in the control and high-exposure animals; no dose-response relationship was apparent from the data. Average body weights of both females and males were decreased at both dose levels at various times throughout the experiment. However, only the body weights of the males exposed to the highest concentration were decreased more than 10% (14% maximum), consistently only during treatment days 82-263. The only concentration-dependent alteration in organ weights observed was in absolute and relative liver weights in females sacrificed at 6 months. At the terminal sacrifice, an increase in absolute liver weights was observed only in the females exposed to the highest concentration; no histopathology accompanied this alteration. The only histological result considered to be concentration-dependent was an increase in incidence of alveolar histiocytosis (areas containing lipid-laden alveolar macrophages) that corresponded to grossly visible subpleural pale foci in the lungs of the females exposed to the highest concentration. No concentration-related effects were reported in any groups for hematology, clinical chemistry, or urinalysis. Deficiencies in this study preclude assigning effect levels.

Conti et al. (1988) exposed Sprague-Dawley rats (30/sex/dose) to 0, 25, 50, 100, 200, or 300 ppm (0, 106, 213, 426, 852, or 1278 mg/cu.m, respectively) styrene for 4 hours/day, 5 days/week for 52 weeks. The animals were kept under observation until spontaneous death. Histopathologic examinations were performed on each animal; tissues examined included brain, liver, kidneys, gonads, spleen, and pancreas. The lungs were apparently the only portion of the respiratory tract examined in this study. No noncancer results were reported or discussed in this study. No effect levels could be assigned in this study.

Effects of styrene on the respiratory tract have been addressed in mouse subchronic studies by the NTP (NTP, 1991a). B6C3F1 mice (10/sex/group) were exposed to 0, 62.5, 125, 250, or 500 ppm (0, 266, 532, 1065, or 2130 mg/cu.m, respectively) styrene for 6 hours/day, 5 days/week for 13 weeks. The duration-adjusted values for this exposure regime are 0, 47.5, 95, 190, or 380 mg/cu.m. Body weight changes, hematology, serum chemistry, sperm morphology, vaginal cytology, gross pathology, and histopathology (including the entire respiratory tract) were monitored for toxicity. Death occurred in the first week of exposure but only in the males exposed to 250 ppm; no deaths at the highest concentration were noted. Histopathology of these animals showed evidence of thymic and renal cortical necrosis. In exposed female mice, the average liver to body weight ratio was increased in the animals at the two highest concentrations. Histopathology revealed concentration-related increases in centrilobular liver cytomegaly, karyomegaly, and necrosis at these same concentrations with no effects being recorded at 125 ppm styrene or below. The lung to body weight ratios were increased at all levels relative to the control values. Histopathology of the respiratory tract revealed that the incidence of metaplasia and degeneration of the olfactory epithelium of the nasal cavity were already total (10/10 mice) in females at the lowest concentration, with necrosis being observed at higher concentrations. Likewise, bronchiolar regeneration was present in all female animals at all concentrations. The incidence of epithelial hyperplasia of the forestomach was also maximal at the lowest concentration. Similar results were noted for the males. No NOAEL for either respiratory or extrarespiratory effects was achieved in this study. The LOAEL(ADJ) for this study would be 47.5 mg/cu.m.

The effects described occurred in both the nasal cavity [extrathoracic (ET)] and bronchiolar region [tracheobronchiolar (TB)]. The LOAEL(HEC) would therefore be based on effects in these regions with an RGDR of 1.55 = 74 mg.cu.m.

In a rat subchronic study (NTP, 1991b), F344/N rats (10/sex/group) were exposed to 0, 125, 250, 500, 1000, or 1500 ppm (0, 532, 1065, 2130, 4260, or 6390 mg/cu.m, respectively) styrene for 6 hours/day, 5 days/week for 13 weeks. The duration-adjusted values for this exposure regime are 0, 95, 190, 380, 761, or 1141 mg/cu.m. The same toxicological endpoints as in the mouse study were monitored. No deaths were recorded. Liver to body weight ratios were elevated at the three highest exposure levels in males and the two highest exposure levels in females, although no histopathology accompanied this alteration. Concentration-related goblet-cell hypertrophy was noted in the nasopharyngeal duct starting at 125 ppm styrene in males and at 250 ppm in females. Concentration-related degeneration of the olfactory epithelium (described as minimal to mild) was noted starting at 1000 ppm styrene in females and at 1500 ppm in males. Degeneration of the olfactory epithelium was noted also at the two highest exposure levels in both sexes. A NOAEL of 500 ppm is designated for extrathoracic effects [NOAEL(ADJ) = 380 mg/cu.m x RGDR of 0.107 = NOAEL(HEC) = 41 mg/cu.m].

The effect of styrene on the trachea of rats was addressed in two studies conducted by Ohashi et al. (1985, 1986). Both ciliary activity and histopathology were evaluated. Male Sprague-Dawley rats (10/exposure group and 10 controls) were exposed to styrene at 30 or 800 ppm for 8 consecutive weeks or at 150 or 1000 ppm for 3 consecutive weeks. Nasal and tracheal mucosa were examined by electron microscopy, immediately and several weeks after cessation of exposure. The 8-week study (Ohashi et al., 1985) found that there was a strong increase in mucus secretion, with an increase in number of dense bodies in the nasal, but not tracheal, mucosal cells after exposure to 30 ppm styrene. There was an increase in secretory granules in goblet cells at 3-weeks postexposure. At the higher concentration in the 8-week exposure, there was a marked increase in mucus secretion, vacuolation, and sloughing of epithelial cells in both the nasal and tracheal epithelium. Compound cilia were observed, together with nuclear pyknosis, vacuolization of epithelial cells, and changes in electron density in goblet cells, which also exhibited cores with high electron density. Sloughing of epithelial cells from the basement membrane also persisted at 3-weeks postexposure. Severe ciliary denudation was observed in the high-exposure group (1000 ppm styrene) in the 3-week exposure, with ciliary activity in the nose disabled and decreased to 18% of control values in the trachea. No effect levels were designated from these studies as the quantitative relationship between ciliary activity and mucus transport is not clear. In his review of mucociliary transport, Wanner (1977) suggests considerable functional reserve of this system; in chicken trachea 30-50% of particle transport activity was present at a time when only 10% of the epithelium was ciliated.

In two studies, Lemasters et al. (1985b, 1989) examined the reproductive outcomes of female workers involved in plastics manufacturing. In the 1985 study, data from a total of 174 styrene-exposed and 449 unexposed women were collected and analyzed. No increased prevalence in menstrual disorders was observed in subgroups of the workers exposed to either 13 or 52 ppm styrene. In the 1989 study, the authors examined the relationship between styrene exposure and lowered birth weights. During the study, the authors collected and analyzed data from 819 no-, 154 low- (2-29 ppm), and 75 high- (30-82 ppm) exposed pregnancies. There was not a statistically significant concentration-response relationship in decreasing average birth weights. In women who worked at the most highly exposed jobs (estimated at 82 ppm), however, a 4%

reduction in average birth weight that approached statistical significance ($p = 0.08$), despite the small sample size ($n = 50$), was detected.

Murray et al. (1978) exposed pregnant Sprague-Dawley rats and New Zealand rabbits to inhaled styrene at concentrations of 0, 300, or 600 ppm (0, 1278, or 2556 mg/cu.m., respectively) for 7 hours/day from gestation days 6-15 (rats) and 6-18 (rabbits). No concentration-related developmental toxicity was evident in either species by either route. Adverse maternal effects (decreased food consumption and a $p < 0.05$ decrease in weight gain only during the first 3 days of exposure) were noted. This study identifies a freestanding NOAEL for developmental effects of 2556 mg/cu.m.

Beliles et al. (1985) conducted a three-generation reproductive study concomitantly with a 2-year chronic study of exposure of rats to styrene in their drinking water. Sprague-Dawley rats were treated with monomeric styrene in their drinking water at 0, 125, or 250 ppm. These doses corresponded to 8-14 mg/kg/day for males and 12-21 mg/kg/day for females. After animals were dosed for 90 days, 20 females and 10 males from the styrene groups and 30 females and 15 males from the controls were used for the F0 generation and then returned to the chronic study. Representatives of these pups, the F1 generation, were then exposed until they were 110 days of age, at which time they were mated to produce the F2 generation. The F3 generation was produced in the same manner. Each generation was evaluated for fertility (male and female), litter size, pup viability, pup survival, sex ratio, pup body weight, weanling liver and kidney weight, physical and behavioral abnormalities on each day of lactation, and marrow cytogenetics. Reduction in the gestation and 1-, 7-, and 14-day survival indices of the high dose F2 pups was observed. A reduction in survival was also noted among the high dose F1 pups, but only at 21 days. No other evidences of fetotoxicity were noted. Although the authors claim these effects to be due to extensive losses in only 1 or 2 litters, only data on individual fetuses is presented. The high-dose level is designated as a NOAEL for reproductive effects.

Kankaanpaa et al. (1980) exposed pregnant BMR/T6T6 mice (15 controls and 13 exposed) to 250 ppm (1065 mg/cu.m) >99% pure styrene on gestation days 6-16 for 6 hours/day. Parameters monitored included number of litters and fetuses (total, live, dead, and malformed). No description of maternal toxicity is given, although narrative is provided on two preliminary experiments, one conducted at 500 ppm (2130 mg/cu.m) in which 2/6 pregnant mice and the surviving females had a fetal death rate of 47%. The other experiment was conducted at 700 ppm (2982 mg/cu.m) in which 3/5 pregnant animals died, with the surviving dams having a 95% fetal death rate. No dams died during the 250 ppm experiment, and the difference in the fetal death rate between controls and exposed dams was not statistically significant (27% vs. 18% in the controls; $p < 0.10$). The number of malformed fetuses was also increased in the exposed vs. the control mice (2.9% vs. 0.9%), but no statistical analysis was performed. A steep concentration response is indicated by this study: 500 ppm bringing death to both dams and fetuses, whereas 250 ppm appears to be without effect [NOAEL(HEC) = 1065 mg/cu.m]. These authors also exposed pregnant Chinese hamsters (2-7/treatment group and 15 controls) to 0, 300, 500, 750, or 1000 ppm (1278, 2130, 3195, or 4260 mg/cu.m, respectively) styrene for 6 hours/day on gestation days 6-18. Although the small number of animals limits the interpretation of this study, the highest concentration appears to be an effect level [LOAEL(HEC) = 4260 mg/cu.m], as the number of dead or resorbed fetuses was 66% as compared with 26% in the controls. There

were no incidences of malformed fetuses in any treatment group or in the controls.

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o INHALATION RFD CONFIDENCE : Study -- Medium Data Base -- Medium RfC -- Medium The study of Mutti et al. (1984) documents concentration-response relationships of CNS effects in a relatively small worker population. However, the results of this study are consistent with a number of other studies showing central effects in chronically exposed worker populations, most notably that of Moller et al. (1990). The urinary metabolites, MA and PGA, are direct biological indicators of exposure to styrene. Numerous studies have demonstrated the relationship between urinary metabolites and air levels of styrene to be reliable and quantitative. Physiologically based pharmacological modeling of this exposure methodology demonstrates that it reflects and incorporates at least a portion of intrahuman variability related to pharmacokinetics. The study is therefore assigned a medium confidence level. The data base can be considered medium to high as chronic laboratory animal studies addressing noncancer endpoints are not yet available, but a number of human exposure studies support the choice of critical effect. Preliminary information in mice indicate that styrene is a respiratory tract irritant in mice at concentrations lower than 47.5 mg/cu.m. The RfC is assigned an overall confidence rating of medium.

o INHALATION RFD SOURCE :

Source Document -- The assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA 1984a,b, 1985, 1989, 1991
DOCUMENT

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o REVIEW DATES : 09/20/89, 03/26/92
o VERIFICATION DATE : 03/26/92
o EPA CONTACTS :

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CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

HAONE-

One-day HA -- 2E+1 mg/L

NOAEL -- 22.5 mg/kg/day
UF -- 10 (allows for intrahuman variability with the use of a NOAEL from a human study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Stewart et al., 1968

Human volunteers exposed to styrene by inhalation at 217 mg/cu.m (51 ppm) and 499 mg/cu.m (117 ppm) for 1 and 2 hours, respectively, showed no signs of toxicity. The moderately strong initial styrene odor diminished after 5 minutes. At 921 mg/cu.m (216 ppm) nasal irritation resulted after 20 minutes.

Eye and nose irritation, strong odor, and altered neurological function were reported for volunteers exposed to styrene at 1600 mg/cu.m (376 ppm) for 1 hour. Most volunteers exposed to this level exhibited reduced performance in the Crawford Manual Dexterity Collar and Pin Test, the modified Romberg Test and the Flannagan Coordination Test. Six subjects were exposed to 422 mg/cu.m (99 ppm) styrene vapor for 7 hours and no serious adverse effects were noted; this level was identified as the NOAEL. Based on the conditions of exposure and an assumed absorption rate of 64%, this level is equivalent to a dose of 22.5 mg/kg/day.

HATEN-

Appropriate data for calculating a Ten-day HA for styrene are not available. It is recommended that the Longer-term HA for a 10-kg child of 2 mg/L be used as the Ten-day HA.

HALTC-

Longer-term (Child) HA -- 2E+0 mg/L

NOAEL -- 200 mg/kg/day
UF -- 1000 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study with a small number of animals per treatment group)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Quast et al., 1978

Beagle dogs (four/dosage group) were given styrene by gavage 7 days/week for 560 days at 200, 400, or 600 mg/kg bw/day. At the two higher dose levels, minimal histopathologic effects were noted in the liver (increased iron deposits within the reticuloendothelial cells) as well as hematologic effects that included increased Heinz bodies in erythrocytes and a decreased packed cell volume. At the lowest dose level, these effects were not noted. Therefore, the NOAEL for this study was 200 mg/kg/day.

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HALTA-

Longer-term (Adult) HA -- 7E+0 mg/L

NOAEL -- 200 mg/kg/day
UF -- 1000 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study with a small number of animals per treatment group)
Assumptions -- 2 L/day water consumption for a 70-kg adult

Principal Study -- Quast et al., 1978 (study described in HALTC)

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HALIF-

Drinking Water Equivalent Level (DWEL) -- 7E+0 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date -- 10/09/85

Lifetime HA -- 1E-1 mg/L

Assumptions -- 20% exposure through drinking water

NOTE: For this chemical the quantitative cancer risk assessment indicates that an additional safety factor of 10 is necessary to account for possible cancer risk.

Principal Study -- Quast et al., 1978

This study is described for the longer-term (child) HA.

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OLEP -

No information is available on the organoleptic properties of styrene.

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ALAB -

Styrene content is determined by a purge-and-trap gas chromatographic procedure used for the determination of volatile aromatic and unsaturated organic compounds in water and unsaturated organic compounds.

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TREAT-

Methods available for the removal of styrene from water include air

stripping, granular activated carbon, and oxidation.

HADR -
o HEALTH ADVISORY SOURCE :

U.S. EPA. 1989. Final Draft of the Drinking Water Criteria Document on Styrene. Office for Drinking Water, Washington, DC.
DOCUMENT

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o HEALTH ADVISORY REVIEW :

U.S. EPA. 1988. Final Health Advisory for Styrene. Rev. Environ. Contam. Toxicol. 107: 131-146.

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Science Advisory Board review of HAs in January, 1986.

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o EPA DRINKING WATER CONTACT :

Julie Du / OST -- (202)260-7583

Edward V. Ohanian / OST -- (202)260-7571

ACUTE- NO DATA
BCF - NO DATA

CAA - NO DATA

WQCHU- NO DATA

WQCAQ- NO DATA

MCLG -

Value (status) -- 0.1 mg/L (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- EPA has identified styrene as a Category II chemical and has promulgated an MCLG based on hepatic and hematologic effects reported in a chronic oral study in dogs. The MCLG is based upon a DWEL of 7 mg/L and an assumed drinking water contribution of 20 percent. In addition, the agency

carefully examined the overall weight of evidence of cancer, especially: (1) the comparatively low estimated cancer potency; and (2) the lack of a carcinogenic response in an adequately conducted drinking water study. Moreover, styrene is not likely to be widespread in drinking water based on occurrence information available to the agency.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST / (202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 0.1 mg/L (Final, 1991)

Considers technological or economic feasibility? -- YES

Discussion -- The EPA has promulgated a MCL equal to the MCLG of 0.1 mg/L.

Monitoring requirements -- All systems initially monitored for four consecutive quarters; repeat monitoring dependent upon detection, vulnerability status
and system size.

Analytical methodology -- Gas chromatographic/mass spectrometry (EPA 524.2); purge and trap capillary gas chromatography (EPA 502.2); gas chromatography/ mass spectrometry (EPA 524.1); purge and trap gas chromatography (EPA 503.1); PQL= 0.005 mg/L.

Best available technology -- Granular activated carbon; packed tower aeration.

Reference -- 56 FR 3526 (01/30/91); 56 FR 30266 (07/01/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

Value -- 0.01 mg/L (Proposed, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- SMCLs are non-enforceable and establish limits for contaminants which may affect the aesthetic qualities (e.g. taste and odor) of drinking water. It is recommended that systems monitor for these contaminants every three years. More frequent monitoring for contaminants such as pH, color, odor or others may be appropriate under certain circumstances. The SMCL for styrene is based on odor qualities. Promulgation has been deferred following public comment (54 FR 22062).

Reference -- 54 FR 22062 (05/22/89); 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on aquatic toxicity [as established under Section 311(b)(4) of the Clean Water Act, 40 CFR 117.3], ignitability, and reactivity. The available data indicate that the aquatic 96-Hour Median Threshold Limit for styrene is between 10 and 100 ppm. In addition, styrene is easily combustible when exposed to heat or flame and can react vigorously with oxidizing materials.

Reference -- 50 FR 13456 (04/04/85); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

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6 - IRIS
NAME - Toluene
RN - 108-88-3
IRSN - 115
DATE - 920813
UPDT - 08/13/92, 1 field
STAT - Oral RfD Assessment (RDO) on-line 08/01/90
STAT - Inhalation RfC Assessment (RDI) on-line 08/01/92
STAT - Carcinogenicity Assessment (CAR) on-line 08/01/90
STAT - Drinking Water Health Advisories (DWHA) on-line 09/01/90
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 04/01/92
IRH - 03/01/88 RDO Text revised
IRH - 09/07/88 CAR Carcinogen summary on-line
IRH - 02/01/89 CARDR Secondary contact's phone number corrected
IRH - 07/01/89 RDI Inhalation RfD now under review
IRH - 03/01/90 REFS Bibliography on-line
IRH - 04/01/90 CREF Combs et al., 1973 citation corrected
IRH - 06/01/90 CAA Area code for EPA contact corrected
IRH - 06/01/90 RCRA EPA contact changed
IRH - 07/01/90 RDO Withdrawn; new RfD verified (in preparation)
IRH - 07/01/90 OREF Oral RfD references withdrawn
IRH - 08/01/90 RDO Oral RfD summary replaced; RfD changed
IRH - 08/01/90 CAR Text edited
IRH - 08/01/90 OREF Oral RfD references revised
IRH - 09/01/90 HADV Health Advisory on-line
IRH - 09/01/90 HAREF Health Advisory references added
IRH - 08/01/91 CREF Litton Bionetics, Inc., 1981 reference title clarified
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 04/01/92 CAA CAA regulatory action withdrawn
IRH - 08/01/92 RDI Inhalation RfC on-line
IRH - 08/01/92 IREF Inhalation references on-line
RLEN - 73413
SY - ANTISAL 1a
SY - BENZENE, METHYL
SY - METHACIDE
SY - METHYL-BENZENE
SY - METHYLBENZOL
SY - NCI-C07272
SY - PHENYL-METHANE
SY - RCRA WASTE NUMBER U220
SY - TOLUEEN
SY - TOLUEN
SY - Toluene
SY - TOLUOL
SY - TOLUOLO
SY - TOLU-SOL
SY - UN 1294
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA
VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

-
RDO -
o ORAL RFD SUMMARY :

Critical Effect	Experimental Doses*	UF	MF	RfD
Changes in liver and kidney weights 13-Week Rat Gavage Study NTP, 1989	NOAEL: 312 mg/kg converted to 223 mg/kg/day LOAEL: 625 mg/kg converted to 446 mg/kg/day	1000	1	2E-1 mg/kg/day

*Conversion Factors: Dose adjusted for gavage schedule of 5 days/week.

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o ORAL RFD STUDIES :

NTP (National Toxicology Program). 1989. Toxicology and Carcinogenesis Studies of toluene in F344/N rats and B6C3F1 mice. Technical Report Series No. 371. Research Triangle Park, NC.

The oral toxicity of toluene was investigated in this subchronic gavage study in F344 rats. Groups of 10 rats/sex/group were administered toluene in corn oil at dosage levels of 0, 312, 625, 1250, 2500, or 5000 mg/kg for 5 days/week for 13 weeks. All animals receiving 5000 mg/kg died within the first week. One female and 8 males in the 2500 mg/kg group died, but 2 of these were due to gavage errors. No deaths occurred at lower doses. Several toxic effects were noted at doses greater than or equal to 2500 mg/kg, including prostration, hypoactivity, ataxia, piloerection, lacrimation, excessive salivation, and body tremors. No signs of biologic significance were seen in groups receiving less than or equal to 1250 mg/kg. The only significant change in body weight was a decrease ($p<0.05$) for males in the 2500 mg/kg group. There were no toxicologically significant changes in hematology or urinalysis for any group of animals. Biochemical changes, including a significant increase ($p<0.05$) in SGOT in 2500 males and a dose-related increase in cholinesterase in females receiving 2500 and 5000 mg/kg, were not considered to be biologically significant. There were several pathologic findings and organ weight changes in the liver, kidney, brain, and urinary bladder. In males, absolute and relative weights of both the liver and kidney were significantly increased ($p<0.05$) at doses greater than or equal to 625 mg/kg. In females, absolute and relative weights of the liver, kidney, and heart were all significantly increased at doses greater than or equal to 1250 mg/kg ($p<0.01$ for all comparisons except $p<0.05$ for absolute kidney and heart weights at 1250 mg/kg). Histopathologic lesions in the liver consisted of hepatocellular hypertrophy, occurring at greater than or equal to 2500 mg/kg.

Nephrosis was observed in rats that died, and damage to the tubular epithelia of the kidney occurred in terminally sacrificed rats. Histopathologic changes were also noted in the brain and urinary bladder. In the brain, mineralized foci and necrosis of neuronal cells were observed in males and females at 2500 mg/kg and males at 1250 mg/kg. In the bladder, hemorrhage of the muscularis was seen in males and females at 5000 mg/kg and males at 2500 mg/kg. The NOAEL for this study is 312 mg/kg/day based on liver and kidney weight changes in male rats at 625 mg/kg. The toxicologic significance of these organ weight

changes is strengthened by the occurrence of histopathologic changes in both the liver and kidney at higher doses. Because the exposure was for 5 days/week, this dose is converted to 312 x 5/7 = 223 mg/kg/day. The LOAEL is 625 mg/kg, which is 446 mg/kg/day when converted.

NTP (1989) also conducted a 13-week gavage study in B6C3F1 mice, following the same regimen described above. All mice receiving 5000 mg/kg died and 8/20 receiving 2500 mg/kg also died. Signs of toxicity seen in animals receiving greater than or equal to 2500 mg/kg included subconvulsive jerking, prostration, impaired grasping reflex, bradypnea, hypothermia, ataxia, and hypoactivity. By week 13, the mean body weight of 2500 mg/kg males was significantly ($p<0.05$) lower than controls. No other significant changes were reported for any group, including macroscopic observation, organ weight means, or clinical pathology parameters. The NOAEL for mice in this study was 1250 mg/kg.

The subchronic study by Wolf et al. (1956) is supportive of the NTP studies. Groups of 10 female Wistar rats were administered gavage doses of 0, 118, 354, or 590 mg/kg toluene dissolved in olive oil. A total of 138 doses were administered over 193 days, resulting in average doses of approximately 0, 84, 253, or 422 mg/kg/day. Hematologic, behavioral, gross and histopathologic examinations were conducted with no toxic effects being reported at any dose.

Therefore, the highest dose of 422 mg/kg/day is considered to be the NOAEL for this study. However, this study is not used as the basis for the RfD because the LOAEL of 446 mg/kg/day identified by NTP (1989) is too close to the NOAEL identified by Wolf et al. (1956). Also, the NTP study indicated that male rats are more sensitive to toluene and the Wolf study utilized only female rats.

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o ORAL RFD UNCERTAINTY :

UF = 1000. An uncertainty factor of 1000 was applied to account for inter- and intraspecies extrapolations, for subchronic-to-chronic extrapolation and for limited reproductive and developmental toxicity data.

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o ORAL RFD MODIFYING FACTOR :

MF = 1.

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o ORAL RFD COMMENTS :

Kostas and Hotchin (1981) exposed NYLAR mice pre- and post-natally to toluene provided in the drinking water at concentrations of 0, 16, 80, or 400 ppm. Effects were noted in all dosed groups on rotorod performance, measured at 45 to 55 days of age, but there was an inverse dose-response relationship. No effects of toluene exposure were seen on maternal fluid consumption, offspring mortality rate, development of eye or ear openings, or surface-righting response. This study is not suitable for use in risk assessment because only 6 to 9 pregnancies/dose group were obtained, and because the dose-response relationship was inverse.

In an abstract providing limited information, Nawrot and Staples (1979) reported an increase in embryonic lethality in mice exposed to toluene from days 6 to 15 of gestation. Pregnant CD-1 dams were administered 0.3, 0.5, or 1.0 mL/kg bw, 3 times/day (equivalent to approximately 780, 1300, or 2600 mg/kg/day). Maternal toxicity was not observed at any dose level, but toluene was shown to be teratogenic at the high dose and embryolethal at the low dose. These levels are higher than the NOAEL demonstrated by the NTP (1989) study.

Several subchronic and chronic inhalation studies have been performed on toluene but are not considered to be suitable for deriving an oral RfD. These studies are summarized nicely in the introduction to the 2-year inhalation bioassay by NTP, 1989. The studies identify the following potential target organs: kidney (male rat); hematologic effects (mice); central nervous system (rats, mice, primates); developmental toxicity (rats, rabbits). It is beyond the scope of this oral RfD summary sheet to describe each of these studies, but the two chronic (2 year) inhalation studies are summarized briefly below.

In a 2-year inhalation study by NTP (1989), F344 rats (60/sex/group) were exposed to 0, 600, or 1200 ppm toluene and B6C3F1 mice (60/sex/group) to 0, 120, 600, or 1200 ppm toluene for 6.5 hours/day, 5 days/week. Ten animals/group (except male mice) were removed at 15 months for toxicologic evaluation. At 15 months, there was an increased incidence and severity of nonneoplastic lesions of the nasal cavity of exposed rats. Minimal hyperplasia of the bronchial epithelium was seen in 4/10 female mice at 1200 ppm. There were no significant differences in survival among any group of animals during the 2-year study. Mean body weights were generally similar for all groups throughout the study. Nephropathy was seen in almost all rats with the severity somewhat increased in exposed rats. There were also effects on the olfactory and respiratory epithelia of exposed rats. No biologically important lesions were seen in any groups of mice. There was no evidence of carcinogenicity for any group of animals in this study.

A chronic inhalation study in rats performed by CIIT (1980) failed to produce an adverse effect. Groups of 40 F344 rats/sex were exposed to 30, 100, or 300 ppm toluene for 6 hours/day, 5 days/week for 24 months. An unexposed group of 120 rats/sex served as a control. Clinical chemistry, hematology, and urinalysis testing were conducted at 18 and 24 months. All parameters measured at the termination of the study were normal except for a dose-related reduction in hematocrit values in females exposed to 100 and 300 ppm toluene.

The highest dose of 300 ppm was considered to be a NOAEL.

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o ORAL RFD CONFIDENCE :

Study: High
Data Base: Medium
RfD: Medium

Confidence in the principal study is high because a sufficient number of animals/sex were tested in each of six dose groups (including vehicle controls) and many parameters were studied. The same protocol was tested in both mice and rats, with rats being identified as the more sensitive species.

The data base is rated medium because it is supported by a 6-month oral study.

It is not higher than medium because there is no reproductive study. Also, the oral studies are all subchronic, with the critical study being only 13 weeks in duration. Medium confidence in the RfD follows.

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o ORAL RFD SOURCE DOCUMENT :

Source Document -- This assessment is not presented in any existing U.S. EPA document.

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o REVIEW DATES : 05/20/85, 08/05/85, 08/05/86, 05/17/90, 06/20/90
o VERIFICATION DATE : 06/20/90
o EPA CONTACTS :

Sue Velazquez / ORD -- (513)569-7571

Krishan Khanna / OST -- (202)260-7588

RDI -
o INHALATION RFD SUMMARY :

Critical Effect	Exposures*	UF	MF	RfC
Neurological effects	NOAEL: None	300	1	4E-1 mg/cu.m
Occupational Study	LOAEL: 332 mg/cu.m (88 ppm)			
	LOAEL(ADJ): 119 mg/cu.m			
Foo et al., 1990	LOAEL(HEC): 119 mg/cu.m			
Degeneration of nasal epithelium	NOAEL: None			
	LOAEL: 2261 mg/cu.m (600 ppm)			
2-Year Rat Chronic	LOAEL(ADJ): 437 mg/cu.m			
Inhalation Study	LOAEL(HEC): 79 mg/cu.m			
NTP, 1990				

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*Conversion Factors: MW = 92.15.

Foo et al., 1990: Assuming 25 C and 760 mmHg, LOAEL (mg/cu.m) = 88 ppm x 92.15/24.45 = 332 mg/cu.m. This is an extrarespiratory effect of a soluble vapor. The LOAEL is based on an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. LOAEL(HEC) = LOAEL(ADJ) = 332 x MVho/MVh x 5 days/7 days = 119 mg/cu.m.

NTP, 1990: Assuming 25 C and 760 mmHg, LOAEL (mg/cu.m) = 600 ppm x 92.15/24.45 = 2261 mg/cu.m. LOAEL(ADJ) = LOAEL (mg/cu.m) x 6.5 hours/24 hours

x 5 days/7 days = 437 mg/cu.m. The LOAEL(HEC) was calculated for a

gas:respiratory effect in the extrathoracic region. MVa = 0.24 cu.m/day, MVh = 20 cu.m/day, Sa (ET) = 11.6 sq.cm, Sh (ET) = 177 sq.cm. RGDR = (MVa/Sa) / (MVh/Sh) = 0.18. LOAEL(HEC) = 437 x RGDR = 79 mg/cu.m.

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o INHALATION RFD STUDIES :

Foo, S., J. Jeyaratnam and D. Koh. 1990. Chronic neurobehavioral effects of toluene. Br. J. Ind. Med. 47(7): 480-484.

NTP (National Toxicology Program). 1990. Toxicology and carcinogenesis studies of toluene in F344/N rats and B6C3F1 mice (inhalation studies). NTP-TR-371. 253 p.

In humans, toluene is a known respiratory irritant with central nervous system (CNS) effects. Because available studies could not provide subthreshold (NOAEL) concentrations for either of these effects, the LOAELs for both effects need to be considered in developing the RfC. Consequently, the study of Foo et al. (1990) was used for the CNS effects, and that of the National Toxicology Program (NTP, 1990) for the irritant effects. Because the CNS effect was judged to be a more severe and relevant endpoint, the LOAEL for this effect was used for deriving the RfC. Further, this effect is supported by a number of other occupational studies that show effects around 100 ppm.

Foo et al. (1990) conducted a cross-sectional study involving 30 exposed female workers employed at an electronic assembly plant where toluene was emitted from glue. Toluene levels reported in the study were from personal sample monitoring and reported as an 8-hour TWA, although the number of samples taken and the actual sampling period were not given. No historical exposure values were given. Co-exposure to other solvents was not addressed in the study. The exposed and control cohorts were matched for age, ethnicity, and use of medications. Members of these cohorts did not use alcohol and were nonsmokers. Medical histories were taken to eliminate any histories of central or peripheral nervous system disorders. The average number of years (+/- SD) worked by the exposed population was 5.7 +/- 3.2 and by the controls was 2.5 +/- 2.7. Exposed workers breathed toluene air levels of 88 ppm (332 mg/cu.m) as a TWA and control workers 13 ppm (49 mg/cu.m) (TWA); both of which are averages of the individual personal samples. A battery of eight neurobehavioral tests were administered to all exposed and control workers. The tests were performed midweek, before the workers reported to their stations for the day. Group means revealed statistically significant differences in 6/8 tests; all tests showed that the exposed workers performed poorly compared with the control cohort. When individual test results were linearly regressed against personal exposure concentrations, poor concentration-response relationships resulted for the six tests, with correlation coefficients ranging from 0.44 to 0.30. Irritation effects were not evaluated in this study, and no clinical signs or symptoms were reported.

The paucity of exposure information, coupled with the small size of the cohort, limits the interpretation of this study, although the results were essentially confirmed in a clinical study in which the toluene concentrations were carefully controlled (Echeverria et al., 1989) at levels bracketing 88 ppm. Although the data in Echeverria et al. (1989) were generated from short-term exposures (3-7 hours over a period of 142 days), the results may be considered relevant to longer-term exposures as several studies indicate the absence of a duration-response relationship in toluene-induced symptomatology.

Fornazzari et al. (1983) noted the absence of a duration-effect relationship among toluene abusers when they were segregated into neurologically impaired

vs. unimpaired (p = 0.65). The human studies of Iregren (1982), Cherry et al. (1985), Baelum et al. (1985), and the principal study of Foo et al. (1990) all report this lack of a duration-response relationship and confirm the occurrence of CNS effects. Foo et al. (1990) indicate a LOAEL of 88 ppm toluene (332 mg/cu.m) for neurobehavioral changes from chronic exposure to toluene.

In a 2-year bioassay, Fischer 344 rats (60/sex/group) were exposed to 0, 600, or 1200 ppm (0, 2261, or 4523 mg/cu.m, respectively) toluene vapors, 6.5 hours/day, 5 days/week (duration-adjusted to 0, 437, and 875 mg/cu.m, respectively) for 103 weeks (NTP, 1990). To generate toluene vapor, the liquid material was heated, and the vapor diluted with nitrogen and mixed with the chamber ventilation air. An interim sacrifice was carried out at 15 months on control and 1200-ppm groups (10/sex/group) to conduct hematology and histopathology of the brain, liver, and kidney. Body weights were measured throughout the study. Gross necropsy and micropathology examinations were performed at the end of the study on all major organs including the nasal passage tissues (three sections), lungs, and mainstem bronchi. Mean body weights in both exposed groups were not different from controls for either sex. No exposure-related clinical signs were reported, and survival rate was similar for all groups. At the interim sacrifice, there was a mild-to-moderate degeneration in the olfactory and respiratory epithelium of the nasal cavity in 39/40 rats of the 600- and 1200-ppm groups compared with 7/20 controls. At the end of 2 years, there was a significant ($p<0.05$) increase in the incidence of erosion of the olfactory epithelium (males: 0/50, 3/50, and 8/49; females: 2/49, 11/50, and 10/50; at 0, 600, and 1200 ppm, respectively) and of degeneration of the respiratory epithelium (males: 15/50, 37/50, and 31/49; females: 29/49, 45/50, and 39/50; at 0, 600, and 1200 ppm, respectively) in the exposed animals. The females exposed to 600 and 1200 ppm also exhibited a significant increase in inflammation of the nasal mucosa (27/49, 42/50, and 41/50 at 0, 600, and 1200 ppm, respectively) and respiratory metaplasia of the olfactory epithelium (0/49, 2/50, and 6/50 at 0, 600, and 1200 ppm, respectively). A LOAEL of 600 ppm toluene was determined for the concentration-dependent increase in erosion of the olfactory epithelium in male rats and the degeneration of the respiratory epithelium in both sexes. No NOAEL could be derived from this study.

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o INHALATION RFD UNCERTAINTY :

UF -- An uncertainty factor of 10 is used to account for intraspecies variability and another factor of 10 for the use of a LOAEL. An additional factor of 3 is applied for data base deficiencies, including the lack of data and well-characterized laboratory animal exposures evaluating neurotoxicity and respiratory irritation.

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o INHALATION RFD MODIFYING :

MF -- None
FACTOR

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o INHALATION RFD COMMENTS :

Toluene-induced neurotoxicity has been documented in humans over a broad spectrum of severity that correlates well with concentration. Numerous case studies on chronic toluene abusers [repeatedly exposed to greater than 30,000 ppm (113,000 mg/cu.m)] have demonstrated functional deficits of the CNS accompanied by abnormal morphology of cerebellar and cortical areas of the brain. Under acute exposure conditions [short exposures to greater than 10,000 ppm (37,690 mg/cu.m)], toluene produces CNS narcosis [American Conference of Governmental Industrial Hygienists (ACGIH), 1991]. Lower concentrations, i.e., 800-400 ppm (3015-1508 mg/cu.m), have been associated with worker complaints of CNS-related effects (ACGIH, 1991). Clinical studies using controlled exposure to toluene have demonstrated concentration-related occurrence of complaints such as drowsiness, ataxia, visual impairment, and headache. A number of occupational studies indicate that these same effects are present in exposed worker populations at concentrations lower than 400 ppm (1508 mg/cu.m) although deficiencies in most of these studies preclude confirming this finding unequivocally. Descriptions of a number of these studies follow. The preponderence of the literature showing CNS effects and the well-known proclivity for solvents to affect CNS processes in humans leave little doubt that the brain is a principal target organ for toluene toxicity in humans.

In cases of inhalation abuse of toluene, Rosenberg et al. (1988) demonstrated diffuse cerebral, cerebellar, and brainstem atrophy in 3 of 11 toluene abusers who also had neurological abnormalities. Filley et al. (1990) were able to correlate neuropsychological impairment with the degree of white matter abnormality ($p<0.01$). Cerebellar and cortical functions were classified as impaired in 15/24 individuals who had abused toluene daily (425 +/- 366 mg/day) for extended periods (6.3 +/- 3.9 years) (Fornazzari et al., 1983). In a limited case study, Metrick and Brenner (1982) demonstrated brainstem atrophy through computerized tomographic scans and abnormal brainstem auditory-evoked potentials in 2/2 chronic toluene abusers (12-16 years of admitted, continuous abuse). These studies confirm the occurrence of severe CNS damage in response to highly abusive concentrations of toluene.

Several studies that have investigated the occurrence of neurotoxicity at lesser concentrations, such as occupational situations, have not demonstrated significant neurological or other effects. Hanninen et al. (1987) performed a battery of 11 psychological tests on 43 printing workers who had been occupationally exposed to approximately 117 ppm (441 mg/cu.m) toluene for an average of 22 years and found only mildly adverse effects in 2/11 tests. The control and exposed cohorts in this study were, however, mismatched in several areas, most notably alcohol use. Iregren (1982) examined the psychological performance of 38 printers who had been occupationally exposed to 50-150 ppm (188-565 mg/cu.m) toluene for an average of 16.3 years (range 3-32 years). No effects were seen, although the cohorts in this study were apparently matched only by age. In a cohort study, Cherry et al. (1985) attempted to better match the control and exposed cohorts and considered alcohol use. Although no differences between the cohorts were statistically significant, the exposed workers performed worse than the nonexposed workers on 10/13 psychological tests. The 52 workers in this study were not, however, rigorously matched, and the concentrations listed in the study ranged up to greater than 500 ppm (1884 mg/cu.m). The cohorts in the study of Foo et al. (1990) were well matched for a number of confounders, including alcohol use, and statistically significant psychological effects were seen.

In the occupational study conducted by Yin et al. (1987), 94 solvent workers (38 men and 56 women; average employment duration, 6.8 years) and 138 controls (48 men and 90 women) were examined for exposure using diffusion dosimeters, subjective symptoms by questionnaire, hematology, and urinalysis. Exposure concentration (7-hour mean TWA) in the workers was estimated at 42.8 ppm (161 mg/cu.m) toluene with a maximum measurement of 123 ppm (464 mg/cu.m). Workers were co-exposed to 1.3 ppm benzene. No exposure-related effects were noted in any of the biochemical tests examined. In considering the prevalence of subjective symptoms (sore throat, headaches, and dizziness) workers were subgrouped into low (6-39 ppm, n = 28) and high (40-123 ppm, n = 29) categories. Although the prevalence of subjective symptoms was significantly higher in the exposed workers compared with the control cohort ($p<0.01$), a concentration-response relationship was not discernable among the groups. No other treatment-related effects were reported. The study was limited because the exposed and unexposed groups were not matched to control for confounding effects (e.g., age, smoking, alcohol consumption, exposure duration). Based on these results, exposure to an average of approximately 42.8 ppm toluene produced no biochemical abnormalities, although neither respiratory irritation nor psychological performance was directly evaluated in these workers.

In the occupational study by Lee et al. (1988), prevalence of subjective symptoms was categorized with respect to exposure levels. The study population (193 women and 65 controls) completed a questionnaire. The exposures were reported as 8-hour TWAs, and workers were grouped in exposure categories of nonexposed, 1-50 ppm, 51-100 ppm, 101-150 ppm, and more than 151 ppm (duration of exposures was not reported). A concentration-dependent increase in prevalence was reported for 25/67 symptoms with increases in complaints over controls occurring at around 100 ppm (348 mg/cu.m). Similar to the Yin et al. study (1987) reported above, symptomatology included headaches, sore throats, and dizziness. Although an effect level in humans of around 100 ppm is indicated by this study, no objective measures of toxicity were examined.

A number of acute human studies have focused on toluene effects. In general, these studies corroborate subjective CNS effects such as headaches and dizziness reported in other longer-term occupational studies (Yin et al., 1987; Lee et al., 1988) and also document irritation effects. The study of Echeverria et al. (1989) correlates the occurrence of these subjective effects with substantial neurological symptoms.

Forty-two college students (21 female and 21 male) were exposed to 0, 74 ppm (279 mg/cu.m), or 151 ppm (569 mg/cu.m) toluene for 7 hours over 3 days (Echeverria et al., 1989). This exposure sequence was repeated for a total of 42 exposures over a 3-month period. The odor of toluene was masked. A battery of performance tests was administered to each participant prior to starting the exposures and again at 4 and 7 hours during the exposure; the initial test served as a control for those tests performed during the exposure. A 5-10% decrement in performance was considered significant if consistent with a linear trend. Test results for visual perception differed from control values for both exposure levels. Results of a manual dexterity test differed from control values at the higher but not the lower exposure level. Psychomotor test results were unaffected by toluene exposure. Subjective symptomatology increased with exposure with increasing numbers of complaints of eye irritation, headache, and somnolence. A NOAEL of 74 ppm (279 mg/cu.m) is

indicated for these results. The duration-adjusted value is 122 mg/cu.m for these acute effects.

Andersen et al. (1983) exposed 16 subjects (average age of 24 years) to 0, 10, 40, or 100 ppm (0, 38, 151, or 377 mg/cu.m) toluene for 6 hours on each of 4 consecutive days. Individuals were tested for nasal mucous flow, lung function, subjective response, and psychometric performance. At 100 ppm, irritation was experienced in the eyes and nose, but no effect on nasal mucous flow or lung function was observed. The subjects frequently reported headaches, dizziness, and a feeling of intoxication. These effects were not reported by the 10- or 40-ppm exposure groups. No effects were seen in performance tests. This study indicates an effect level of 100 ppm, and a NOAEL of 40 ppm (151 mg/cu.m).

The acute study by Baelum et al. (1990) evaluated 32 males and 39 females exposed to 0 or 100 ppm (0 or 377 mg/cu.m), or to varying exposures of 50-300 ppm (188-1131 mg/cu.m) (TWA = 102 ppm), for 7 hours. Volunteers exercised on an ergometer cycle for 3 periods of 15 minutes each during the exposure. No significant differences were found in the performances between the exposed and control groups in a battery of tests for performance, visual attention, and reaction times. Exposed subjects reported an increase over nonexposed subjects ($p<0.1$) in nose and lower respiratory irritation, feelings of intoxication, dizziness, increased coughing, and headaches. Differences were not noted between the group exposed to a constant level (100 ppm) and the group exposed to the same TWA, but with peaks of up to 300 ppm.

Baelum et al. (1985) investigated the effects of a 6.5-hour toluene exposure to 43 printers with a long-term occupational exposure to a mixture of solvents including toluene and 43 controls with no history of exposure to solvents or other chemicals. The duration of employment for the workers ranged from 9-25 years. Each individual was exposed only once to either 0 or 100 ppm (0 or 377 mg/cu.m) toluene during a 6.5-hour exposure period, preceded by a 1-hour acclimatization period. These subjects were then subgrouped into printers exposed to toluene (n = 20), printers exposed to air (n = 23), controls exposed to toluene (n = 21), and controls exposed to air (n = 22). All subjects carried out a battery of tests for psychometric performance, visual perception, and vigilance evaluation. Both printers and controls complained of nasal and eye irritation, unacceptable air quality, and unacceptable odor level during the toluene exposure. Signs of neurotoxicity, including moderate fatigue, sleepiness, headaches, and a feeling of intoxication, were likewise similarly reported for both groups. A significant decrease in performance was found for the pegboard visual motor function test in the exposed printers, but not in the controls exposed to 100 ppm toluene. A decrease in psychometric performance, primarily in visual perception and accuracy, was observed in toluene-exposed individuals. Acute exposure to toluene resulted in a lower performance in 4/10 tests conducted, 3 of these 4 evaluated visual perception. The most profound difference between subjects exposed to 100 ppm toluene and those exposed to clean air was observed in the color discrimination test; this difference was seen in both exposed vs. nonexposed printers and exposed vs. nonexposed controls. This study indicates that little tolerance develops to the irritative and central effects in humans exposed to toluene and that 100 ppm (377 mg/cu.m) is the effect level for these symptoms.

Von Oettingen et al. (1942) exposed 3 humans to 100 or 200 ppm (377 or 754

mg/cu.m) toluene vapors for 8 hours. At 200 ppm, the subjects experienced muscular weakness, confusion, impaired coordination, and dilated pupils, with after-effects including fatigue, general confusion, and moderate insomnia. In 1 subject exposed to 100 ppm toluene, moderate fatigue, sleepiness, and headaches were reported.

Hepatotoxicity has also been examined as a toxicologic endpoint of toluene exposure in humans. Fornazzari et al. (1983) described moderate elevation of serum AP levels in 13/24 (and SGOT in 7/24) toluene abusers upon admission to a clinic. These elevated levels were normal after 2 weeks of solvent abstinence, although the accompanying CNS effects were only minimally improved. In a cross-sectional study of 181 printing workers in which toluene exposures were less than 200 mg/cu.m, no adverse effects were apparent as judged from serum liver enzymes (Boewer et al., 1988). In another cross-sectional occupational study conducted by Guzelian et al. (1988) that involved 289 printing factory employees, 8 workers were found who had an increase described as "marked" in the ratio of ALT/AST enzyme serum activity. Biopsies revealed mild pericentral fatty livers in each of the eight cases. Based on environmental data (probably area monitors) the levels of toluene to which these workers were exposed was less than 200 mg/cu.m., 2-8 hours/day.

Fischer 344 rats (120/sex/group) inhaled 0, 30, 100, or 300 ppm (0, 113, 377, or 1130 mg/cu.m, respectively) toluene (99.9% purity), 6 hours/day, 5 days/week (duration-adjusted to 0, 20, 67, or 202 mg/cu.m, respectively) for 106 weeks (CIIT, 1980; Gibson and Hardisty, 1983). Vapor, generated by bubbling clean air through toluene, was passed through the air supply duct and mixed with air by turbulent flow to produce the desired concentration. Hematology, blood chemistry, and urinalysis were conducted in all groups at 6 (5/sex), 17 (5/sex), 18 (10-20/sex), and 24 months (10/sex). Histopathology was evaluated only in the control and 300-ppm groups at 6 (5/sex), 12 (5/sex), and 18 months (20/sex). At 24 months, histopathological examinations were conducted in organs of all surviving animals, including the respiratory system and sections through the nasal turbinates (number not indicated). No treatment-related non-neoplastic effects were observed in the exposed animals.

Although the male rats exposed to 300 ppm had a significant increase in body weight compared to controls, no concentration-response was evident. At the end of the exposure period, the female rats exposed to 100 or 300 ppm exhibited a slight but significant reduction in hematocrit; an increase in the mean corpuscular hemoglobin concentration was also noted but only in the females exposed to 300 ppm. The highest concentration examined in this study, 300 ppm, is designated as a NOAEL for toxicity remote from the respiratory tract in rats. CIIT (1980) reported that the technical and raw data were not audited by their quality assurance group during the study period, although CIIT did conduct a quality assessment procedure to review the data. The available pathology reports containing these data indicate that at least the lower respiratory tract was examined. Communication with the testing sponsor has provided information indicating that only one section was examined from the nasal cavity of these test animals. It is not clear whether this single section would have been sufficient to elucidate the areas of lesions noted in the NTP (1990) study. Consequently, the designation of the 300-ppm exposure level as a NOAEL for respiratory lesions (see NTP,1990) is problematic.

Fischer 344/N rats (10/sex/group) were exposed to toluene vapors at 0, 100, 625, 1250, 2500, and 3000 ppm (0, 377, 2355, 4711, 9422, and 11,307 mg/cu.m, respectively) 6.5 hours/day, 5 days/week (duration-adjusted to 0, 73, 455, 911, 1823, and 2187 mg/cu.m, respectively) for 15 weeks (NTP, 1990). Organ weights were measured and histological examinations were performed only on controls, 2500- and 3000-ppm groups, and animals that died before the end of the study. Eight of 10 males exposed to 3000 ppm died, all during the 2nd exposure week. No females died at any exposure level. Compared to the controls, final body weights were 15 and 25% lower in the males and 15 and 14% lower in the females of the 2500- and 3000-ppm groups, respectively. There was a concentration-related increase in the relative liver weight, significant at 1250, 2500, and 3000 ppm in males and at 2500 and 3000 ppm in females. The relative weights of the heart, lung, kidney, and right testis were also significantly elevated in the 2500- and 3000-ppm animals compared to those of the controls, although no histopathology was observed in any exposure group. Toxic effects noted in a concurrently conducted gavage study (urinary bladder hemorrhages in the two highest exposure groups) were not noted in this subchronic inhalation study. A LOAEL of 2500 ppm [LOAEL(HEC) = 1823 mg/cu.m] was determined for the decrease in body weight gain in both males and females, and the NOAEL for this effect was 1250 ppm [NOAEL(HEC) = 911 mg/cu.m].

Toluene has been suspected to cause congenital defects in infants born to mothers who were exposed to or who abused toluene during pregnancy. In a case report study, Hersh et al. (1985) describes clinical and morphometric characteristics common to 3 children whose mothers had abused toluene (but apparently not alcohol or any other substance) for a period of 4-5 years including during their pregnancies with the affected children. Clinical findings common to these three children included microcephaly, CNS dysfunction, attention deficits, and developmental delay/mental deficiency. Phenotypic similarities included a small midface, deep-set eyes, micrognathia (smallness of the jaws), and blunting of the fingertips. A retrospective cohort study was conducted by McDonald et al. (1987) who examined the history of exposure to chemicals of 301 women who had recently given birth to an infant with an important congenital defect. An identical number of women (referents) who had given birth to normal children were matched with respect to age, employment (hours/week), date of delivery, and educational level. In initial matched-pair analysis, chemical exposure was higher in the cases than in the referents (63 cases:47 referents) due to excess cardiac and miscellaneous defects. In further analysis by chemical categories, only exposure to aromatic solvents showed a clear excess of defects, mostly in the urinary tract. Details of these cases (n = 19) showed that toluene was identified as the solvent in 11 of these cases.

Hudak and Ungvary (1978) exposed three groups of pregnant CFY rats to toluene during different periods of gestation and for different durations of exposure. Two of the groups had their own control group exposed to air only and matched for period and daily duration. The first of these (n = 19) was exposed to 1500 mg/cu.m for 24 hours/day during gestational days 9 to 14. Two dams died during these exposures. No details on the deaths are given but no other maternal toxicity was observed. Fetotoxicity was also in evidence as sternebral alterations (6% vs. 1% in controls), extra ribs (22% vs. 0% in controls), and the presence of fetuses with missing tails (2/213, none observed in 315 controls) were recorded. Under these exposure conditions, 1500 mg/cu.m is a LOAEL for fetotoxicity and a frank effect level (FEL) for maternal toxicity. The second group (n = 14) received this same concentration continuously but on days 1-8 of gestation. Five dams died under these exposure

conditions although toxicity parameters of the surviving dams were identical with the controls from the first group (gestational days 9-14). Slight hydrocephaly was noted in 4 fetuses (all from the same litter), and 17% growth retardation was noted vs. 7% in the controls. Thus these exposure conditions are a FEL for maternal toxicity and a LOAEL for fetotoxicity. A third group was exposed to 1000 mg/cu.m for 8 hours/day from the 1st to the 21st day of gestation. No maternal deaths or toxicity occurred. Minor skeletal retardation was present in the exposed fetuses at a higher incidence rate (25%)
than in concurrent controls (0%). These results indicate that 1000 mg/cu.m is a LOAEL for developmental effects under these exposure conditions. This concentration is also a NOAEL for maternal effects. These workers also exposed
groups of pregnant CFLP mice (n = 11-15) to either air or 1500 or 500 mg/cu.m toluene continuously during days 6-13 of pregnancy. All mice exposed to the high concentration died within 24 hours of the beginning of exposure. No dams died in the lower exposure group. In this group, the average fetal weight decreased to 0.96 g from the average control weight of 1.07 g, and the percentage of weight-retarded fetuses (less than 0.9 g) increased to 27.6% from
6.5% in the controls. No difference in incidence of skeletal malformations or anomalies was noted between these and control fetuses. For mice, 1500 mg/cu.m is an FEL and 500 mg/cu.m is a mild LOAEL. Since duration adjustment is not performed for developmental effects, this concentration is also the LOAEL(HEC).

B6C3F1 mice (60/sex/group) were exposed to 0, 120, 600, or 1200 ppm (0, 452, 2261, or 4523 mg/cu.m, respectively) toluene 6.5 hours/day, 5 days/week (duration-adjusted to 0, 87, 47, and 875 mg/cu.m, respectively) for 2 years (NTP, 1990). Mean body weights were not significantly different among groups and no treatment-related clinical signs were observed. Deaths (moribund and natural) occurred in all exposure groups but were not related to exposure and were not greater than the control rates. An excess incidence of non-neoplastic inflammatory lesions of the urinary and genital system was observed

in all the groups of male mice. At the 15-month interim sacrifice, minimal hyperplasia in the bronchial epithelium was observed in 4/10 females exposed to 1200 ppm. At the end of the study, there was a concentration-dependent increase in the incidence of splenic pigmentation in the exposed males (9/60, 11/60, and 18/59 at 120, 600, and 1200 ppm, respectively) compared to controls

(4/60). In the females, the incidence was 37/50, 33/50, 34/49, and 28/47 at 0, 120, 600, and 1200 ppm, respectively. The occurrence of endometrial hyperplasia was present in 14% of the animals exposed to the highest concentration but only in 4% in the low-exposure groups and controls. No differences were noted between the exposed and control mice of either sex in the incidence of degeneration of either the olfactory or respiratory epithelium. No other non-neoplastic lesions were observed in exposed mice. As no adverse effects were noted in this study, the highest concentration, 1200 ppm was designated as a NOAEL in mice for this chronic study [NOAEL(HEC) = 875 mg/cu.m].

Sprague-Dawley rats (15/sex/group) were exposed to cumulative mean exposures of 0, 100, or 1481 ppm (0, 377, or 5653 mg/cu.m) toluene vapors, 6 hours/day, 5 days/week (duration-adjusted to 0, 67, and 1009 mg/cu.m, respectively) for 26 weeks (API, 1981). On weeks 9, 18, and 27, neurohistopathological examinations were conducted in 3-5 rats/sex/group. Hematology, clinical chemistry, and urinalysis parameters were evaluated after

13 and 26 weeks of exposure. Body weights were measured weekly. No significant treatment-related effects were reported. Therefore, a NOAEL of 1481 ppm [NOAEL(HEC) = 1009 mg/cu.m] toluene was determined for systemic effects in rats. The study was limited because there were no other neurohistopathological examinations or organ weight measurements conducted on

the animals.

Inhalation exposure to toluene has been shown to result in irreversible high-frequency hearing loss in rats. Pryor et al. (1984) exposed young male Fischer 344 rats to a variety of exposure concentrations and durations. Hearing loss was evaluated by a behavioral technique (avoidance response elicited to an auditory signal) or brainstem auditory-evoked responses (elicited by tone pips of differing loudness and frequency and detected by subdural scalp electrodes). Hearing loss, as measured by both techniques, was observed after as few as 2 weeks exposure to 1000 ppm toluene for 14 hours/day. Lower concentrations of 700 ppm for 14 hours/day were without effect after 16 weeks of exposure. Intermittent exposure to 3000 ppm for 30 minutes/hour for 8 hours/day caused hearing loss within 2 weeks, whereas a similar exposure schedule for only 4 hours/day was without effect after 9 weeks. These data define a NOAEL for hearing loss in rats of 700 ppm [NOAEL(HEC) = 2638 mg/cu.m]. The duration-adjusted HEC (assumed 5 days/week) would be 14/24 hours x 5/7 days = 1100 mg/cu.m. Although these results clearly document hearing loss in young adult rats, their direct significance to humans remains unclear. Among chronic toluene abusers there is only a single report of adverse effects on hearing; Metrick and Brenner (1982) claimed that the abnormal auditory-evoked potentials recorded in two chronic toluene abusers was evidence of brainstem abnormalities.

Pregnant Wistar rats and hamsters (group size not indicated) inhaled 0 or 800 mg/cu.m toluene vapors 6 hours/day on gestational days 14-20 (rats) or gestational days 6 to 11 (hamsters) (DaSilva et al., 1990). In the exposed rats, there was a significant ($p<0.05$) increase in the number of litters with one or more low birth weight pups (less than 4.9 g), from 10% in the controls to 54% in the exposed dams. A decrease ($p<0.05$) in the number of live pups at birth was also noted in the litters of exposed dams. No evaluation of malformations or anomalies was performed. The neurobehavioral development of the offspring of the exposed rats was assessed using tests of spontaneous alternation, rim escape, and avoidance responses. The only effect noted in the rats, a shortened first trial latency in choosing one side of a maze, was minimal and its significance unclear. No comparable reproductive deficits occurred in the exposed hamsters. The only effect noted in the neurobehavioral tests of the hamster offspring was an equivocal effect in rota-rod performance.
No neurobehavioral effect levels were designated from this study, although it appears that the rat developmental processes are more sensitive than those of the hamster, exhibiting adverse effects at 800 mg/cu.m.

Ungvary and Tatrai (1985) exposed New Zealand rabbits (8-10/group) to 0, 500, or 1000 mg/cu.m toluene, 24 hours/day, on gestational days 7-20, and CFLP mice (15 females/group) to 0, 500, 1000, or 1500 mg/cu.m toluene, also continuously, on gestational days 6-15. The control groups consisted of 115 mice and 60 rabbits. All the female mice exposed to 1500 mg/cu.m died. In the mice exposed to 1000 mg/cu.m, there was an increase in fetuses with retarded weight (29%, level of retardation not indicated) and in fetuses with skeletal retardation (12%) compared to 7% and 5%, respectively, in the controls, which did not differ from the animals exposed to 500 mg/cu.m. Of the 8 pregnant rabbits exposed to 1000 mg/cu.m, 2 died, 4 had spontaneous abortions, and the remaining 2 had total litter resorption. No deaths occurred in the 10 rabbits exposed to 500 mg/cu.m but 1/10 rabbits had a spontaneous abortion (as compared to 0/60 reported for the controls). A NOAEL(HEC) of 500 mg/cu.m toluene was determined for reproductive effects in mice. For rabbits, the 500 mg/cu.m concentration is designated as a LOAEL. These results indicate that pregnant mice may be a sensitive population to the effects of toluene.

Pregnant Charles River CD-1 mice (15-16 females/group) inhaled filtered air or 200 or 400 ppm (754 and 1508 mg/cu.m) toluene 7 hours/day on gestational days 7-16 (Courtney et al., 1986). The relative liver weight in the exposed dams was reported to be significantly lower in the two exposed groups compared to the controls, although no data were presented. A statistically significant increase in lactate dehydrogenase activity in the brain of the dams exposed to 400 ppm was also reported. The exposed pregnant mice did not exhibit any significant differences in the number of implantation sites, number of live fetuses, fetal deaths, or fetal body weight compared to the control values. A statistically significant increase over controls in the incidence (both per litter and per fetus) of enlarged renal pelves was noted in dams exposed to 200 ppm but not 400 ppm. A statistically significant alteration from controls in the rib profile (percentage of fetuses with 1 or 2 additional/fewer ribs) was reported for fetuses from dams exposed to 400 ppm but not 200 ppm. The toxicological significance of this finding is not clear.

As no clearly significant toxicological effects were observed, the highest concentration used, 400 ppm [NOAEL(HEC) = 1508 mg/cu.m] is designated as a NOAEL for reproductive and developmental effects in mice.

A 2-generation inhalation reproductive study was conducted in CD rats (10-40 males, 20-80 females/group) (API, 1985). Animals were exposed by whole-body inhalation to toluene at 0, 100, 500, or 2000 ppm (0, 377, 1885, or 7538 mg/cu.m, respectively) 6 hours/day, 7 days/week for 80 days and a 15-day mating period. The mated females were then exposed to the same concentrations during days 1-20 of gestation and days 5-20 of lactation. After weaning, the pups in this generation (F1) were exposed 80 times and then randomly mated with members of the same exposure group (2 females/1 male) to produce the second generation (F2). Mean male body weights were slightly reduced (maximum of 10%) in the first 2 weeks of the exposure in the animals exposed to 500 and 2000 ppm, although the size of the reduction was not related to exposure. No differences were observed in male or female fertility indices, length of gestation, mean numbers of viable and nonviable pups at birth, or pup survival indices during lactation. No abnormal histopathology was noted in organs examined. A significant decrease ($p<0.05$) in weight relative to controls was observed in the first generation offspring. The decrease was maintained throughout the lactation period in the pups from dams exposed to the highest exposure and in those from the ancillary group in which females exposed to the 2000 ppm concentration were mated with males having no exposure. No data were available in the report about the F2 generation. Based on the effects on the pups of the first generation (F1), a LOAEL of 2000 ppm [LOAEL(HEC) = 7538 mg/cu.m] is designated, the NOAEL being 500 ppm [NOAEL(HEC) = 1885 mg/cu.m].

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o INHALATION RFD CONFIDENCE : Study -- Medium Data Base -- Medium RfC -- Medium The study of Foo et al. (1990) indicates adverse neurological effects of toluene in a small worker population. These effects are consistent with more severe CNS effects occurring at abusive concentrations of toluene and could not have been confounded by alcohol as the control and exposed populations did not use alcohol. However,

the paucity of exposure information and identification of only a LOAEL is not sufficient to warrant a higher confidence than medium for this study. Other studies indicate that irritation may occur at around the same concentration, 100 ppm (Baelum et al., 1985; Echeverria et al., 1989). In regard to this effect, the NTP (1990) rat chronic inhalation study was well conducted, established the rat as the most sensitive species, examined an adequate number of animals, and performed histopathology on all major organs, including the brain and the respiratory tract. The sensitive endpoint was the concentration-dependent degeneration of the nasal epithelium characterized by the erosion of the olfactory epithelium and degeneration of the respiratory epithelium in male rats. The NTP study is also given medium confidence, however, as it did not establish a NOAEL. Although this data base has a complement of chronic laboratory animal studies, long-term data in humans are not available for either the neurotoxicity or irritation endpoints. The reproductive/developmental studies in three species were not comprehensive in endpoint evaluation but do identify the rabbit as the most sensitive species. The data base is thus given a medium confidence rating. A medium confidence rating for the RfC follows.

o INHALATION RFD SOURCE :

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1984, 1985
DOCUMENT

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o REVIEW DATES : 04/21/88, 05/26/88, 02/16/89, 03/21/89, 05/18/89, 08/15/91, 12/11/91
o VERIFICATION DATE : 05/18/89, 12/11/91
o EPA CONTACTS :

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CAREV-
o CLASSIFICATION : D; not classified
o BASIS FOR CLASSIFICATION : No human data and inadequate animal data. Toluene did not produce positive results in the majority of genotoxic assays.

o HUMAN CARCINOGENICITY DATA :

None.

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o ANIMAL CARCINOGENICITY DATA :

A chronic (106-week) bioassay of toluene in F344 rats of both sexes reported no carcinogenic responses (CIIT, 1980). A total of 960 rats were exposed by inhalation for 6 hours/day, 5 days/week to toluene at 0, 30, 100, or 300 ppm. Groups of 20/sex/dose were sacrificed at 18 months. Gross and microscopic examination of tissues and organs identified no increase in neoplastic tissue or tumor masses among treated rats when compared with controls. The study is considered inadequate because the highest dose administered was well below the MTD for toluene and because of the high incidence of lesions and pathological changes in the control animals.

Several studies have examined the carcinogenicity of toluene following repeated dermal applications. Toluene (dose not reported) applied to shaved interscapular skin of 54 male mice (strains A/He, C3HeB, SWR) throughout their lifetime (3 times weekly) produced no carcinogenic response (Poel, 1963). One drop of toluene (about 6 mL) applied to the dorsal skin of 20 random-bred albino mice twice weekly for 50 weeks caused no skin papillomas or carcinomas after a 1-year latency period was allowed (Coombs et al., 1973). No increase in the incidence of skin or systemic tumors was demonstrated in male or female mice of three strains (CF, C3H, or CBaH) when toluene was applied to the back of 25 mice of each sex of each strain at 0.05-0.1 mL/mouse, twice weekly for 56 weeks (Doak et al., 1976). One skin papilloma and a single skin carcinoma were reported among a group of 30 mice treated dermally with one drop of 0.2% (w/v) solution toluene twice weekly, administered from droppers delivering 16-20 uL per drop for 72 weeks (Lijinsky and Garcia, 1972). It is not reported whether evaporation of toluene from the skin was prevented during these studies.

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o SUPPORTING DATA :

Toluene was found to be nonmutagenic in reverse mutation assays with S. typhimurium (Mortelmans and Riccio, 1980; Nestmann et al., 1980; Bos et al., 1981; Litton Bionetics, Inc., 1981; Snow et al., 1981) and E. coli (Mortelmans and Riccio, 1980), with and without metabolic activation. Toluene did not induce mitotic gene conversion (Litton Bionetics, Inc., 1981; Mortelmans and Riccio, 1980) or mitotic crossing over (Mortelmans and Riccio, 1980) in S. cerevisiae. Although Litton Bionetics, Inc. (1981) reported that toluene did not cause increased chromosomal aberrations in bone marrow cells, several Russian studies (Dobrokhotov, 1972; Lyapkalo, 1973) report toluene as effective in causing chromosal damage in bone marrow cells of rats. There was no evidence of chromosomal aberrations in blood lymphocytes of workers exposed to toluene only (Maki-Paakkanen et al., 1980; Forni et al., 1971), although a slight increase was noted in workers exposed to toluene and benzene (Forni et al., 1971; Funes-Craviota et al., 1977). This finding is supported by studies of cultured human lymphocytes exposed to toluene in vitro; no elevation of chromosomal aberrations or sister chromatid exchanges was observed (Gerner-Smidt and Friedrich, 1978).

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CARO - NO DATA
CARI - NO DATA
CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1987. Drinking Water Criteria Document for Toluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN-408.

The values in the 1987 Drinking Water Criteria Document for Toluene have received peer and administrative review.
DOCUMENT

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o REVIEW DATES : 09/15/87
o VERIFICATION DATE : 09/15/87
o EPA CONTACTS :

Dharm V. Singh / OHEA -- (202)260-5958

Robert E. McGaughy / OHEA -- (202)260-5898

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HAONE-

One-day HA -- 2E+1 mg/L

NOAEL -- 21.5 mg/kg/day
UF -- 10 (allows for intrahuman variability with the use of a NOAEL from a human study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Gamberale and Hultengren, 1972

This study reported that a 20-minute exposure to 100 ppm toluene was a no-effect level when determined by perceptual speed and reaction time tests in human volunteers. At 200 ppm, toluene was noted as clearly causing toxic effects such as incoordination, exhilaration, and prolonged reaction time. These and other data support the selection of 100 ppm (377 mg/cu.m) toluene as

the NOAEL in humans exposed for up to 8 hours. Based on the conditions of exposure and an assumed absorption rate of 60%, this level is equivalent to 21.5 mg/kg/day.

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HATEN-

No information was found in the available literature that was suitable for determination of a Ten-day HA value. It is, therefore, recommended that the DWEL, adjusted for a 10-kg child (3 mg/L) be used as the Ten-day HA value.

HALTC-

No information was found in the available literature that was suitable for determination of a Longer-term HA value. It is, therefore, recommended that the DWEL, adjusted for a 10-kg child (3 mg/L) be used as the Longer-term HA value for a child.

HALTA-

No information was found in the available literature that was suitable for determination of a Longer-term HA value. It is, therefore, recommended that the DWEL, adjusted for a 70-kg adult (10 mg/L) be used as the Longer-term HA value for an adult.

HALIF-

Drinking Water Equivalent Level (DWEL) -- 7E-0 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date -- 06/20/90

Lifetime HA -- 1E-0 mg/L

Assumptions -- 20% exposure by drinking water

Principal Study -- NTP, 1989 (This study was used in the derivation of the chronic oral RfD; see RDO)

OLEP -

Taste threshold in water is reported as 0.04 and 1 mg/L. Odor threshold in water is reported as 0.04 and 1 mg/L.

ALAB -

Analysis of toluene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile aromatic and unsaturated organic compounds in water.

TREAT-

Treatment options for removing toluene form drinking water sources include air stripping and adsorption onto granular activated carbon.

HADR -

o HEALTH ADVISORY SOURCE :

U.S. EPA. 1990. Final Draft of the Drinking Water Criteria Document for Toluene. Office of Drinking Water, Washington, DC.
DOCUMENT

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o HEALTH ADVISORY REVIEW :

EPA review of HAs in 1986.

Public review of HAs in 1987.

Science Advisory Board review to be determined.

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o EPA DRINKING WATER CONTACT :

Krishan Khanna / OST -- (202)260-9568

Edward V. Ohanian / OST -- (202)260-7571

ACUTE- NO DATA
BCF - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption: 1.43E+4 ug/L

Fish Consumption Only: 4.24E+5 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 1.43E+4 ug/L is based on consumption of contaminated aquatic organisms and water. A WQC of 4.24E+5 ug/L has also been established based on consumption of contaminated aquatic organisms alone.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute LEC -- 1.75E+4 ug/L
Chronic LEC -- none

Marine:

Acute LEC -- 6.3E+3 ug/L
Chronic LEC -- 5.0E+3 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria,but are the lowest effect levels found in the literature. LEC's are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 1 mg/L (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- EPA has set a MCLG for toluene based on its potential adverse effects reported in a 13-week oral study in rats. The MCLG is based upon a DWEL of 7 mg/L and an assumed drinking water contribution of 20 percent.

Reference -- 54 FR 22062 (05/22/89)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value -- 1 mg/L (Final, 1991)

Considers technological or economic feasibility? -- YES

Monitoring requirements -- All systems initially monitored for four consecutive quarters; repeat monitoring dependent upon detection, vulnerability status and system size.

Analytical methodology -- Gas chromatography (EPA 502.2, 503.1); gas chromatography/mass spectrometry (EPA 524.1, 524.2): PQL= 0.005 mg/L.

Best available technology -- Granular activated carbon; packed tower aeration

Reference -- 56 FR 3526 (01/30/91); 56 FR 30266 (07/01/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

Value -- 0.04 mg/L (Proposed, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- SMCLs are non-enforceable and establish limits for contaminants which may affect the aesthetic qualities (e.g. taste and odor) of drinking water. It is recommended that systems monitor for these contaminants every three years. More frequent monitoring for contaminants such as pH, color, odor or others may be appropriate under certain circumstances. The SCML for toluene is based on odor detection. Promulgation deferred following public comment (56 FR 3526).

Reference -- 54 FR 22062 (05/22/89); 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on aquatic toxicity, as established under

Section 311(b)(4) of the Clean Water Act, ignitability, and chronic toxicity. Available data indicate that the aquatic 96-Hour Median Threshold Limit for Toluene is between 10 and 100 ppm. Its closed-cup flash point is less than 100F and its boiling point is >100F. RQ assignments based on chronic toxicity

reflect two primary attributes of the hazardous substance, the minimum effective dose (MED) levels for chronic exposure (mg/day for a 70-kg person) and the type of effect (liver necrosis, teratogenicity, etc). A composite score is determined from an evaluation of these two attributes. Toluene was determined to have a composite score between 6 and 20, corresponding to a chronic toxicity RQ of 1000 pounds.

Reference -- 50 FR 13456 (04/04/85); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

No data available

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IREF - API (American Petroleum Institute). 1985. Two-generation inhalation reproduction/fertility study on a petroleum-derived hydrocarbon. Doc. ID FYI- AX-0284-0294 IN. Microfiche No. 0294.
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IREF - Boewer, C., G. Enderlein, U. Wollgast, S. Nawka, H. Palowski, and R. Bleiber. 1988. Epidemiological study on the hepatotoxicity of occupational toluene exposure. Int. Arch. Occup. Environ. Health. 60: 181-186.
IREF - Cherry, N., H. Hutchins, T. Pace and H.A. Waldron. 1985. Neurobehavioral effects of repeated occupational exposure to toluene and paint solvents. Br. J. Ind. Med. 42(5): 291-300.
IREF - CIIT (Chemical Industry Institute of Toxicology). 1980. A twenty-four month inhalation toxicology study in Fischer-344 rats exposed to atmospheric toluene. Conducted by Industrial Bio-Test Laboratories, Inc., Decatur, IL, and Experimental Pathology Laboratories, Inc., Raleigh, NC, for CIIT, Research Triangle Park, NC. October 15, 1980.
IREF - Courtney, K.D., J.E. Andrews, J. Springer et al. 1986. A perinatal study of toluene in CD-1 mice. Fund. Appl. Toxicol. 6: 145-154.
IREF - DaSilva, V.A., L.R. Malheiros and F.M.R. Bueno. 1990. Effects of toluene exposure during gestation on neurobehavioral development of rats and hamsters. Brazil J. Med. Biol. Res. 23: 533-537.
IREF - Echeverria, D., L. Fine, G. Langolf, A. Schork and C. Sampio. 1989. Acute neurobehavioral effects of toluene. Br. J. Ind. Med. 46(7): 483-495.
IREF - Filley, C.M., R.K. Heaton and N.L. Rosenberg. 1990. White matter dementia in chronic toluene abuse. Neurology. 40: 532-534.
IREF - Foo, S.C., J. Jeyaratnam and D. Koh. 1990. Chronic neurobehavioral effects of toluene. Br. J. Ind. Med. 47(7): 480-484.
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IREF - Guzelian, P., S. Mills and H.J. Fallon. 1988. Liver structure and function in print workers exposed to toluene. J. Occup. Med. 30(10): 791-796.
IREF - Hanninen, H., M. Antti-Poika and P. Savolainen. 1987. Psychological performance, toluene exposure and alcohol consumption in rotogravure printers. Int. Arch. Occup. Environ. Health. 59(5): 475-483.
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IREF - Hudak, A. and G. Ungvary. 1978. Embryotoxic effects of benzene and its methyl derivatives: Toluene, xylene. Toxicology. 11: 55-63.
IREF - Iregren, A. 1982. Effects on psychological test performance of workers

exposed to a single solvent (toluene) - a comparison with effects of exposure to a mixture o oranc solvents. Neurobehav. Toxicol. Teratol. 4(6): 695- 701.
IREF - Lee, B., S. Lee, K. Lee et al. 1988. Dose-dependent increase in subjective symptom prevalence among toluene-exposed workers. Ind. Health. 26(1): 11-23.
IREF - McDonald, J.C., J. Lavoie, R. Cote and A.D. McDonald. 1987. Chemical exposures at work in early pregnancy and congenital defect: A case-referent study. Br. J. Ind. Medicine. 44: 527-533.
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IREF - Pryor, G.T., C.S. Rebert, J. Dickinson and E.M. Feeney. 1984. Factors affecting toluene-induced ototoxicity in rats. Neurobehav. Toxicol. Teratol. 6: 223-238.
IREF - Rosenberg, N.L., M.C. Spitz, C.M. Filley, K.A. Davis, and H.H. Schaumburg. 1988. Central nervous system effects of chronic toluene abuse - clinical, brainstem evoked response and magnetic resonance imaging studies. Neurotoxicol. Teratol. 10: 489-495.
IREF - Ungvary, G. and E. Tatrai. 1985. On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats, and rabbits. Arch. Toxicol. Suppl. 8: 425-430.
IREF - U.S. EPA. 1984. Health Effects Assessment for Toluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. EPA-600/X-84-188.
IREF - U.S. EPA. 1985. Drinking Water Criteria Document for Toluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Drinking Water, Washington, DC. EPA/540/1-86-033.
IREF - Von Oettingen, W.F., P.A. Neal, D.D. Donahue et al. 1942. The toxicity and potential dangers of toluene, with special reference to its maximal permissible concentration. U.S. Public Health Service, Public Health Bulletin No. 279: 50.
IREF - Yin, S., G. Li, Y. Hu et al. 1987. Symptoms and signs of workers exposed to benzene, toluene or the combination. Ind. Health. 25(3): 113-130.
CREF - Bos, R.P., R.M.E. Brouns, R. van Doorn, J.L.G. Theuws and P.Th. Henderson. 1981. Non-mutagenicity of toluene, o-, m- and p-xylene, o-methylbenzylalcohol and o-methylbenzylsulfate in the Ames assay. Mutat. Res. 88(3): 273-279.
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CREF - Coombs, M.M., T.S. Bhatt and C.J. Croft. 1973. Correlation between carcinogenicity and chemical structure in cyclopenta(a)phenanthrenes. Cancer Res. 33(4): 832-837.
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CREF - Nestmann, E.R., E.G.H. Lee, T.I. Matula, G.R. Douglas and J.C. Mueller. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat. Res. 79: 203-212.
CREF - Poel, W.E. 1963. Skin as a test site for the bioassay of carcinogens and carcinogen precursors. Natl. Cancer Inst. Monogr. 10: 611-625.
CREF - Snow, L., P. MacNair and B.C. Casto. 1981. Mutagenesis testing of toluene in Salmonella strains TA100 and TA98. Report prepared for the U.S. EPA by Northrup Services, Inc., Research Triangle park, NC.
CREF - U.S. EPA. 1987. Drinking Water Criteria Document for Toluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.
HAREF- Gamberale, F. and M. Hultengren. 1972. Toluene exposure. II. Psychophysiological functions. Work Environ. Health. 9(3): 131-139. (CA 79: 950-1973).
HAREF- U.S. EPA. 1990. Final Draft of the Drinking Water Criteria Document for Toluene. Office of Drinking Water, Washington, DC.

1 - IRIS
NAME - 1,1,1-Trichloroethane
RN - 71-55-6
IRSN - 194
DATE - 930401
UPDT - 04/01/93, 5 fields
STAT - Oral RfD Assessment (RDO) withdrawn 08/01/91
STAT - Inhalation RfC Assessment (RDI) pending
STAT - Carcinogenicity Assessment (CAR) on-line 09/01/90
STAT - Drinking Water Health Advisories (DWHA) on-line 09/01/90
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 04/01/93
IRH - 09/30/87 EXSR Regulatory Action section on-line
IRH - 03/01/88 RDO Text clarified
IRH - 06/30/88 MCL Units corrected for MCL
IRH - 06/30/88 RDO Contacts switched
IRH - 09/07/88 CAR Carcinogen summary on-line
IRH - 06/01/89 CARDR Secondary contact deleted
IRH - 03/01/90 REFS Bibliography on-line
IRH - 05/01/90 RDO Oral RfD summary noted as pending change
IRH - 05/01/90 RDI Inhalation RfC now under review
IRH - 09/01/90 RDO Text edited
IRH - 09/01/90 CAR Text edited
IRH - 09/01/90 HADV Health Advisory on-line
IRH - 09/01/90 RCRA EPA contact changed
IRH - 09/01/90 CREF Snow et al. 1979 citation clarified
IRH - 09/01/90 HAREF Health Advisory references added
IRH - 08/01/91 RDO Withdrawn pending further review
IRH - 08/01/91 OREF Oral RfD references withdrawn
IRH - 08/01/91 CREF Citations clarified
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 10/01/92 MCLG MCLG value corrected
IRH - 10/01/92 MCL MCL value corrected
IRH - 04/01/93 WQCHU Withdrawn; mandated by National Toxics Rule
RLEN - 16494
SY - AEROTHENE TT
SY - CHLOROETENE
SY - CHLOROETHENE
SY - CHLOROETHENE NU
SY - CHLOROFORM, METHYL-
SY - CHLOROTHANE NU
SY - CHLOROTHENE
SY - CHLOROTHENE NU
SY - CHLOROTHENE VG
SY - CHLORTEN
SY - ETHANE, 1,1,1-TRICHLORO-
SY - INHIBISOL
SY - METHYLCHLOROFORM
SY - METHYLTRICHLOROMETHANE
SY - NCI-C04626
SY - RCRA WASTE NUMBER U226
SY - STROBANE
SY - alpha-T
SY - 1,1,1-TCE
SY - 1,1,1-TRICHLOORETHAAN
SY - 1,1,1-TRICHLORAETHAN
SY - Trichloroethane, 1,1,1-
SY - alpha-TRICHLOROETHANE
SY - 1,1,1-TRICLOROETANO
SY - TRI-ETHANE
SY - UN 2831

RDO - NO DATA

RDI -

o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

CAREV-

o CLASSIFICATION : D; not classifiable as to human carcinogenicity.

o BASIS FOR CLASSIFICATION : There are no reported human data and animal studies (one lifetime gavage, one intermediate-term inhalation) have not demonstrated carcinogenicity. Technical grade 1,1,1-trichloroethane has been shown to be weakly mutagenic, although the contaminant, 1,4-dioxane, a known animal carcinogen, may be responsible for this response.

o HUMAN CARCINOGENICITY DATA :

None.

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o ANIMAL CARCINOGENICITY DATA :

Inadequate. The NCI (1977) treated Osborne-Mendel rats (50/sex/dose) with 750 or 1500 mg/kg technical-grade 1,1,1-trichloroethane 5 times/week for 78 weeks by gavage. The rats were observed for an additional 32 weeks. Twenty rats of each sex served as untreated controls. Low survival of both male and female treated rats (3%) may have precluded detection of a significant number of tumors late in life. Although a variety of neoplasms was observed in both treated and matched control rats, they were common to aged rats and were not dose-related. Similar results were obtained when the NCI (1977) treated B6C3F1 hybrid mice with the time-weighted average doses of 2807 or 5615 mg/kg 1,1,1-trichloroethane by gavage 5 days/week for 78 weeks. The mice were observed for an additional 12 weeks. The control and treated groups had 20 and 50 animals of each sex, respectively. Only 25 to 45% of those treated survived until the time of terminal sacrifice. A variety of neoplasms were observed in treated groups, but the incidence not statistically different from matched controls.

Quast et al. (1978) exposed 96 Sprague-Dawley rats of both sexes to 875 or 1750 ppm 1,1,1-trichloroethane vapor for 6 hours/day, 5 days/week for 12 months, followed by an additional 19-month observation period. The only significant sign of toxicity was an increased incidence of focal hepatocellular alterations in female rats at the highest dosage. It was not evident that a maximum tolerated dose (MTD) was used nor was a range-finding study conducted. No significant dose-related neoplasms were reported, but these dose levels were below those used in the NCI study.

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o SUPPORTING DATA :

Mutagenicity testing of 1,1,1-trichloroethane has produced positive results in S. typhimurium strain TA100 (Simmon et al., 1977; Fishbein, 1979; Snow et al., 1979) as well as some negative results (Henschler et al., 1977; Taylor, 1978).

It was mutagenic for S. typhimurium strain TA1535 both with exogenous metabolic activation (Farber, 1977) and without activation (Nestmann et al., 1980). 1,1,1-Trichloroethane did not result in gene conversion or mitotic recombination in Saccharomyces cerevisiae (Farber, 1977; Simmon et al., 1977) nor was it positive in a host-mediated forward mutation assay using Schizosaccharomyces pombe in mice. The chemical also failed to produce chromosomal aberrations in the bone marrow of cats (Rampy et al., 1977), but responded positively in a cell transformation test with rat embryo cells (Price et al., 1978).

An isomer, 1,1,2-trichloroethane, is carcinogenic in mice, inducing liver cancer and pheochromocytomas in both sexes. Dichloroethanes, tetrachloroethanes and hexachloroethanes also produced liver cancer in mice and other types of neoplasms in rats.

It should be noted that 1,4-dioxane, a known animal carcinogen that causes liver and nasal tumors in more than one strain of rats and hepatocellular carcinomas in mice, is a contaminant of technical-grade 1,1,1-trichlorethane.

CARO - NO DATA
CARI - NO DATA
CARDR-
o CARCINOGENICITY SOURCE :

U.S. EPA. 1984a. Health Effects Assessment for 1,1,1-Trichloroethane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1984b. Health Assessment Document for 1,1,1-Trichloroethane. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-82-003F.

The 1984 Health Effects Assessment for 1,1,1-Trichloroethane has received limited Agency review. The values in the 1984 Health Assessment Document for 1,1,1-Trichloroethane have received both Agency and public review.

DOCUMENT

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o REVIEW DATES : 08/05/87
o VERIFICATION DATE : 08/05/87
o EPA CONTACTS :

Charlingayya Hiremath / OHEA -- (202)260-5898

HAONE-

One-day HA -- 1E+2 mg/L

NOAEL -- 1400 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Vainio et al., 1976

A single oral dose of approximately 1400 mg/kg of 1,1,1-trichloroethane depressed some hepatic microsomal metabolic indices (including cytochrome P-450 and epoxide hydrase) in rats but resulted in no other adverse effects. This level can be viewed as a NOAEL in this study.

HATEN-

Appropriate data for calculating a Ten-day HA are not available. It is recommended that the Longer-term HA for the 10-Kg child of 40 mg/L be used as

the Ten-day HA.

HALTC-

Longer-term (Child) HA -- 4E+1 mg/L

NOAEL -- 350 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Bruckner et al., 1985

Rats were administered 1,1,1-trichloroethane by gavage 5 times/week for 12 weeks at levels of 0, 0.5, 2.5, or 5.0 g/kg/day. At levels above 0.5 g/kg reduced body weight gain and CNS effects were observed. Approximately 35% of these rats died during the first 50 days of the study. Also, the 5.0 g/kg/day dose group showed an increase in serum enzyme levels. The 0.5 g/kg/day level is identified as the NOAEL for this study. Based on a 7-day per week dosing regimen, this level would be equivalent to 350 mg/kg/day.

HALTA-

Longer-term (Adult) HA -- 1E+2 mg/L

NOAEL -- 350 mg/kg/day
UF -- 100 (allows for interspecies and intrahuman variability with the use of a NOAEL from an animal study)
Assumptions -- 2 L/day water consumption for a 70-kg adult

Principal Study -- Bruckner et al., 1985 (study described in HALTC)

HALIF-

Drinking Water Equivalent Level (DWEL) -- 1E+0 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date -- 05/15/86

Lifetime HA -- 2E-1 mg/L

Assumptions -- 20% exposure by drinking water

Principal Study -- McNutt et al., 1975

Male mice were continuously exposed to 1,1,1-trichloroethane via inhalation at 0, 1365 mg/cu.m, or 5460 mg/cu.m 6 hours/day for 14 weeks. Animals exposed to 5460 mg/cu.m displayed significant changes in the centrilobular hepatocytes. Based on the conditions of exposure and an assumed absorption rate of 30%, the LOAEL of 1365 mg/cu.m is equivalent to 35 mg/kg/day.

OLEP -

No information is available on the organoleptic properties of 1,1,1-trichloroethane.

ALAB -

Analysis of 1,1,1-trichloroethane is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water. Confirmatory analysis is by mass spectrometry.

TREAT-

Treatment technologies which will remove 1,1,1-trichloroethane from water include granular activated carbon adsorption and boiling. Air stripping is also an effective method; however, this process transfers the contaminant directly to the air stream.

HADR -

o HEALTH ADVISORY SOURCE :

U.S. EPA. 1985. Final Drinking Water Criteria Document on 1,1,1-Trichloroethane. Office of Drinking Water, Washington, DC.
DOCUMENT

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o HEALTH ADVISORY REVIEW :

EPA review of HAs in 1985.

Public reviews of HAs folling notification of availability in October, 1985.

Science Advisory Board review of HAs in January, 1986.

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o EPA DRINKING WATER CONTACT :

Charles Abernathy / OST -- (202)260-5374

Edward V. Ohanian / OST -- (202)260-7571

CAA - NO DATA

WQCHU-

No data available

WQCAQ-

Freshwater:

Acute LEC -- 1.8E+4 ug/L
Chronic LEC -- None

Marine:

Acute LEC -- 3.12E+4 ug/L
Chronic LEC -- None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 0.2 mg/L (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 200 ug/L (0.2 mg/L) for 1,1,1-trichloroethane is proposed based upon a DWEL and an assumed drinking water contribution of 20%. A DWEL of 1.0 mg/L was calculated based on liver toxicity in mice (inhalation study).

Reference -- 50 FR 46880 (11/13/85)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value (status) -- 0.2 mg/L (Final, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- EPA has set an MCL equal to the MCLG.

Reference -- 52 FR 25690 (07/08/87); 56 FR 30266 (07/01/91)

Monitoring requirements -- All systems to be monitored for four consecutive quarters; repeat monitoring dependent upon detection, vulnerability status and system size.

Analytical methodology -- Gas chromatography (EPA 502.1, 502.2, 503.1); gas chromatographic/mass spectrometry (EPA 524.1, 524.2).

Best available technology -- Packed tower aeration; granular activated carbon.

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD-

Status -- List "C" Pesticide

Reference -- 54 FR 30846 (07/24/89)

EPA Contact -- Registration Branch / OPP
(703)557-7760 / FTS 557-7760

FIREV-

No data available

CERC -

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on aquatic and chronic toxicity. Available data indicate a 96-hour Median Threshold Limit between 10 and 100 ppm, which corresponds to an RQ of 1000 pounds. RQ assignments based on chronic toxicity reflect two primary attributes, the minimum effect dose (MED) levels for chronic exposure (mg/day for 70-kg man) and the type of effect (teratogenicity, etc.). The composite score of these attributes for this substance is 6.0, corresponding to an RQ of 1000 pounds.

Reference -- 50 FR 13456 (04/04/85); 54 FR 33418 (08/14/89)
EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

___IV.E.1. TSCA, SECTION 6

Status -- Advance Notice of Proposed Rulemaking (ANPR) (1985)

Discussion -- EPA is developing a comprehensive and integrated strategy for a regulatory investigation of six solvents, including 1,1,1-trichloroethane.

Reference: 50 FR 42005 (10/17/85); 40 CFR 754

EPA Contact -- Chemical Control Division / OTS (202)260-3749 / FTS 260-3749

OREF - Not available at this time
IREF - None

CREF - Farber, H. 1977. Manager of Environmental Affairs, Dow Chemical letter to James Price, Chief of Air Quality Data Analysis, Texas Air Control Board, Austin, TX. (Cited in: NCI, 1977)
CREF - Fishbein, L. 1979. Potential halogenated industrial carcinogenic and mutagenic chemicals. II. Halogenated saturated hydrocarbons. Sci. Total Environ. 11: 163.
CREF - Henschler, D., E. Eder, T. Neudecker and M. Metzler. 1977. Carcinogenicity of trichloroethylene: Fact or artifact? Arch. Toxicol. 37: 233-236.
CREF - NCI (National Cancer Institute). 1977. Bioassay of 1,1,1-trichloroethane for possible carcinogenicity. Carcinog. Tech. Rep. Ser. No. 3, NCI-CG-TR-3.
CREF - Nestmann, E.R., E.G.H. Lee, T.I. Matula, G.R. Douglas and J.C. Mueller. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat. Res. 79: 203-212.
CREF - Price, P.J., C.M. Hassett and J.I. Mansfield. 1978. Transforming activities of trichloroethylene and proposed industrial alternatives. In vitro. 14: 290-293.
CREF - Quast, J.F., B.K.J. Leong, L.W. Rampy and P.J. Gehring. 1978. Toxicologic and carcinogenic evaluation of a methylchloroform (1,1,1-trichloroethane) formulation by chronic inhalation in rats - interim report after 24 months. Dow Chemical Co., Midland, MI.
CREF - Rampy, L.W., J.F. Quast, B.K.J. Leong and P.J. Gehring. 1977. Results of long-term inhalation toxicity studies on rats of 1,1,1-trichloroethane and perchloroethylene formulations. In: Proc. Int. Cong. Toxicol. Toronto.
CREF - Simmon, V.F., K. Kauhanen and R.G. Tardiff. 1977. Mutagenic activity of chemicals identified in drinking water. In: Progress in Genetic Toxicology, D. Scott et al., Ed. Elsevier/North Holland Biomedical Press, Amsterdam.
CREF - Snow, L.P., B.C. Nair and B.C. Castro. 1979. Mutagenesis testing of methylene chloride and 1,1,1-trichloroethane in Salmonella strains TA100 and TA98. Northrop Services, Inc., Research Triangle Park, NC.
CREF - Taylor, G. 1978. Personal communication. NIOSH, Morgantown, WV. (Cited in: U.S. EPA, 1984a)
CREF - U.S. EPA. 1984a. Health Effects Assessment for 1,1,1-Trichloroethane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.
CREF - U.S. EPA. 1984b. Health Assessment Document for 1,1,1-Trichloroethane. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-82-003F.
HAREF- Bruckner, J.B., S. Muralidhara, W.F.Mackenzie, G.M. Kyle and R. Luthra. 1985. Acute and subacute oral toxicity studies of 1,1,1-trichloroethane (TRI) in rats. The Toxicologist. 5(1): 100.
HAREF- McNutt, N., R. Amster, E. McConnell and F. Morris. 1975. Hepatic lesions in mice after continuous exposure to 1,1,1-trichloroethane. Lab. Invest. 32: 642-654.
HAREF- U.S. EPA. 1985. Final Drinking Water Criteria Document on 1,1,1-Trichloroethane. Office of Drinking Water, Washington, DC.
HAREF- Vainio, H., M.A. Parkki and J.A. Marniemi. 1976. Effects of aliphatic chlorohydrocarbons on drug-metabolizing enzymes in rat liver in vivo. Xenobiotica. 6: 599.

6 - IRIS
NAME - Trichloroethylene
RN - 79-01-6
IRSN - 196
DATE - 920807
UPDT - 08/07/92, 52 fields
STAT - Oral RfD Assessment (RDO) pending 08/01/92
STAT - Inhalation RfC Assessment (RDI) pending 08/01/92
STAT - Carcinogenicity Assessment (CAR) withdrawn 07/01/92
STAT - Drinking Water Health Advisories (DWHA) no data
STAT - U.S. EPA Regulatory Actions (EXSR) on-line 04/01/92
IRH - 03/01/88 CARO Text revised
IRH - 03/01/88 CARO Confidence statement revised
IRH - 03/01/88 CARI Text added
IRH - 03/01/88 CARI Confidence statement revised
IRH - 03/01/88 ? Documentation corrected
IRH - 05/01/89 CAR Carcinogen assessment summary noted as pending change
IRH - 06/01/89 CARDR Primary contact changed
IRH - 07/01/89 CAR Withdrawn; new assessment verified (in preparation)
IRH - 12/01/89 RDI Inhalation RfD now under review
IRH - 06/01/90 CAA Area code for EPA contact corrected
IRH - 06/01/90 RCRA EPA contact changed
IRH - 01/01/92 EXSR Regulatory actions updated
IRH - 04/01/92 CAA CAA regulatory action withdrawn
IRH - 07/01/92 CAR EPA contact changed; work group review dates added
IRH - 08/01/92 RDO Oral RfD now under review
RLEN - 6258
SY - ACETYLENE TRICHLORIDE
SY - ALGYLEN
SY - ANAMENTH
SY - BENZINOL
SY - BLACOSOLV
SY - BLANCOSOLV
SY - CECOLENE
SY - CHLORILEN
SY - 1-CHLORO-2,2-DICHLOROETHYLENE
SY - CHLORYLEA
SY - CHLORYLEN
SY - CHORYLEN
SY - CIRCOSOLV
SY - CRAWHASPOL
SY - DENSINFLUAT
SY - 1,1-DICHLORO-2-CHLOROETHYLENE
SY - DOW-TRI
SY - DUKERON
SY - ETHINYL TRICHLORIDE
SY - ETHYLENE TRICHLORIDE
SY - ETHYLENE, TRICHLORO-
SY - FLECK-FLIP
SY - FLOCK FLIP
SY - FLUATE
SY - GEMALGENE
SY - GERMALGENE
SY - LANADIN
SY - LETHURIN
SY - NARCOGEN
SY - NARKOGEN
SY - NARKOSOID
SY - NCI-C04546
SY - NIALK
SY - PERM-A-CHLOR
SY - PERM-A-CLOR
SY - PETZINOL
SY - PHILEX

SY - RCRA WASTE NUMBER U228
SY - TCE
SY - THRETHYLEN
SY - THRETHYLENE
SY - TRETHYLENE
SY - TRI
SY - TRIAD
SY - TRIAL
SY - TRIASOL
SY - TRICHLOORETHEEN
SY - TRICHLOORETHYLEEN, TRI
SY - TRICHLORAETHEN
SY - TRICHLORAETHYLEN, TRI
SY - TRICHLORAN
SY - TRICHLOREN
SY - TRICHLORETHENE
SY - TRICHLORETHYLENE
SY - TRICHLORETHYLENE, TRI
SY - TRICHLOROETHENE
SY - Trichloroethylene
SY - 1,1,2-TRICHLOROETHYLENE
SY - 1,2,2-TRICHLOROETHYLENE
SY - TRI-CLENE
SY - TRICLORETENE
SY - TRICLOROETILENE
SY - TRIELENE
SY - TRIELIN
SY - TRIELINA
SY - TRIKLONE
SY - TRILEN
SY - TRILENE
SY - TRILINE
SY - TRIMAR
SY - TRIOL
SY - TRI-PLUS
SY - TRI-PLUS M
SY - UN 1710
SY - VESTROL
SY - VITRAN
SY - WESTROSOL
MF - NO DATA
USE - NO DATA
COFO - NO DATA
ODOR - NO DATA
BP - NO DATA
MP - NO DATA
MW - NO DATA
DEN - NO DATA
VAP - NO DATA
VAPD - NO DATA
EVAP - NO DATA
SOLW - NO DATA
FLPT - NO DATA
FLMT - NO DATA
AVOI - NO DATA
DCMP - NO DATA

RDO -
o ORAL RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

---

o REVIEW DATES : 06/24/85, 07/08/85, 07/22/85, 06/23/92

RDI -
o INHALATION RFD SUMMARY :

A risk assessment for this substance/agent is under review by an EPA work group.

---

o REVIEW DATES : 04/21/88, 11/17/89, 02/22/90
CAREV- NO DATA
CARO - NO DATA
CARI - NO DATA
CARDR- NO DATA

HAONE- NO DATA

HATEN- NO DATA

HALTC- NO DATA

HALTA- NO DATA

HALIF- NO DATA

OLEP - NO DATA

ALAB - NO DATA

TREAT- NO DATA

HADR - NO DATA

ACUTE- NO DATA
BCF - NO DATA

CAA - NO DATA

WQCHU-

Water and Fish Consumption -- 2.7E+0 ug/L

Fish Consumption Only -- 8.07E+1 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, zero may not be attainable at this time, so the recommended criteria represents a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

WQCAQ-

Freshwater:

Acute LEC -- 4.5E+4 ug/L
Chronic LEC -- 2.19E+4 ug/L

Marine:

Acute LEC -- 2.0E+3 ug/L
Chronic LEC -- None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80); Quality Criteria for Water, EPA 440/5-86-001 (5/87).

EPA Contact -- Criteria and Standards Division / OWRS (202)260-1315 / FTS 260-1315

MCLG -

Value (status) -- 0 mg/L (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0 mg/L for trichloroethylene is proposed based on carcinogenic effects. Significant increases in the incidence of liver tumors have been reported in B6C3F1 mice of both sexes. Malignant lymphomas and pulmonary adenocarcinomas were also reported in mice. EPA has classified trichloroethylene in Group B2: sufficient evidence in animals and inadequate evidence in humans.

Reference -- 50 FR 46880 (11/13/85)

EPA Contact -- Health and Ecological Criteria Division / OST / (202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

MCL -

Value (status) -- 0.005 mg/L (Final, 1987)

Considers technological or economic feasibility? -- YES

Discussion -- EPA has set an MCL based on detection limits.

Monitoring requirements -- All systems to be monitored for four consecutive quarters; repeat monitoring dependent upon detection and vulnerability status and system size.

Analytical methodology -- Gas chromatography (EPA 502.1, 502.2, 503.1): gas chromatographic/mass spectrometry (EPA 524.1, 524.2).

Best available technology -- Packed tower aeration; granular activated carbon.

Reference -- 52 FR 25690 (07/08/87); 56 FR 30266 (07/01/91).

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

SMCL - NO DATA

FISTD- NO DATA

FIREV- NO DATA

CERC -

Value (status) -- 100 pounds (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The RQ for trichloroethylene is 100 pounds, based on potential carcinogenicity. The available data indicate a hazard ranking of low, based on a potency factor of 0.070 (mg/kg/day)-1 and weight-of-evidence classification B2, which corresponds to an RQ of 100 pounds.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

SARA - NO DATA

RCRA -

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

TSCA -

___IV.E.1. TSCA, SECTION 6

Status -- Advance Notice of Proposed Rulemaking (ANPR) (1985)

Discussion -- EPA is developing a comprehensive and integrated strategy for a regulatory investigation of six solvents, including trichloroethylene.

Reference: 50 FR 42005 (10/17/85); 40 CFR 754

EPA Contact -- Chemical Control Division / OTS (202)260-3749 / FTS 260-3749

OREF - NO DATA
IREF - NO DATA
CREF - NO DATA
HAREF- NO DATA

1
HSDB
NAME - MESITYLENE
RN - 108-67-8
HSN - 92
DATE - 920123
RVDT - NO DATA
UPDT - 12/10/92, 1 field
UPDT - 01/23/92, 1 field
UPDT - 10/10/90, 2 fields
UPDT - 06/04/90, 3 fields
UPDT - 09/29/89, 3 fields
UPDT - 04/13/89, 1 field
UPDT - 10/14/86
RLEN - 20578
RELT - NO DATA
SY - 1,3,5-TRIMETHYLBENZENE **PEER REVIEWED**
SY - FLEET-X **PEER REVIEWED**
SY - SYM-TRIMETHYLBENZENE **PEER REVIEWED**
SY - TMB **PEER REVIEWED**
SY - TRIMETHYLBENZOL **PEER REVIEWED**
MF - C9-H12 **PEER REVIEWED**
WLN - 1R C E **PEER REVIEWED**
RTEC - NIOSH/OX6825000
OHMN - NO DATA
SHPN - NO DATA
STCC - NO DATA
HAZN - NO DATA
ASCH - NO DATA
MMFG - EXTRACTED FROM COAL TAR [SRI] **PEER REVIEWED**
MMFG - BY DEHYDRATING ACETONE WITH SULFURIC ACID. [MERCK INDEX 9TH ED 1976 , p. 768] **PEER REVIEWED**
MMFG - BY FRACTIONATION OF COAL TAR & PETROLEUM DISTILLATES. [BROWNING. TOX & METAB INDUS SOLV 1965 , p. 111] **PEER REVIEWED**
IMP - Mesitylene contains 1 wt% pseuodocumeme and 0.5 wt% other aromatic compounds [KIRK-OTHMER ENCYC CHEM TECH 3RD ED 1978-PRESENT V18 p.883] **QC REVIEWED**
FORM - Mesitylene is 98.5 wt% pure [KIRK-OTHMER ENCYC CHEM TECH 3RD ED 1978-PRESENT V18 p.883] **QC REVIEWED**
MFS - Koch Industries, Inc, Hq, PO Box 2256, Wichita, KS 67201, (316) 832-5500; Subsidiaries: Koch Refining Co, PO Box 2256, Wichita, KS 67201, (316) 832-5259; Koch Specialties Group, division; Corpus Christi Specialties Plant; Production site: Corpus Christi, TX 78403 [SRI. DIRECTORY CHEM PRODUCERS - USA 1989 , p. 1047] **UNREVIEWED**
OMIN - /MESITYLENE (1,3,5)/ IS ONE OF THREE ISOMERS OF TRIMETHYLBENZENE. ...EXPOSURE TO ANY OF ISOMERS ALONE IS POSSIBLE...MORE PROBABLE THAT EXPOSURE WOULD BE TO AN ISOMETRIC MIXTURE WHICH IS IN ITSELF PORTION OF COAL TAR OR PETROLEUM DISTILLATE. [ACGIH. TLVS 3RD ED & SUPPL 1971-1979 , p. 269] **PEER REVIEWED**
USE - DYESTUFF INTERMEDIATE, SOLVENT, PAINT THINNER [ENCYC OCCUPAT HEALTH & SAFETY 1971 , p. 692] **PEER REVIEWED**
USE - CHEM INT FOR ANTHRAQUINONE VAT DYES & FOR UV OXIDATION STABILIZERS FOR PLASTICS [SRI] **PEER REVIEWED**
CPAT - ND [SRI] **PEER REVIEWED**
PROD - (1972) PROBABLY GREATER THAN 4.54X10+5 GRAMS [SRI] **PEER REVIEWED**
PROD - (1975) PROBABLY GREATER THAN 4.54X10+5 GRAMS [SRI] **PEER REVIEWED**
PROD - (1986) ND [CITATION] **QC REVIEWED**
IMPT - (1972) ND [SRI] **PEER REVIEWED**
IMPT - (1975) ND [SRI] **PEER REVIEWED**
IMPT - (1984) 1.58x10+8 g [BUREAU OF THE CENSUS. U.S. IMPORTS FOR CONSUMPTION AND GENERAL IMPORTS 1984 p.1-327] **QC REVIEWED**
EXPT - (1972) ND [SRI] **PEER REVIEWED**
EXPT - (1975) ND [SRI] **PEER REVIEWED**
EXPT - (1986) ND [CITATION] **QC REVIEWED**

COFO - LIQUID [MERCK INDEX 9TH ED 1976 , p. 768] **PEER REVIEWED**
COFO - CLEAR, COLORLESS [BROWNING. TOX & METAB INDUS SOLV 1965 , p. 111] **PEER REVIEWED**
ODOR - PECULIAR ODOR [MERCK INDEX 9TH ED 1976 , p. 768] **PEER REVIEWED**
TAST - NO DATA
BP - 164.7 DEG C @ 760 MM HG [MERCK INDEX 9TH ED 1976 , p. 768] **PEER REVIEWED**
MP - -44.8 DEG C [MERCK INDEX 9TH ED 1976 , p. 768] **PEER REVIEWED**
MW - 120.19 [MERCK INDEX 9TH ED 1976 , p. 768] **PEER REVIEWED**
CORR - NO DATA
CTP - NO DATA
DEN - 0.8637 @ 20 DEG C/4 DEG C [MERCK INDEX 9TH ED 1976 , p. 768] **PEER REVIEWED**
DSC - NO DATA
HTC - NO DATA
HTV - NO DATA
OWPC - NO DATA
PH - NO DATA
SOL - PRACTICALLY INSOL IN WATER; MISCIBLE WITH ALCOHOL, ETHER, BENZENE [MERCK INDEX 9TH ED 1976 , p. 768] **PEER REVIEWED**
SOL - MISCIBLE WITH ACETONE, CARBON TETRACHLORIDE, PETROLEUM ETHER [WEAST. HDBK CHEM & PHYS 60TH ED 1979 C-172] **PEER REVIEWED**
SPEC - INDEX OF REFRACTION: 1.49541 @ 18 DEG C/D [MERCK INDEX 9TH ED 1976 , p. 768] **PEER REVIEWED**
SPEC - MAX ABSORPTION (ALCOHOL): 258 NM (LOG E= 2.2); 263 NM (LOG E= 2.2); 267 NM (LOG E= 2.2); 273 NM (LOG E= 2.3) [WEAST. HDBK CHEM & PHYS 60TH ED 1979 C-172] **QC REVIEWED**
SPEC - IR: 6116 (Coblentz Society Spectral Collection) [WEAST. CRC HDBK DATA ORGANIC CPDS VOL I, II 1985 V1 186] **QC REVIEWED**
SPEC - UV: 1256 (Sadtler Research Laboratories Spectral Collection) [WEAST. CRC HDBK DATA ORGANIC CPDS VOL I, II 1985 V1 186] **QC REVIEWED**
SPEC - NMR: 241 (Varian Associates NMR Spectra Catalogue) [WEAST. CRC HDBK DATA ORGANIC CPDS VOL I, II 1985 V1 186] **QC REVIEWED**
SPEC - MASS: 485 (Atlas of Mass Spectral Data, John Wiley & Sons, New York) [WEAST. CRC HDBK DATA ORGANIC CPDS VOL I, II 1985 V1 186] **QC REVIEWED**
SURF - NO DATA
VAPD - 1.006 @ 20 DEG C (AIR= 1) [BROWNING. TOX & METAB INDUS SOLV 1965 , p. 111] **PEER REVIEWED**
VAP - 1.86 MM HG @ 20 DEG C [BROWNING. TOX & METAB INDUS SOLV 1965 , p. 111] **PEER REVIEWED**
EVAP - NO DATA
VISC - NO DATA
OCPP - CONVERSION FACTORS: 1 PPM= 4.92 MG/CU M; 1 MG/L= 203.5 PPM [BROWNING. TOX & METAB INDUS SOLV 1965 , p. 111] **PEER REVIEWED**
HAZS - NO DATA
DOT - Health Hazards: Poisonous; may be fatal if inhaled, swallowed or absorbed through skin. Contact may cause burns to skin and eyes. Runoff from fire control or dilution water may cause pollution. [DOT. EMERGENCY RESPONSE GUIDEBOOK 1987 G-28] **QC REVIEWED**
DOT - Fire or Explosion: Flammable/combustible material; may be ignited by heat, sparks or flames. Vapors may travel to a source of ignition and flash back. Container may explode in heat of fire. Vapor explosion and poison hazard indoors, outdoors or in sewers. Runoff to sewer may create fire or explosion hazard. [DOT. EMERGENCY RESPONSE GUIDEBOOK 1987 G-28] **QC REVIEWED**
DOT - Emergency Action: Keep unnecessary people away; isolate hazard area and deny entry. Stay upwind; keep out of low areas. Self-contained breathing apparatus and chemical protective clothing which is specifically recommended by the shipper or producer may be worn but they do not provide thermal protection unless it is stated by the clothing manufacturer. Structural firefighter's protective clothing is not effective with these materials. Isolate for 1/2 mile in all directions if tank car or truck is involved in fire. CALL CHEMTREC AT

1-800-424-9300 FOR EMERGENCY ASSISTANCE. If water pollution occurs, notify the appropriate authorities. [DOT. EMERGENCY RESPONSE GUIDEBOOK 1987 G-28] **QC REVIEWED**

DOT - Fire: Small Fires: Dry chemical, CO2, Halon, water spray or standard foam. Large Fires: Water spray, fog or standard foam is recommended. Move container from fire area if you can do it without risk. Dike fire control water for later disposal; do not scatter the material. Cool containers that are exposed to flames with water from the side until well after fire is out. Stay away from ends of tanks. Withdraw immediately in case of rising sound from venting safety device or any discoloration of tank due to fire. [DOT. EMERGENCY RESPONSE GUIDEBOOK 1987 G-28] **QC REVIEWED**

DOT - Spill or Leak: Shut off ignition sources; no flares, smoking or flames in hazard area. Do not touch spilled material; stop leak if you can do it without risk. Water spray may reduce vapor; but it may not prevent ignition in closed spaces. Small Spills: Take up with sand or other noncombustible absorbent material and place into containers for later disposal. Large Spills: Dike far ahead of liquid spill for later disposal. [DOT. EMERGENCY RESPONSE GUIDEBOOK 1987 G-28] **QC REVIEWED**

DOT - First Aid: Move victim to fresh air and call emergency medical care; if not breathing, give artificial respiration; if breathing is difficult, give oxygen. Remove and isolate contaminated clothing and shoes at the site. In case of contact with material, immediately flush skin or eyes with running water for at least 15 minutes. Keep victim quiet and maintain normal body temperature. Effects may be delayed; keep victim under observation. [DOT. EMERGENCY RESPONSE GUIDEBOOK 1987 G-28] **QC REVIEWED**

FPOT - MODERATE, VIA HEAT, FLAMES, OXIDIZERS [SAX. DANGER PROPS INDUS MATER 5TH ED 1979 , p. 799] **PEER REVIEWED**

NFPA - NO DATA

FLMT - NO DATA

FLPT - 122 DEG F [BROWNING. TOX & METAB INDUS SOLV 1965 , p. 111] **PEER REVIEWED**

AUTO - 1022 DEG F [SAX. DANGER PROPS INDUS MATER 5TH ED 1979 , p. 799] **PEER REVIEWED**

FIRP - WATER SPRAY, FOG, FOAM, CO2 [SAX. DANGER PROPS INDUS MATER 5TH ED 1979 , p. 799] **PEER REVIEWED**

INTH - NO DATA

TOXC - NO DATA

OFHZ - NO DATA

EXPL - ...RISK OF...EXPLOSION REQUIRES THAT CONCN OF VAPOR IN ATMOSPHERE IS KEPT BELOW 35-50 PPM BY MEANS OF EFFECTIVE VENTILATION OR, PREFERABLY, LOCAL APPLIED EXHAUST VENTILATION. /TRIMETHYLBENZENES/ [ENCYC OCCUPAT HEALTH & SAFETY 1971 , p. 692] **PEER REVIEWED**

REAC - REACTS VIOLENTLY WITH NITRIC ACID. [SAX. DANGER PROPS INDUS MATER 5TH ED 1979 , p. 799] **PEER REVIEWED**

DCMP - NO DATA

POLY - NO DATA

OHAZ - NO DATA

ODRT - NO DATA

SERI - NO DATA

EQUP - NO DATA

OPRM - WHEN, FOR PURPOSE OF WELDING OR CUTTING, HEAT HAS TO BE APPLIED TO VESSEL THAT HAS CONTAINED TRIMETHYLBENZENE VESSEL SHOULD FIRST BE DRAINED, PURGED & TESTED AS FOR ENTRY. /TRIMETHYLBENZENES/ [ENCYC OCCUPAT HEALTH & SAFETY 1971 , p. 692] **PEER REVIEWED**

SSL - NO DATA

SHIP - CONTAINERS: DRUMS, TANK TRUCKS [HAWLEY. CONDENSED CHEM DICTNRY 9TH ED 1977 , p. 551] **PEER REVIEWED**

STRG - STORAGE TANKS SHOULD BE MOUNDED TO CONFINE ESCAPING LIQUID & ESCAPE FROM PROCESS VESSELS SHOULD BE CONTROLLED IN SIMILAR MANNER BY SILLS @ DOORWAYS, DESIGN OF FLOORS, ETC. /TRIMETHYLBENZENES/ [ENCYC OCCUPAT HEALTH & SAFETY 1971 , p. 692] **PEER REVIEWED**

CLUP - NO DATA

DISP - NO DATA
RADL - NO DATA
TOXS - NO DATA
TXHR - NO DATA

-

THE FOLLOWING OVERVIEW IS A SUMMARY. CONSULT THE COMPLETE POISINDEX (R) DATABASE FOR TREATMENT PURPOSES.

-

Overview Title: MESITYLENE

EMT -

o EMLS - LIFE SUPPORT :

This overview assumes that basic life support measures have been instituted.

-

o EMCE - CLINICAL EFFECTS :

SUMMARY

- Mesitylene is an irritant of eyes, skin, and the respiratory tract. Chronic exposure may cause an asthmatic-like bronchitis. Aspiration may cause chemical pneumonitis with pulmonary edema and hemorrhage. Mesitylene causes CNS depression and narcosis. Thrombocytopenia, mild anemia, and coagulation disorders may also occur. Elevations in liver function tests have been noted.

-

o EMTR - TREATMENT OVERVIEW :

SUMMARY

- Move victims of inhalation exposure from the toxic environment and administer 100 percent humidified supplemental oxygen with assisted ventilation as required. Exposed eyes and skin should be thoroughly flushed with water. Inducing EMESIS should MOST LIKELY BE AVOIDED. Cautious gastric lavage and administration of activated charcoal might be beneficial. If CNS depression is present, airway compromise and inadequate ventilation may occur.

ORAL EXPOSURE

- Ensure airway patency and adequacy of ventilation and oxygenation. Endotracheal intubation, supplemental oxygenation, and assisted ventilation could be required.
- Carefully monitor complete blood count and clotting parameters. If severe anemia or bleeding disorders occur, transfusion therapy with whole blood or packed red blood cells and fresh frozen plasma could be required. Vitamin K therapy could be required for correction of clotting abnormalities.

INHALATION EXPOSURE

EYE EXPOSURE

DERMAL EXPOSURE

-

o EMTOX- RANGE OF TOXICITY :

- o 4 of 10 rats died following inhalation of 2400 ppm for 24 hours. An oral dose of 5 mL/kg caused death in 1 of 10 rats. The TCLo for humans is 10 ppm with somnolence and respiratory tract irritation noted.

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o REFERENCE : [Rumack BH & Spoerke DG: POISINDEX(R) Information System. Micromedex Inc., Denver, CO, 1993; CCIS CD-ROM Volume 78, edition exp November, 1993.] **PEER REVIEWED**

ANTR - NO DATA
MEDS - NO DATA
HTOX - ...THE LIQUID SOLVENT IS PRIMARY SKIN IRRITANT, BUT SYSTEMIC INTOXICATION DUE TO ABSORPTION THROUGH THE SKIN IS NOT PROBABLE. DEPOSITION OF LIQUID INTO THE LUNGS CAUSES CHEMICAL PNEUMONITIS AT SITE OF CONTACT. HIGH CONCENTRATIONS OF VAPORS (5000 TO 9000 PPM) CAUSES CNS DEPRESSION. [ACGIH. TLVS 3RD ED & SUPPL 1971-1979 , p. 269] **PEER REVIEWED**
HTOX - WORKERS EXPOSED FOR YEARS TO SOLVENT "FLEET-X-OV-99" (30% MESITYLENE & 50% PSEUDOCUMENE)/...HAD SYMPTOMS OF NERVOUSNESS, TENSION, ANXIETY AND ASTHMATIC BRONCHITIS. ...PERIPHERAL BLOOD SHOWED TENDENCY TO HYPOCHROMIC ANEMIA AND DEVIATION FROM NORMAL COAGULATION...VAPOR CONCN WAS 10-60 PPM... [ACGIH. TLVS 3RD ED & SUPPL 1971-1979 , p. 269] **PEER REVIEWED**
NTOX - IN ANIMALS SUBJECTED TO ACUTE LETHAL INTOXICATION, DEATH WAS PRECEDED BY CNS DEPRESSION AND RESPIRATORY FAILURE. [ENCYC OCCUPAT HEALTH & SAFETY 1971 , p. 692] **PEER REVIEWED**
NTOX - ...RATS...INHALATION...AUTOPSY SHOWED HYPEREMIA OF LUNGS WITH THICKENING OF ALVEOLAR WALLS AND SOME FATTY CHANGES IN THE LIVER. [BROWNING. TOX & METAB INDUS SOLV 1965 , p. 114] **PEER REVIEWED**
NTOX - DURING A SINGLE CONTINUOUS 24-HOUR EXPOSURE AT 2400 PPM MESITYLENE, 4 OUT OF 16 RATS DIED OF RESPIRATORY FAILURE... [ACGIH. TLVS 3RD ED & SUPPL 1971-1979 , p. 269] **PEER REVIEWED**
NTOX - ...EXPOSED RATS AT 1700 PPM OF AN ISOMERIC MIXTURE FOR 10-21 DAYS...NO FATALITIES OR OTHER ADVERSE TOXICOLOGICAL EFFECTS. EXPOSURE FOR 4 MONTHS TO SAME CONCENTRATION CAUSED DIMINISHED WEIGHT GAIN AND INCREASING LYMPHOPENIA AND NEUTROPHILIA. MARKED CNS DEPRESSION WAS ALSO OBSERVED. /ISOMERIC MIXTURE/ [ACGIH. TLVS 3RD ED & SUPPL 1971-1979 , p. 269] **PEER REVIEWED**
NTOX - 21 day Daphnia reproduction tests were conducted in line with the provisional procedure proposed by the Federal Environmental Agency (Umweltbundesamt, FRG), as of Jan 1, 1984. Groups of 20, 24-hr old Daphnia magna Straus were exposed to 0.125 to 16 mg/l 1,3,5-trimethylbenzene (mesitylene) in semi-static test vessels. Parent animals in the test and control vessels had to be pipetted 3 times/wk in freshly prepared test and control media at the corresponding concn level. The no observed effect concn (NOEC) was determined from the parameters of mortality of the parent animals, reproduction rate and appearance of the first offspring during the test period. In preliminary acute Daphnia tests, the 24 hr EC50 was approx 50 mg/l for mesitylene, the EC0 was 40 mg/l. The nominal 21 day no observed effect concn was 2.0 mg/l, with the most sensitive parameter being the reproductive rate. [Kuhn R et al; Water Res 23 (4): 501-10 (1989)] **QC REVIEWED**
HTXV - NO DATA
NTXV - NO DATA
ETXV - NO DATA
NTP - NO DATA
IARC - NO DATA
TCAT - NO DATA
POPL - NO DATA

ADE - ABSORPTION TAKES PLACE MOST READILY BY INHALATION OF THE VAPOR, BUT THE LIQUID CAN BE ABSORBED FROM THE GASTRO-INTESTINAL TRACT, AND PROBABLY, THOUGH SLOWLY, BY THE INTACT SKIN. [BROWNING. TOX & METAB INDUS SOLV 1965 , p. 112] **PEER REVIEWED**

ADE - ...ONLY A SMALL PORTION IS EXCRETED UNCHANGED BY THE LUNGS, THE GREATER PART IS OXIDIZED TO WATER-SOLUBLE METABOLITES, WHICH ARE EXCRETED BY THE URINE, PARTLY FREE, PARTLY CONJUGATED WITH GLYCINE AND MESITYLENIC ACID [BROWNING. TOX & METAB INDUS SOLV 1965 , p. 112] **PEER REVIEWED**

ADE - ...INCR IN URINARY PHENOLS, BOTH FREE & BOUND, IN RATS SUBJECTED TO INHALATION OF 200, 580 & 1700 PPM OF 'FLEET-X-DV-99'. ...SINGLE SC INJECTION OF MESITYLENE (5 ML/KG BODY WT) INCR URINARY EXCRETION OF ORG SULFATES. /ISOMERIC MIXT OF 30% MESITYLENE & 50% PSEUDOCUMENE USED/ [BROWNING. TOX & METAB INDUS SOLV 1965 , p. 112] **PEER REVIEWED**

METB - ...ONLY A SMALL PORTION IS EXCRETED UNCHANGED BY THE LUNGS, THE GREATER PART IS OXIDIZED TO WATER-SOLUBLE METABOLITES, WHICH ARE EXCRETED BY THE URINE, PARTLY FREE, PARTLY CONJUGATED WITH GLYCINE AND MESITYLENIC ACID [BROWNING. TOX & METAB INDUS SOLV 1965 , p. 112] **PEER REVIEWED**

METB - MESITYLINE YIELDS 2,4,6-TRIMETHYLPHENOL IN RAT. BAKKE, OM & SCHELINE, RR, TOXICOL APPL PHARMAC, 16, 691 (1970). /FROM TABLE/ [GOODWIN. HDBK INTERMED METAB AROMAT COMPD 1976 M-5] **PEER REVIEWED**

METB - ONE METABOLITE OF MESITYLENE IS 3,5-DIMETHYLBENZOIC ACID. [LAHAM S, MATUTINA EO; MICRODETERMINATION OF MESITYLENIC ACID IN HUMAN URINE; ARCH TOXIKOL 30 (3) 199-205 (1973)] **PEER REVIEWED**

METB - APPROX 78% OF ORAL DOSE OF MESITYLENE WAS EXCRETED AS 3,5-DIMETHYLHIPPURIC ACID; ADDITIONAL 7.6 & 8.2% WERE EXCRETED AS GLUCURONIC & SULFURIC ACID CONJUGATES. [MIKULSKI PI, WIGLUSZ R; THE COMPARATIVE METABOLISM OF MESITYLENE, PSEUDOCUMENE, & HEMIMELLITENE IN RATS; TOXICOL APPL PHARMACOL 31 (1) 21-31 (1975)] **PEER REVIEWED**

BHL - NO DATA

ACTN - NO DATA

INTC - EFFECT OF PHENOBARBITAL ADMIN ON METABOLISM IS DUE TO INCR IN RATE OF AROMATIC HYDROXLATION RATHER THAN IN RATE OF FORMATION OF CORRESPONDING CARBOXYLIC ACID. [MIKULSKI PI, WIGLUSZ R; THE COMPARATIVE METABOLISM OF MESITYLENE, PSEUDOCUMENE, & HEMIMELLITENE IN RATS; TOXICOL APPL PHARMACOL 31 (1) 21-31 (1975)] **PEER REVIEWED**

INTC - Groups of 5 female SPF Sprague-Dawley rats (200 to 220 g) were exposed via inhalation for 2 hr to 120, 180, 400, or 720 ppm mesitylene, without or in combination with 1000 or 4000 ppm ethyl acetate. Immediately after exposure, blood samples were collected. Co-exposure with ethyl acetate lowered blood concn of inhaled mesitylene, but the effect was not statistically significant. For example, at 400 ppm mesitylene, control blood concn was (75.8 + or - 2.1) x 10-6 mol/l vs 68.8 + or - 7.8) x 10-6 mol/l at 4000 ppm ethyl acetate. [Freundt KJ et al; Bull Environ Contam Toxicol 42 (4): 495-8 (1989)] **QC REVIEWED**

BION - NO DATA

THER - NO DATA

MINF - NO DATA

WARN - NO DATA

IDIO - NO DATA

TOLR - NO DATA

MXDD - NO DATA

ENVS - NO DATA

NATS - OCCURS IN COAL TAR & IN PETROLEUM CRUDES. [MERCK INDEX 9TH ED 1976 , p. 768] **PEER REVIEWED**

ARTS - A component of high octane gasoline at 1.32 wt% [VERSCHUEREN. HDBK ENVIRON DATA ORG CHEM 1983 p.812] **QC REVIEWED**

FATE - NO DATA

BIOD - NO DATA

ABIO - NO DATA

BIOC - NO DATA

KOC - NO DATA

VWS - NO DATA

WATC - TRIMETHYLBENZENE: 6.1 UG/L IS HIGHEST CONCN IN FINISHED WATER. /FROM TABLE; TRIMETHYBENZENE/ [NRC. DRINKING WATER & HEALTH 1977 , p. 799]

PEER REVIEWED
EFFL - NO DATA
SEDS - NO DATA
ATMC - NO DATA
FOOD - NO DATA
PLNT - NO DATA
FISH - NO DATA
ANML - NO DATA
MILK - NO DATA
OEVC - NO DATA
RTEX - NO DATA
AVDI - NO DATA
PBEX - NO DATA
BODY - NO DATA
IDLH - NO DATA
ADI - NO DATA
ATOL - NO DATA
OSHA - NO DATA
NREC - NO DATA
TLV - NO DATA
OOPL - NO DATA
WSTD - NO DATA
ASTD - NO DATA
SSTD - NO DATA
CERC - NO DATA
TSCA - NO DATA
RCRA - NO DATA
FIFR - NO DATA
FDA - NO DATA
SAMP - NO DATA
ALAB - NO DATA
CLAB - THE EXTRACT OF METABOLITE 3,5-DIMETHYLBENZOIC ACID, IS DETERMINED BY MEANS OF THIN LAYER CHROMATOGRAPHY, UV LIGHT, & FINALLY SPECTROPHOTOMETER. METHOD IS SPECIFIC FOR 3,5-DIMETHYLBENZOIC ACID. [LAHAM S, MATUTINA EO; MICRODETERMINATION OF MESITYLENIC ACID IN HUMAN URINE; ARCH TOXIKOL 30 (3) 199-205 (1973)] **PEER REVIEWED**
RPTS - NO DATA
TEST - NO DATA
HIST - NO DATA
EXP - NO DATA

[HSDB] SS 9 /cf?
USER:
find 79-01-6

Search in progress

SS (9) PSTG (1)

[HSDB] SS 10 /cf?
USER:

END

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