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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR CHLORAL

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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16. ABSTRACT

Health and Environmental Effects Documents (HEEDS) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference Doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. In the case of suspected carcinogens, RfDs may not be estimated. Instead, a carcinogenic potency factor, or q_1^*, is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively. Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA.

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained for Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval that does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. Instead, a carcinogenic potency factor, or q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984 and 1986a, respectively.

EXECUTIVE SUMMARY

Chloral (75-87-6) is a colorless, oily liquid at room temperature with a pungent, irritating odor (Windholz, 1983). Chloral hydrate (302-17-0) occurs in the form of transparent, colorless crystals at room temperature and has a penetrating, slightly acrid odor (Hawley, 1981). Upon release to water chloral will spontaneously form chloral hydrate (Windholz, 1983; U.S. EPA, 1982). Montrose Chemical was the last U.S. manufacturer of chloral, but production was discontinued when production of DDT ceased (U.S. EPA, 1986b). There are two domestic importers for chloral and four domestic importers for chloral hydrate (CMR, 1986; U.S. EPA, 1986b). During 1984, 11,902 pounds of chloral was imported into the United States (HSDB, 1987b). Chloral is used in the production of chloral hydrate, plastics and some pesticides, including methoxychlor and DDVP (Windholz, 1983; U.S. EPA, 1982; Martin and Worthing, 1977). Chloral hydrate is used in medication as a CNS depressant and sedative, and in liniments (HSDB, 1987b).

If released to the atmosphere, both chloral and chloral hydrate are expected to exist almost entirely in the vapor form (Perry and Green, 1984; Eisenreich et al., 1981). Half-lives for the reaction of these compounds with photochemically generated hydroxyl radicals were estimated to be 7 and 12 days, respectively. Anhydrous chloral may react with water vapor in the atmosphere and form chloral hydrate. Because of its extremely high water solubility, chloral hydrate would be highly susceptible to removal from the atmosphere by wet deposition. Dry deposition is probably not an important fate process. If released to water, chloral would react spontaneously with water molecules to form chloral hydrate. The ratio of chloral to chloral hydrate at equilibrium would be 28,000:1 (U.S. EPA, 1982). Chloral hydrate

decomposes in neutral, acidic and basic solutions, and produces chloroform and formic acid by an elimination reaction catalyzed by water, OH^- and chloralate anion. The half-life for this reaction is 17.5 days at pH 8 and 20°C and is 2 days at pH 9 and 20°C (Luknitskii, 1975). Chloral hydrate is not expected to volatilize significantly, bioaccumulate in aquatic organisms or adsorb significantly to suspended solids or sediment in water. If released to moist soil, chloral would probably react with soil moisture to form chloral hydrate. Chloral hydrate is expected to be highly mobile in moist soil. Volatilization from moist soils is not expected to be significant; however, both chloral and its hydrate are expected to volatilize fairly rapid from dry soil surfaces.

Chloral hydrate has been identified as an aqueous chlorination product of humic substances and amino acids, ubiquitous components of natural waters (Trehy et al., 1986; Miller and Uden, 1983; Norwood et al., 1983; Sato et al., 1985). Thus, chloral can occur in drinking water as a result of disinfection of raw water by chlorination. During the mid to late 1970s chloral hydrate was detected in various drinking water supplies throughout the United States (Keith et al., 1976; Fielding et al., 1981; Kloepfer, 1976). Disinfection of some wastewater streams by chlorination may also result in the formation of chloral hydrate. Chloral hydrate has been detected in the spent chlorination liquor from the bleaching of sulfite pulp and chlorinated wastewater from an extended aeration treatment plant (Carlberg et al., 1986; Trehy et al., 1986).

Little information was available concerning the toxicity of chloral hydrate to aquatic organisms. The only LC_{50} for freshwater fish is a value of 1720 mg/ℓ for golden orfe (Juhnke and Luedemann, 1978).

Bringmann and Kuehn (1980) reported that inhibition of growth occurs at 1.6, 2.8 and 79 mg/ℓ for Pseudomonas putida, Scenedesmus quadricauda and Entosiphon sulcatum, respectively. Studies in species of Chlamydomonas have observed effects beginning at ~0.17 g/ℓ (Cross and McMahon, 1976). No data for saltwater species were found in the available literature.

Since chloral hydrate is readily absorbed from the gastrointestinal tract and rapidly metabolized, only metabolites are detected in the blood. Chloral hydrate is metabolized to TCE and TCA, with further metabolism of TCE to TCA in humans and dogs (Marshall and Owens, 1954), but not in mice (Cabana and Gessner, 1970). In humans, the amount of TCA produced is highly variable, with Marshall and Owens (1954) reporting that 5-47% of an oral dose may be metabolized to TCA. TCE is conjugated with glucuronide and is excreted in the urine and bile (Harvey, 1975).

Studies of binding of TCA and TCE to plasma protein from monkeys and humans indicate similar levels of binding for TCE, with increased binding of TCA to plasma proteins from humans compared with monkeys (Peters et al., 1975). Plasma and urine levels of TCE and TCA in humans indicate that TCE is readily excreted, while the excretion of TCA is more prolonged.

Inhalation studies of chloral are limited to abstracts of Russian studies (Biostov et al., 1970; Pavlova, 1975) that reported adverse effects but did not report the frequency or duration of exposure.

Oral toxicity studies of chloral consist of a series of 90-day studies in which mice were provided with drinking water containing chloral at 0.07 or 0.7 mg/mℓ (Sanders et al., 1982; Kauffmann et al., 1982; Kallman et al., 1984). The most sensitive endpoint of toxicity in male mice was liver toxicity (Sanders et al., 1982), while the most sensitive endpoint in female mice was immunotoxicity (Kauffmann et al., 1982). Both effects were

observed at 0.07 mg/mℓ, a dose of 16 mg/kg/day in males and 18 mg/kg/day in females. However, the biological significance of the immune toxicity test results at 18 mg/kg is questionable. No effects on behavior were observed in male mice, although body temperature was found to be depressed at both concentrations (Kallman et al., 1984).

Chloral hydrate has been used as a sedative for humans. Adverse effects that have been reported at therapeutic doses (0.5-2 g) include epigastric distress, nausea, vomiting, allergic skin reactions, eosinophilia, leukopenia and interactions with a number of drugs (Harvey, 1975). At higher doses, chloral hydrate has been reported to cause cardiac arrhythmias (Bowyer and Glasser, 1980; Wiseman and Hampel, 1978).

Chloral hydrate is lethal to humans at a dose of ~10 g (Harvey, 1975). An oral LD_{50} of 479 mg/kg has been reported in adult rats (Goldenthal, 1971). Kallman et al. (1984) reported an ED_{50} of 84.5 mg chloral/kg for disruption of a screen test in male mice 5 minutes after the mice were treated by gavage with chloral hydrate.

A single dose oral study reported a dose-related increase in liver tumors in mice examined 48-92 weeks after they were treated with chloral hydrate at 5 or 10 μg/g (Rijhsinghani et al., 1986). The increase was statistically significant only at 10 μg/g. A nonstatistically significant increase in skin tumor incidences was observed in mice given 2 weekly applications of chloral hydrate followed by 18 weekly applications of croton oil. A metabolite of chloral, trichloroacetic acid, has induced a significant tumor response in a mouse liver bioassay. Studies of DNA effects have reported positive results in mutation assays and assays of aneuploidy inducing activity, and chloral hydrate was found to decrease testicular DNA synthesis in an intratesticular injection study using mice (Borzelleca and Carchman, 1982). In addition, chloral shares a common

metabolite (TCA) with trichloroethylene which has been shown to be carcinogenic in animal test systems.

Chloral hydrate exposure did not result in any changes in litter parameters or in any gross malformations in offspring of mice provided with drinking water containing chloral hydrate at 0.06 or 0.6 mg chloral/mℓ from 3 weeks before mating through weaning (Kallman et al., 1984). At 0.6 mg/mℓ, an impairment of retention of an avoidance learning task was observed in 24-day-old mice. Because pups had access to the chloral hydrate dosing solution, it is not clear if the effect was a result of in utero or postnatal exposure.

The lack of inhalation data precluded the derivation of inhalation RfDs. Using the 90-day study by Sanders et al. (1982), subchronic and chronic oral RfDs of 1 mg/day (0.02 mg/kg/day) and 0.1 mg/day (0.002 mg/kg/day), respectively, were calculated. Confidence in the oral RfDs is low. An RQ for systemic toxicity of 1000 was calculated on the basis of liver toxicity in mice in the Sanders et al. (1982) study. Based on a weight of the evidence classification of C but no quantitative evaluation, a carcinogenicity RQ of 100 was assigned.

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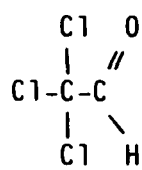
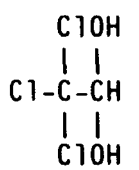
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
ED_{50}	Dose effective to 50% of recipients
GC	Gas chromatography
IR	Infra red
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LD_{LO}	Lowest lethal dose
LDH	Lactate dehydrogenase
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MS	Mass spectrometry
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NOAEL	No-observed-adversed-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RBC	Red blood cell
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TCE	Trichloroethanol
TCE-G	Trichloroethanol glucuronide
TCA	Trichloroacetic acid
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Chloral is also known as trichloroacetaldehyde. Chloral hydrate is also known as trichloroacetaldehyde monohydrate and 2,2,2-trichloro-1,1-ethanediol (Windholz, 1983). The structure, molecular weight, empirical formula and CAS Registry number for chloral and chloral hydrate are given below.

	Chloral	Chloral hydrate
		
Molecular weight:	147.22	165.23
Empirical formula:	C_2HCl_3O	$C_2H_3Cl_3O_2$
CAS Registry number:	75-87-6	302-17-0

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Chloral is a colorless, oily liquid at room temperature and has a pungent irritating odor (Windholz, 1983). Chloral hydrate exists as transparent, colorless crystals at room temperature. The hydrate has an aromatic, penetrating, slightly acrid odor and a slightly bitter, sharp taste (Hawley, 1981). Upon release to water, chloral will spontaneously form choral hydrate (Windholz, 1983; U.S. EPA, 1982). Selected physical properties for these compounds are listed in Table 1-1. Chloral is soluble in ether and is soluble in alcohol, forming chloral alcoholate (Windholz, 1983). Chloral hydrate is highly soluble in alcohol, chloroform, ether, carbon disulfide and olive oil; it is freely soluble in acetone and methyl ethyl ketone; and it is moderately or sparingly soluble in turpentine, petroleum ether, carbon tetrachloride, benzene and toluene (Windholz, 1983).

TABLE 1-1

Selected Physical Properties for Chloral and Chloral Hydrate

Property	Chloral	Chloral hydrate	Reference
Melting point:	-57.7°C	57°C	Windholz, 1983
Boiling point:	97.8°C	98°C (with dissociation to chloral and water)	Windholz, 1983
Vapor pressure at 25°C:	51 mm Hg	16 mm Hg	Perry and Green, 1984
Water solubility at 25°C:	exists in hydrated form in water*	8.25×10^6 mg/ℓ	Seidell, 1941
Log K_{ow}:	exists in hydrated form in water*	0.99	Hansch and Leo, 1985
Specific gravity, 25/4°C:	1.505	NA	Windholz, 1983
Refractive index, n_D^{20}:	1.45572	NA	Windholz, 1983

*See value for chloral hydrate

NA = Not available

PRODUCTION DATA

Chloral can be prepared by two methods: by direct chlorination of either acetaldehyde or paraldehyde in the presence of antimony chloride or by chlorination of ethyl alcohol followed by treatment with concentrated sulfuric acid and then distillation (HSDB, 1987a; Windholz, 1983). Chloral hydrate is prepared by addition of water to anhydrous chloral (Windholz, 1983).

Production data regarding chloral and chloral hydrate from the U.S. EPA TSCA Production file are provided in Table 1-2. Montrose Chemical was the last U.S. manufacturer of chloral, but production was discontinued when production of DDT ceased (U.S. EPA, 1986b). There are two domestic importers for chloral: R.W. Greef and Co. and Lobel Chemical Corp., and four domestic importers for chloral hydrate: Centerchem., Ceres Chemical Co., Nipa Laboratories and Spectrum Chemical Manufacturing Corp. (CMR, 1986; U.S. EPA, 1986b). During 1984, 11,902 pounds of chloral hydrate were imported into the United States (HSDB, 1987b).

1.4. USE DATA

Chloral is used in the production of chloral hydrate, plastics and some pesticides, including methoxychlor and DDVP (Windholz, 1983; U.S. EPA, 1982; Martin and Worthing, 1977). Chloral also has been used in the production of DDT and has potential for use in the production of trichloroacetic acid (Freiter, 1978; U.S. EPA, 1982). Chloral hydrate is used in medication as a CNS depressant and sedative, and in liniments (HSDB, 1987b). Chloral hydrate has also been used as an intermediate in the production of dichloroacetic acid and DDT (HSDB, 1987b; Mitchell, 1980).

TABLE 1-2

1977 Production Data for Chloral and Chloral Hydrate[a]

Compound	Company/Location	Production/Import Volume (million pounds)
Chloral	Diamond Shamrock Houston, TX	1.0-10
	Montrose Chemical of California Henderson, NV	confidential
	Texas Eastman Longview, TX	1.0-10 (site limited use)
	Continental Oil Co. Westlake, LA	1.0-10
	confidential	0.10-1.0
Chloral hydrate	Diamond Shamrock Houston, TX	1.0-10
	Centerchem Inc. New York, NY (importer)	0.01-0.10
	JCD Group Inc. New York, NY (importer)	none[b]

[a]Source: U.S. EPA, 1977

[b]This company imported chloral hydrate in previous years.

1.5. SUMMARY

Chloral (75-87-6) is a colorless, oily liquid at room temperature with a pungent, irritating odor (Windholz, 1983). Chloral hydrate (302-17-0) occurs in the form of transparent, colorless crystals at room temperature and has a penetrating, slightly acrid odor (Hawley, 1981). Upon release to water chloral will spontaneously form chloral hydrate (Windholz, 1983; U.S. EPA, 1982). Montrose Chemical was the last U.S. manufacturer of chloral, but production was discontinued when production of DDT ceased (U.S. EPA, 1986b). There are two domestic importers for chloral and four domestic importers for chloral hydrate (CMR, 1986; U.S. EPA, 1986b). During 1984, 11,902 pounds of chloral was imported into the United States (HSDB, 1987b). Chloral is used in the production of chloral hydrate, plastics and some pesticides, including methoxychlor and DDVP (Windholz, 1983; U.S. EPA, 1982; Martin and Worthing, 1977). Chloral hydrate is used in medication as a CNS depressant and sedative, and in liniments (HSDB, 1987b).

2. ENVIRONMENTAL FATE AND TRANSPORT

Limited data regarding the environmental fate and transport of chloral and chloral hydrate were located in the available literature. When possible, predictions concerning environmental fate and transport of this compound were based on physical properties or molecular structure.

2.1. AIR

These compounds are expected to exist almost entirely in the vapor phase in the atmosphere (Perry and Green, 1984; Eisenreich et al., 1981) because of the relatively high vapor pressure of chloral (51 mm Hg at 25°C) and chloral hydrate (16 mm Hg at 25°C).

2.1.1. Reaction with Hydroxyl Radicals. Using the method of Atkinson (1985), the rate constants for the reaction of chloral and chloral hydrate with photochemically generated hydroxyl radicals in the atmosphere at 25°C were estimated to be 2.3×10^{-12} and 1.3×10^{-12} cm^3/molecule-sec, respectively. Assuming an ambient hydroxyl radical concentration of 5.0×10^5 molecules/cm^3 (Atkinson, 1985), the respective HO• reaction half-lives for chloral and chloral hydrate were determined to be ~7 and 12 days. Ohta and Mizoguchi (1980) investigated the photooxidation products of chloral in a glass cell using IR absorption spectroscopy. Major products were determined to be HCl, CO, CO_2 and $COCl_2$. The photooxidation was a chain reaction and the chain carrier was chlorine; however, the wavelength of light used in this study was not reported.

2.1.2. Reaction with Ozone. Chloral and chloral hydrate will not react with ozone molecules in the atmosphere (U.S. EPA, 1987a).

2.1.3. Physical Removal Processes. Given its high water solubility, chloral hydrate would be highly susceptible to removal from the atmosphere

by wet deposition. Anhydrous chloral may react with water vapor in the atmosphere to form chloral hydrate and subsequently be removed from the atmosphere by wet deposition. Dry deposition is probably not an important fate process for these compounds since both chloral and chloral hydrate are expected to exist almost entirely in the vapor phase in the atmosphere.

2.2. WATER

2.2.1. Chemical Reactions. Chloral reacts spontaneously with water to form chloral hydrate. The ratio of chloral hydrate to chloral at equilibrium is 28,000:1 (U.S. EPA, 1982). Although chloral itself is stable, its aqueous solutions are not (Luknitskii, 1975). Chloral hydrate decomposes in neutral, acidic and basic solutions. The initial step in the decomposition of chloral hydrate can be described by the following elimination reaction:

$$CCl_3CH(OH)_2 \xrightarrow{OH^-} CCl_3H + HCOO^-$$

This reaction is catalyzed by water, OH^- and chloralate anion. The half-life for this reaction is reported to be 17.5 days at pH 8 and 20°C and 4 days at pH 9 and 20°C (Luknitskii, 1975). Large decreases in pH of aqueous solutions have been found to occur over time as the result of CCl_3-group destruction with HCl formation (Luknitskii, 1975).

2.2.2. Microbial Degradation. Pertinent data regarding the microbial degradation of chloral hydrate were not located in the available literature cited in the Appendix.

2.2.3. Volatilization. Keith et al. (1976) determined that chloral hydrate is so highly polar that it does not appreciably strip out of aqueous solution even at elevated temperatures. Henry's Law constant for chloral hydrate was estimated to be 1×10^{-10} atm-m³/mol at 25°C using the group

contribution method of Hine and Mookerjee (1975). This value indicates that volatilization from all bodies of water would not be significant (Lyman et al., 1982).

2.2.4. Adsorption. Pertinent data regarding the adsorption of chloral hydrate to suspended solids and sediments in water were not located, although the relatively high water solubility and low K_{ow} suggest that adsorption is not likely.

2.2.5. Bioaccumulation. Pertinent data regarding the bioaccumulation of chloral hydrate in aquatic organisms were not located. A BCF of 5 was estimated for this compound using a linear regression equation based on a measured log K_{ow} of 0.99. This BCF value and the extremely high water solubility of chloral hydrate suggest that this compound would not bioaccumulate significantly in aquatic organisms.

2.3. SOIL

2.3.1. Hydration. If released to moist soil, anhydrous chloral would probably react with soil moisture to form chloral hydrate.

2.3.2. Adsorption. A K_{oc} of 75 was estimated for chloral hydrate using the molecular topology and quantitative structure-activity relationship analysis of Sabljic (1984); a K_{oc} of 82 was estimated using a linear regression equation based on a log K_{ow} of 0.99 (Hansch and Leo, 1985; Lyman et al., 1982). These K_{oc} values suggest that chloral hydrate would be highly mobile in soil and may leach into groundwater (Swann et al., 1983).

2.3.3. Volatilization. Because of the relatively low value of Henry's Law constant for chloral hydrate ($1x10^{-10}$ atm-m^3/mol at 25°C), this compound is not expected to volatilize significantly from moist soil surfaces. The relatively high vapor pressures of chloral and chloral hydrate suggest, however, that these compounds would volatilize fairly rapidly from dry soil surfaces.

2.4. SUMMARY

If released to the atmosphere, both chloral and chloral hydrate are expected to exist almost entirely in the vapor form (Perry and Green, 1984; Eisenreich et al., 1981). Half-lives for the reaction of these compounds with photochemically generated hydroxyl radicals were estimated to be 7 and 12 days, respectively. Anhydrous chloral may react with water vapor in the atmosphere and form chloral hydrate. Because of its extremely high water solubility, chloral hydrate would be highly susceptible to removal from the atmosphere by wet deposition. Dry deposition is probably not an important fate process. If released to water, chloral would react spontaneously with water molecules to form chloral hydrate. The ratio of chloral to chloral hydrate at equilibrium would be 28,000:1 (U.S. EPA, 1982). Chloral hydrate decomposes in neutral, acidic and basic solutions, producing chloroform and formic acid by an elimination reaction catalyzed by water, OH^- and chloralate anion. The half-life for this reaction is 17.5 days at pH 8 and 20°C and is 2 days at pH 9 and 20°C (Luknitskii, 1975). Chloral hydrate is not expected to volatilize significantly, bioaccumulate in aquatic organisms or adsorb significantly to suspended solids or sediment in water. If released to moist soil, chloral would probably react with soil moisture to form chloral hydrate. Chloral hydrate is expected to be highly mobile in moist soil. Volatilization from moist soils is not expected to be significant; however, both chloral and its hydrate are expected to volatilize fairly rapid from dry soil surfaces.

3. EXPOSURE

Monitoring data were not available to indicate that the general population is exposed to chloral or its hydrate by inhalation, ingestion of contaminated food or dermal contact. Limited monitoring data are available on chloral hydrate in drinking water.

3.1. WATER

Chloral hydrate has been identified as a product of aqueous chlorination of humic substances at pH 4-9 and amino acids at pH 7-8 (Trehy et al., 1986; Miller and Uden, 1983; Norwood et al., 1983; Sato et al., 1985). Humic substances and amino acids are ubiquitous constituents of natural waters. Thus, chloral hydrate can occur in drinking water as a result of disinfection of raw water by chlorination. During the 1975 National Organics Reconaissance Study (NORS) chloral hydrate was identified in drinking water supplies from 6 out of 10 cities. Locations at which samples were taken and the corresponding concentrations of chloral hydrate are as follows: Cincinnati, OH, 2.0 µg/ℓ; Philadelphia, PA, 5.0 µg/ℓ; Seattle, WA, 3.5 µg/ℓ; Grand Forks, ND, 0.01 µg/ℓ; New York City, 0.02 µg/ℓ; Terrebonne Parish, LA, 1.0 µg/ℓ; Miami, FL, not detected; Ottumwa, IA, not detected; Lawrence, MA, not detected; and Tucson, AZ, not detected (Keith et al., 1976). Chloral hydrate was not identified in any of the NORS samples analyzed by the inert gas stripping technique referred to as Volatile Organics Analysis (Keith et al., 1976). Keith et al. (1976) determined that because of the high polarity of chloral hydrate, Volatile Organics Analysis is not a suitable technique for isolating and concentrating chloral hydrate before analysis by GC or GC/MS. Consequently, data

provided in the NORS may be incomplete. Chloral hydrate was also qualitatively identified in finished drinking waters from 1 out of 14 cities sampled throughout the United States between 1977 and 1979 and the finished drinking water supply of Kansas City, Kansas between 1973 and 1975 (Fielding et al., 1981; Kloepfer, 1976). Although these data suggest that there may be widespread distribution of chloral hydrate in drinking waters, statistical confirmation of this distribution is not possible because of the lack of sufficient monitoring data.

Disinfection of some wastewater streams by chlorination may also cause the formation of chloral hydrate. Chloral hydrate has been identified in the spent chlorination liquor from the bleaching of sulfite pulp at high and low lignin content. Concentrations of chloral corresponded to <0.1 and 0.5/g per ton of pulp processed, respectively (Carlberg et al., 1986). Samples of chlorinated wastewater from an extended aeration treatment plant collected on 2 days were found to contain 20-38 µg/ℓ chloral hydrate (Trehy et al., 1986).

3.2. SUMMARY

Chloral hydrate has been identified as an aqueous chlorination product of humic substances and amino acids, ubiquitous components of natural waters (Trehy et al., 1986; Miller and Uden, 1983; Norwood et al., 1983; Sato et al., 1985). Thus, chloral can occur in drinking water as a result of disinfection of raw water by chlorination. During the mid to late 1970s chloral hydrate was detected in various drinking water supplies throughout the United States (Keith et al., 1976; Fielding et al., 1981; Kloepfer, 1976). Disinfection of some wastewater streams by chlorination may also result in the formation of chloral hydrate. Chloral hydrate has been

detected in the spent chlorination liquor from the bleaching of sulfite pulp and chlorinated wastewater from an extended aeration treatment plant (Carlberg et al., 1986; Trehy et al., 1986).

4. AQUATIC TOXICITY

4.1. ACUTE TOXICITY

Juhnke and Luedemann (1978) reported a 48-hour LC_{50} value of 1720 mg chloral hydrate/ℓ for golden orfe, Leuciscus idus melanotus, under static conditions. Bringmann and Kuehn (1980) found that chloral hydrate at 1.6 and 79 mg/ℓ resulted in a ≥3% decrease in growth in cultures of the bacteria, Pseudomonas putida, and the protozoan, Entosiphon sulcatum, respectively. The bacteria were exposed to chloral hydrate for 16 hours, while the protozoa were exposed for 72 hours.

No effects were observed in trout, bluegill or lamprey larvae exposed to chloral hydrate at 0.1 or 1.0 ppm for 24 hours (Applegate et al., 1957).

4.2. CHRONIC EFFECTS

Pertinent data regarding effects of chronic chloral hydrate exposure in aquatic organisms were not located in the available literature cited in Appendix A.

4.3. PLANT EFFECTS

A chloral hydrate concentration of 2.8 mg/ℓ resulted in a ≥3% decrease in growth of cultures of the algae, Scenedesmus quadricauda, exposed for 7 days (Bringmann and Kuehn, 1980). Lewin et al. (1982) found that chloral hydrate inhibited the motility of four species of the flagellated green algae, Chlamydomonas, grown in cultures without inducing death or flagellar autonomy (Table 4-1). The results indicated that C. dysosmos was most sensitive in the test for immobilization, while C. moewussi (-) died at the lowest concentration.

Cross and McMahon (1976) added chloral hydrate to cultures of Chlamydomonas reinhardi and observed the breakdown of polysomes and inhibition of protein synthesis at chloral hydrate concentrations of ≥10 mM (0.17 g/ℓ).

TABLE 4-1

Effects of Chloral Hydrate on Four Species of *Chlamydomonas*[a]

Species	Lowest Concentration Resulting in 100% Immobilization (mM)	Highest Concentration Permitting Survival for 5 minutes (mM)
C. moewussii (+)[b]	60 (9.9 g/ℓ)	120 (19.8 g/ℓ)
(-)	60	60
C. reinhardtii (+)[b]	60	120
(-)	60	125 (20.1 g/ℓ)
C. dysosmos	30 (4.9 g/ℓ)	120
C. monoica	120	500+ (8.3 g/ℓ)

[a]Source: Lewin et al., 1982

[b]Mating types

Because significant levels of the chloral hydrate metabolites, TCA and TCE were not found in the cultures, the investigators concluded that chloral hydrate itself produced the observed effects.

4.4. SUMMARY

Little information was available concerning the toxicity of chloral hydrate to aquatic organisms. The only LC_{50} for freshwater fish is a value of 1720 mg/ℓ for golden orfe (Juhnke and Luedemann, 1978). Bringmann and Kuehn (1980) reported that inhibition of growth occurs at 1.6, 2.8 and 79 mg/ℓ for Pseudomonas putida, Scenedesmus quadricauda and Entosiphon sulcatum, respectively. Studies in species of Chlamydomonas have observed effects beginning at ~0.17 g/ℓ (Cross and McMahon, 1976). No data for saltwater species were found in the available literature.

5. PHARMACOKINETICS

5.1. ABSORPTION

Quantitative data concerning the absorption of choral hydrate from the gastrointestinal and respiratory tracts were not located. The appearance of chloral hydrate metabolites in the plasma of humans and dogs 5-10 minutes following an oral dose indicated that it was readily absorbed from the gastrointestinal tract (Marshall and Owens, 1954). Because chloral hydrate is metabolized quickly, it is not usually found in the blood.

5.2. DISTRIBUTION

Data regarding tissue distribution of chloral hydrate and its metabolites were not located. Using equilibrium dialysis, Peters et al. (1975) examined the plasma protein binding of chloral hydrate metabolites in plasma from rhesus monkeys, squirrel monkeys and man. The results indicated similar levels of binding for TCE, with 19, 24 and 25% binding in rhesus monkeys, squirrel monkeys and man, respectively. Results of TCA binding indicated levels of 69 and 64% binding for rhesus and squirrel monkeys, respectively, in contrast to ~85% for man.

Sellers et al. (1978) found that after seven men were given single oral doses of chloral hydrate at 15 mg/kg, peak plasma TCE concentrations of 8.5 ± 1.5 mg/ℓ were reached in <2 hours. TCA accumulated in the plasma during the 24 hours after dosing. Mean serum half-lives of TCE and TCA were estimated at 8 and 75 hours, respectively. In another study by Sellers et al. (1978), the same seven subjects were given oral doses (15 mg/kg) of chloral hydrate each night for 8 nights. At the end of the dosing period, mean plasma TCA concentrations were 82.3 mg/ℓ, indicating that TCA tends to accumulate in the plasma.

5.3. METABOLISM

The metabolism of chloral is presented in Figure 5-1. Chloral is rapidly reduced to trichloroethanol (TCE). In vitro studies have shown that chloral is an effective substrate for the cytosolic, NADH requiring enzyme, alcohol dehydrogenase. In addition, in rat liver cytosol two additional NADPH-dependant enzymes have been demonstrated (U.S. EPA, 1985a). In vitro studies also indicate that chloral can be reduced by human red blood cells (Sellers et al., 1972).

As reviewed by U.S. EPA (1985a), the origin of the plasma and urinary metabolite trichloroacetic acid (TCA) is less clear. Acetaldehyde dehydrogenase had been proposed as a likely candidate for this oxidation reaction; however, chloral hydrate has been reported not to be a substrate for human acetaldehyde dehydrogenase. A chloral hydrate dehydrogenase has been reported in the rabbit. An aldehyde dehydrogenase prepared from rat liver mitochondria has been shown to convert chloral to TCA. While the liver appears to be the primary metabolic site, other tissues such as lung, brain and RBCs may be involved.

In 18 humans given a constant daily oral dose of chloral hydrate at 1-6 g for 5-20 days, Marshall and Owens (1954) estimated that 5-47% of the dose was oxidized to TCA. These values, estimated from the amount of TCA excreted in the urine, were minimum values according to the authors. Results of a single dose study showed that as much as 87% of chloral hydrate is metabolized to TCA in humans. In dogs, Marshall and Owens (1954) estimated that >26% of an oral dose of chloral hydrate was oxidized to TCA.

Müller et al. (1974) treated three male volunteers with a single oral dose of chloral hydrate at 15 mg/kg, and determined levels of TCE (free and glucuronide) and TCA in the urine for up to 168 hours after dosing. The

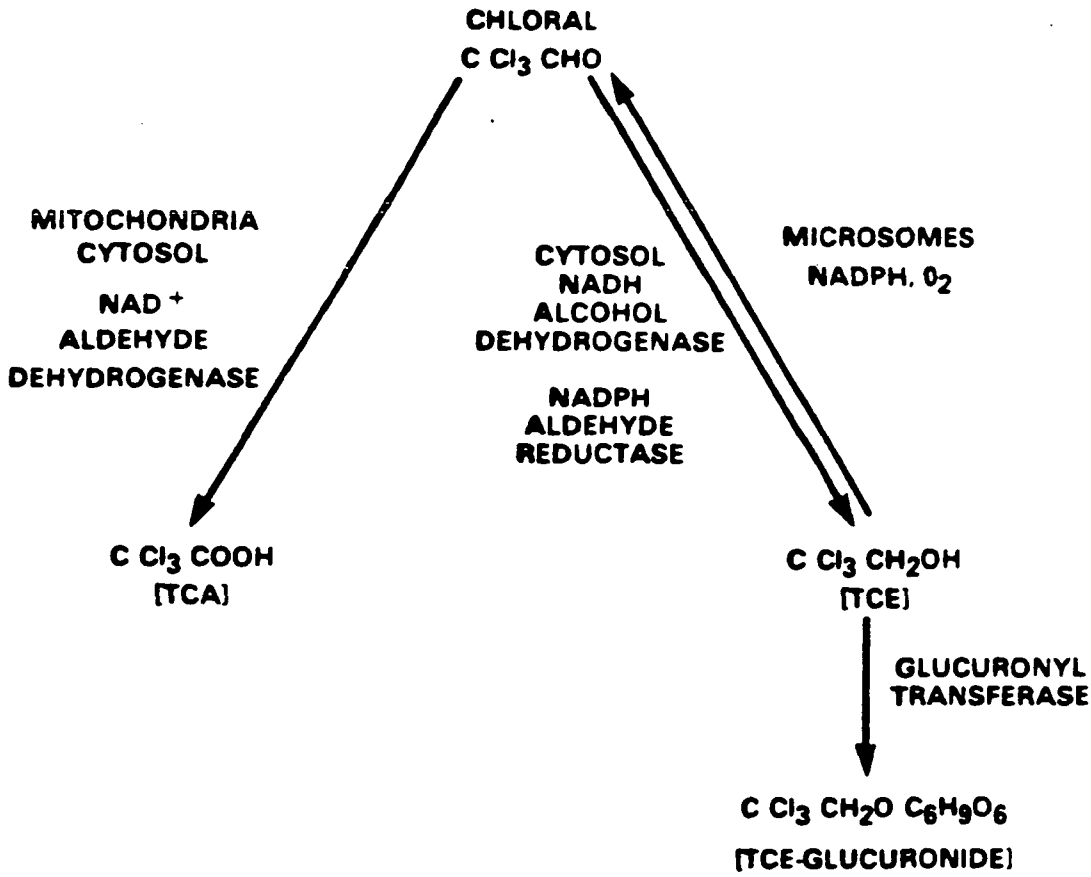


FIGURE 5-1

Metabolism of Chloral Hydrate

Source: Ikeda et al., 1980; U.S. EPA, 1985a

level of TCE in the urine accounted for ~23% of the dose, while the level of TCA accounted for ~24% of the dose.

In a study of chloral hydrate metabolism (Cabana and Gessner, 1970), male Swiss Webster mice were treated with an intraperitoneal injection of the compound at 500 mg/kg. Of the administered dose, 56% was reduced to TCE, 11% was oxidized to TCA, with ~9.6% not metabolized. These values are based on analysis of whole body homogenates at up to 360 minutes after dosing. Following injection of mice with TCE, TCA was not detected.

Peters et al. (1975) studied the metabolism of chloral hydrate in rhesus and squirrel monkeys treated by stomach tube with a single dose that resulted in similar sedative effects. Four male rhesus monkeys received doses of chloral hydrate at 500 mg/kg and six male squirrel monkeys were treated at 150 mg/kg. Plasma levels of TCE, TCE-G and TCA were determined 2, 4 and 7.5 hours after dosing. Chloral hydrate was not detected in the plasma from any monkey. At 2 hours after dosing, plasma levels of TCE, the active metabolite, were markedly lower in the squirrel monkey, but concentrations of TCE-G were 2-fold higher, indicating that the squirrel monkey has a greater capacity to detoxify TCE by glucuronide conjugation. The total levels of TCE and TCE-G in squirrel and rhesus monkeys were 103 and 136 μmol/100 mℓ, respectively. TCA was detected in the plasma of both species of monkeys, but at levels below TCE concentrations, indicating that the oxidation of chloral hydrate to TCA may be a less significant pathway. Because recovery of chloral hydrate metabolites was lower in the urine of squirrel monkeys compared with rhesus monkeys, the authors suggested that squirrel monkeys may be capable of forming a TCA conjugate that was not measured.

5.4. EXCRETION

In a comparative study where dogs and humans were treated orally with chloral hydrate, Marshall and Owens (1954) found that the dog excreted 0.83% of the total TCE in the urine as free TCE, with remaining TCE excreted as the glucuronide conjugate. In humans, 4.6% of the TCE in the urine was free-TCE. Renal excretion of free and conjugated TCE accounted for 16-35% of a 16.5 mg/kg dose of chloral hydrate given to six volunteers.

Müller et al. (1974) found that urinary TCE and TCA accounted for 47% of a single oral dose of 15 mg chloral hydrate/kg given to three volunteers. The determination of metabolite levels for up to 168 hours after dosing revealed that TCE levels in the urine peaked at 24 hours after dosing, while peak TCA levels were found at 48 hours. TCE was not detected in the urine 120 hours after dosing, while TCA was still detected 168 hours after dosing.

Sellers et al. (1978) collected urine from seven men for 36 hours after they received single oral doses of chloral hydrate at 15 mg/kg. After 6, 18 and 36 hours, 7.1, 10.5 and 24.1% of the dose was recovered as TCE, TCE-G and TCA. During the collection period, the proportion of TCA steadily increased.

Urinary excretion data for chloral hydrate metabolites in rhesus and squirrel monkeys are presented in Table 5-1. The monkeys were given single oral doses of chloral hydrate that resulted in a similar sedative effect. As indicated in Table 5-1, 76.1% of the dose administered to rhesus monkeys was recovered in the urine, while only 46.2% was recovered in urine from squirrel monkeys. Feces were not examined for metabolites.

Hobara et al. (1986) examined the biliary excretion of chloral hydrate and its metabolites in anesthetized dogs given single intravenous injections at 25 mg/kg. Analysis of bile samples taken at half-hour intervals for 2 hours showed that 19.2% of the dose was excreted in the bile, with 95.2% of

TABLE 5-1

Mean Cumulative Urinary Excretion (% of Dose) of Chloral Hydrate Metabolites by Five Male Rhesus Monkeys Receiving 500 mg Chloral Hydrate/kg and by Six Male Squirrel Monkeys Receiving 150 mg Chloral Hydrate/kg *per os**

Metabolite(s)	Time After Administration (hours)	Rhesus Monkeys Mean	Squirrel Monkeys Mean
TCE	24	0.51	0.36
	60	0.53	0.36
TCE-G	24	70.22	44.14
	60	71.1	45.2
TCA	24	3.73	0.19
	60	4.47	0.5
Total metabolites	24	74.57	44.79
	60	76.1	46.2

*Source: Peters et al., 1975

the biliary excretion in the form of conjugated TCE, 3% as chloral hydrate, 1% as free TCE and 0.8% as TCA.

5.5. SUMMARY

Since chloral hydrate is readily absorbed from the gastrointestinal tract and rapidly metabolized, only metabolites are detected in the blood. Chloral hydrate is metabolized to TCE and TCA, with further metabolism of TCE to TCA in humans and dogs (Marshall and Owens, 1954), but not in mice (Cabana and Gessner, 1970). In humans, the amount of TCA produced is highly variable; Marshall and Owens (1954) reported that 5-87% of an oral dose may be metabolized to TCA. TCE is conjugated with glucuronide and is excreted in the urine and bile (Harvey, 1975).

Studies of binding of TCA and TCE to plasma protein from monkeys and humans indicate similar levels of binding for TCE, with increased binding of TCA to plasma proteins from humans compared to monkeys (Peters et al., 1975). Plasma and urine levels of TCE and TCA in humans indicate that TCE is readily excreted, while the excretion of TCA is more prolonged.

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposures. The only inhalation data available were abstracts of two Russian studies. Biostov et al. (1970) exposed mice to chloral at 0.06 mg/ℓ (60 mg/m³) and reported depressed growth rate, leukocytosis, decreased A/G ratio and changes in arterial blood pressure and CNS responses. In a study by Pavlova (1975), rats and rabbits exposed to chloral at 0.1 mg/ℓ (100 mg/m³) developed altered CNS functions, impaired "antitoxic and enzyme-synthesizing" functions of the liver and morphological changes in the blood cells. These studies did not report either the frequency or duration of exposure.

6.1.2. Oral Exposures.

6.1.2.1. SUBCHRONIC -- Sanders et al. (1982) treated groups of 140 CD-1 mice/sex (4 weeks old at start of study) with chloral hydrate in the drinking water at 0.07 or 0.7 mg/mℓ for 90 days. Groups of 260 mice/sex provided with deionized water served as controls. Body weight and fluid consumption was determined twice weekly for 48 mice/sex for the control group and 32 mice/sex in the treatment groups. Based on these data, the TWA chloral hydrate intake was 18 and 173 mg/kg/day for females and 16 and 160 mg/kg/day for males at 0.07 and 0.7 mg/mℓ, respectively. Male mice showed a dose-dependent increase in body weight. This effect was confirmed by increased final body weights observed in mice used for gross pathology (n=15-21). A similar effect on growth rate was not observed in females, except body weights were increased compared with controls in female mice used for gross pathology (n=13-22) at 0.7 mg/mℓ. A significant ($p<0.05$) increase in both relative and absolute liver weight in males at both concentrations was observed. Lung and brain weights were slightly decreased in males, but the effect was not dose-related. Serum and liver chemistries,

which were examined in 4-8 mice/sex/group, provided further evidence that the liver is the target of chloral toxicity. In male mice, an increase in serum SGOT and LDH (but not SGPT) activity was observed. These increases were significant ($p<0.05$) in high-dose males. Hepatic microsomal aminopyrine N-demethylase and aniline hydroxylase activity and cytochrome b5 content were significantly increased ($p<0.05$) in males at both doses. Hepatic P-450 content was not increased. In females at 0.7 mg/mℓ, aniline hydroxylase activity was increased, while liver nonprotein sulfhydryl and cytochrome b5 levels were decreased. No dose-related changes in hematological, coagulation or urinalysis parameters were noted in either sex. Histopathological examinations were not performed.

Kauffmann et al. (1982) reported on the immunological status of 12 mice/sex from the exposure groups described in the Sanders et al. (1982) study. Humoral immunity, assessed by measuring the production of antibody-forming cells, hemagglutination titers and spleen cell response to lipopolysaccharide from Salmonella typhosa, showed no significant changes in male mice. In female mice, the number of antibody-forming cells (AFC) produced against sheep RBCs was depressed significantly on day 4 after immunization at both concentrations when expressed as AFC/spleen, but only at the high dose when expressed as AFC/10^6 cells. Other measures of humoral immunity, hemagglutination titers and spleen cell response to lipopolysaccharide were not affected in females. Cell-mediated immunity, measured by a delayed hypersensitivity to sheep RBC did not show a significant dose-related response in either male or female mice. The investigators concluded that the immune system was the most sensitive endpoint in female mice, with effects occurring at 0.07 mg/mℓ (18 mg/kg/day). The liver was the most sensitive endpoint in male mice, with effects also occurring at 0.07 mg/mℓ (16 mg/kg/day) (Sanders et al., 1982).

Kallman et al. (1984) exposed groups of 24 male CD-1 mice (~5 weeks old) to chloral hydrate in the drinking water for 90 days at the same doses and in the same manner as described for the Sanders et al. (1982) study. Each test group was divided into 2 squads of 12 mice that were subjected to different batteries of behavioral evaluations. Measurements completed on mice from squad 1 included weekly body weights, activity measurements during exposure, screen testing 24 hours after the last exposure day (91) and swimming endurance on day 92. In squad 2 mice, biweekly food consumption and rectal temperature on exposure days 45 and 91 were measured. Forepaw grip strength and response to olfactory and pain stimuli were measured in squad 2 mice on day 91, while passive avoidance learning (i.e., learning to avoid an electric shock) was examined on days 91 and 92. The results of the study did not show significant changes in any of the behavioral parameters. Body weights (squad 1) were significantly ($p<0.05$) reduced in both dose groups between weeks 5 and 7, but were similar to control levels by the end of the exposure period. Food intake was not affected by chloral treatment (squad 2). Body temperature was significantly ($p<0.05$) reduced in mice treated at 160 mg/kg/day at both day 45 and day 91 but was reduced significantly only on day 91 in mice treated at 16 mg/kg/day.

6.1.2.2. **CHRONIC** -- Pertinent data regarding the toxicity of chloral following chronic oral intake were not located in the available literature cited in Appendix A.

6.1.3. **Other Relevant Information.** Chloral hydrate was introduced as a therapeutic agent in 1869. The compound was used as a hypnotic until well into the 20th century, and it is still used as a sedative in humans (Sanders et al., 1982). Chloral hydrate is irritating to the skin and mucous membranes. Death in humans occurs at an oral dose of ~10 g, although death

has been reported at a dose of 4 g and individuals have survived oral doses of 30 g (Harvey, 1975). The recommended oral dose for the relief of insomnia in adults is 500 mg to 1 g, with some individuals requiring doses as high as 2 g. The therapeutic blood level for TCE, the active metabolite, is 10-15 μg/mℓ (Rumack and Peterson, 1980). Treatment with chloral hydrate causes an excessive contraction of the pupil of the eye (Hecht, 1978), and habitual use can result in the development of tolerance and addiction. Adverse side effects of chloral hydrate treatment at recommended doses include epigastric distress, nausea, vomiting, allergic skin reactions, eosinophilia and leukopenia. At higher doses, chloral hydrate can cause objects to appear smaller than they are (Hecht, 1978), and the compound has been reported to cause cardiac arrhythmia (Bowyer and Glasser, 1980; Wiseman and Hampel, 1978). In reviewing 12 cases of chloral hydrate poisoning, Wiseman and Hampel (1978) found no correlation between plasma TCE concentrations 24 hours after ingestion and cardiac effects.

Additional adverse reactions of chloral hydrate treatment include interactions with a number of drugs. In man, chloral hydrate accelerates the rate of metabolic disposition of the anticoagulants, dicumarol and warfarin with a potentially fatal outcome (Harvey, 1975). Because the metabolite, TCA, displaces acidic drugs from plasma proteins, chloral hydrate has the potential of interacting with many drugs. The potentiation of effects following co-administration of chloral hydrate and alcohol has long been known. This potentiation occurs because ethanol accelerates the reduction of chloral hydrate to the active TCE metabolite (Harvey, 1975).

Acute oral lethality data in animals are presented in Table 6-1. The lowest LD_{50} was observed in rats, with a value of 285 mg/kg in 1- to 2-day-old rats, and an LD_{50} of 479 mg/kg in adult rats (Goldenthal, 1971).

TABLE 6-1

Acute Oral Lethality Data of Chloral Hydrate

Species	Result (mg/kg)	Reference
Mouse, female	LD_{50} 1265	Sanders et al., 1982
Mouse, male	LD_{50} 1442	Sanders et al., 1982
Rat, adult	LD_{50} 479	Goldenthal, 1971
Rat, 1-2 days old	LD_{50} 285	Goldenthal, 1971
Rabbit	LD_{LO} 1000	Adams, 1943
Dog	LD_{LO} 1000	Adams, 1943
Cat	LD_{LO} 400	Adams, 1943

In a range-finding study (Sanders et al., 1982), groups of 60 male CD-1 mice were treated by gavage with chloral hydrate at 0, 14.4 or 144 mg chloral/kg for 14 consecutive days. Treatment-related deaths were not observed and body weights of treated mice were similar to controls. Organ weight measurements, completed on 11-12 mice/group, showed that liver weights were increased by 18% and spleen weights were decreased by 27% in the 144 mg/kg group compared with controls. These changes were significant at $p<0.05$. Similar but not significant changes in organ weights were observed at 14.4 mg/kg. No changes were noted in hematological parameters, coagulation values, SGPT activity or blood urea nitrogen levels (measured in 10-12 mice/group). Although LDH activity was significantly ($p<0.05$) depressed compared with controls, the authors stated that this effect was difficult to interpret because most reported abnormalities result in elevated LDH levels. Kauffmann et al. (1982) studied the immunological status of these mice. No significant ($p<0.05$) changes were noted in spleen weight, spleen antibody-forming cells or delayed type hypersensitivity response to sheep RBC.

Kallman et al. (1984) determined an ED_{50} of 84.5 mg chloral/kg for disruption of a motor coordination test (screen test) in male CD-1 mice 5 minutes after the mice were treated by gavage with a single dose of chloral hydrate. In male CD-1 mice treated by gavage with chloral hydrate for 14 days at 0, 14.4 or 144.4 mg chloral/kg/day, no effects on body weight or on a battery of behavioral tests (locomotor activity, screen test, swimming endurance) were observed (Kallman et al., 1984).

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the carcinogenicity of chloral following inhalation exposure were not located in the available literature cited in Appendix A.

6.2.2. Oral. Rijhsinghani et al. (1986) treated 15-day-old male C57BLxC3HF1 mice by gavage with a single dose of chloral hydrate in distilled water at 0 (35 mice), 5 (25 mice) or 10 μg/g (20 mice) body weight. Twenty-four hours after dosing, 6-10 mice in each group were sacrificed, and the mitotic index of liver cells was determined (Section 6.3.). The remaining mice were sacrificed when moribund or were killed at intervals up to 92 weeks after treatment. The livers of these mice were fixed and examined histologically. No hepatic nodules were observed in mice sacrificed before 48 weeks. In mice sacrificed between weeks 48 and 92, relative liver weights were increased at 10 μg/g compared with controls. Examination of the livers revealed a significant ($p<0.05$) increase in the number of mice with hepatic nodules in mice treated at 10 μg/g. The tumor incidences and the types of tumors found are presented in Table 6-2. As shown in Table 6-2, tumors in the treatment groups tended to appear earlier than in controls. The authors stated that their results indicated that the carcinogenic potency of chloral hydrate should be investigated further.

6.2.3. Other Relevant Information. Roe and Salaman (1955) studied the ability of chloral hydrate to initiate skin tumors in mice. Groups of 20 S strain male mice were given 2 weekly skin applications of chloral hydrate in acetone for a total dose of 24 or 225 mg. The chloral hydrate treatment was followed by 18 skin applications of 3 mℓ of a 0.5% croton oil solution. The croton oil treatment began 3 days after the first chloral hydrate application. A group of 20 mice receiving 18 croton oil applications served as controls. The described treatment resulted in a nonstatistically significant increase in skin tumors, with 4/17 and 4/20 mice with skin tumors in the low- and high-dose groups, respectively, compared with 1/20 control mice with tumors.

TABLE 6-2

Histological Classification of Hepatic Nodules and Their Distribution in C57BLxC3HF1 Male Mice Sacrificed Between Weeks 48 and 92 After a Single Intragastric Dose of Chloral Hydrate[a]

Dose of Chloral Hydrate (µg/g bw)	No. of Mice with Nodules/ No. of Mice Examined (%)	Histology of Hepatic Nodules[b]		
		Hyperplastic	Adenomatous	Trabecular Carcinoma
0.00	2/19 (10.5)	0	0	2 (89, 89)
5	3/9 (33.3)	1 (88)[c]	1 (50)	1 (78)
10	6/8 (75)[d]	0	3 (48, 67, 78)	3 (60, 78, 88)

QUALITY OF EVIDENCE

Strengths of study: Controls were used; the compound was administered daily.

Weaknesses of study: Inadequate numbers of mice of one sex were used; mice were treated with a single dose; mice were examined 48-92 weeks after dosing.

Overall adequacy: Inadequate

[a]Source: Rijhsinghani et al., 1986

[b]Nodules were categorized on the basis of the most advanced lesion in the nodule.

[c]Figures in parentheses represent the interval in weeks between the administration of chloral hydrate and sacrifice.

[d]The difference in the incidence of nodules between the groups given 10 µg/g of chloral hydrate and distilled water is significant ($p<0.05$).

TCA, which is a metabolite of both trichloroethylene and chloral, has been shown to be related to an increased incidence in liver carcinomas in mice exposed to TCA in their drinking water (Herren-Freund, 1986). These data are evaluated more fully in U.S. EPA (1987c).

6.3. MUTAGENICITY

The genotoxicity data for chloral and chloral hydrate are presented in Table 6-3. Both chloral and chloral hydrate have tested positive for mutation in Salmonella typhimurium, both with and without activation (Waskell, 1978; Bignami et al., 1980; Bruce and Heddle, 1979). Positive results for mutation have also been reported for chloral hydrate (but not chloral) in Streptomyces coelicolor, and both chloral and the hydrate have tested positive for mutation in Aspergillus nidulans (Bignami et al., 1980). Studies of mutation and mitotic gene conversion in Saccharomyces cerevisiae have found negative results for mutation with positive results for gene conversion (Bronzetti et al., 1984). Chloral hydrate has been evaluated for its ability to produce aneuploidy in several test systems.

Aneuploidy tests in A. nidulans have consistently shown positive results (Singh and Sinha, 1976; Crebelli et al., 1985; Käfer, 1986), and chloral hydrate has been shown to induce aneuploidy in S. cerevisiae (Sora and Carbone, 1987). In an in vivo study of chloral hydrate, an increase in nondisjunction of sperm from mice treated by an intraperitoneal injection has been reported (Russo et al., 1984). According to Russo et al. (1984), who reviewed studies in grasshopper spermatocytes (Ris, 1949) and in Pleurodeles waltlii eggs (Sentein and Ated, 1974), the target of chloral hydrate is the mitotic spindle. It appears to block spindle elongation.

Additional studies using mammals have not been conclusive. Cassidy and Boshell (1980) did not find any effects on mitosis in the basal cells of the tongue or acinar cells of the parotid gland from rats given a single

TABLE 6-3

Genotoxicity of Chloral and Chloral Hydrate

Assay	Indicator Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1535, TA1537 TA98, TA100	chloral hydrate	plate incorporation	0.05-5000 µg/plate	±S-9	‡	NC	Bruce and Heddle, 1979
	S. typhimurium TA100, TA98, TA1535, his G	chloral hydrate/ recrystallized	plate incorporation	10 mg/plate	±S-9	weakly ‡ in TA100, - in TA98, TA1535 and his G	Chloral hydrate resulted in 0.00145 revertants/mol compared with 0.06 revertants/mol for the (+) control diethyl sulfate	Waskell, 1978
	S. typhimurium TA100, TA1535	chloral	plate incorporation and spot test	0.25-1 µl/plate	±S-9	‡ in TA100 - in TA1535	Number of revertants greater without S-9	Bignami et al., 1980
	S. typhimurium TA100, TA1535	chloral hydrate	plate incorporation and spot test	1-5 mg/plate	±S-9	‡ in TA100 - in TA1535	NC	Bignami et al., 1980
Reverse and forward mutation	Streptomyces coelicolor A3(2)	chloral	plate incorporation and spot test	10-40 µl/plate	none	-	NC	Bignami et al., 1980
	S. coelicolor A3(2)	chloral hydrate	plate incorporation and spot test	2-10 mg/plate	none	weakly +	Weakly + for both forward and reverse mutations	Bignami et al., 1980
Forward mutation	Aspergillus nidullans 35	chloral	plate incorporation and spot test	1-20 µl/plate	none	weakly +	NC	Bignami et al., 1980
	A. nidullans 35	chloral hydrate	plate incorporation and spot test	1-10 mg/plate	none	weakly +	NC	Bignami et al., 1980
Reverse mutation, mitotic gene conversion	Saccharomyces cerevisiae D7	chloral hydrate	suspension test	5-20 mM	±S-9	- mutation ± gene conversion	A dose-related increase in gene conversion was observed only with metabolic activation	Bronzetti et al., 1984

TABLE 6-3 (cont.)

Assay	Indicator Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation, mitotic gene conversion	S. cerevisiae D7	chloral hydrate	host-mediated assay, mice were treated orally	500 mg/kg	NA	- mutation + gene conversion	+ results were observed in the tester strain recovered from the lungs but not the liver or kidney	Bronzetti et al., 1984
Induced aneuploidy	S. cerevisiae	chloral hydrate/ 99%	dissolved in sporulation media	1-25 mM	none	+	Sporulation was inhibited and a net increase of diploid and disomic clones was observed	Sora and Carbone, 1987
	A. nidulans diploid	chloral hydrate	plate incorporation	0.001-0.04 M	none	+	An increased number of haploids was observed	Singh and Sinha, 1976
	A. nidulans 35y17	chloral hydrate/ 99%	plate incorporation	5, 10 mM	none	+	Chloral hydrate induced haploid and nondisjunctional diploid somatic segregants	Crebelli et al., 1985
	A. nidulans	chloral hydrate/ lab grade	"in liquid"	5-40 mM	none	+	Chloral hydrate induced polyploidy	Käfer, 1986
Sex-linked recessive lethal	Drosophila melanogaster	chloral hydrate/ 99%	feeding injection	5500 ppm 10,000 ppm	NA	equivocal feeding, - injection	% lethal in flies fed chloral hydrate was 0.13 compared with 0.04-0.05 in controls and those injected with chloral hydrate	Yoon et al., 1985
Effects on mitosis in basal cells of tongue and acinar cells of parotid gland	rats, 8 weeks old	chloral hydrate	injected (specific route not stated)	200 mg/kg	NA	-	3 rats/group (- control, + control, treatment group)	Cassidy and Boshell, 1980
Micronucleus, sperm abnormalities	C57Bl/6y C3H/He mice	chloral hydrate	intraperitoneal injections, 5 daily doses	0-2500 mg/kg	NA	-	Micronucleus studies were conducted 4 hours after the last injection; sperm were examined 35 days after the last injection	Bruce and Heddle, 1979

TABLE 6-3 (cont.)

Assay	Indicator Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Testicular DNA synthesis	mice, 3-Y	chloral hydrate	oral	50 mg/kg	NA	-	A decrease in DNA synthesis was not observed	Seiler, 1977
	mice, ICR Swiss Webster	chloral hydrate	intratesticular injection	10-900 mg/kg	NA	+ at doses ≥75 mg/kg	At 75 mg/kg, DNA synthesis was 30% of control; at 300 mg/kg, DNA synthesis was 3% of control	Borzelleca and Carchman, 1982
Nondisjunction in sperm	mice (C57Bl/Cncx C3H/Cnc) F_1	chloral hydrate/ 99%	intraperitoneal injection	82.7, 165.4, 413.5 mg/kg	NA	+ at each dose and cell stage - the index of hyperhaploidy was greater than controls	Mice treated at high dose remained under anesthesia for ~5 hours; mice sacrificed at 5, 12, 21 or 42 days after treatment	Russo et al., 1984
Mitotic index	C57BLxC3HF1 mice	chloral hydrate/ laboratory grade	oral, single dose	5 or 10 µg/g	NA	increased mitotic index of liver cells - significantly increased only at 5 µg/g	Mitotic indices were determined 24 hours after mice were treated	Rijhsinghani et al., 1986

NA = Not applicable; NC = no comment

injection of chloral hydrate. An increase in the mitotic index of liver cells was observed in mice given a single oral dose of chloral hydrate (Rijhsinghani et al., 1986).

6.4. TERATOGENICITY

In a study by Kallman et al. (1984), female CD-1 mice were provided with drinking water containing chloral at 0, 0.06 or 0.6 mg/mℓ for 3 weeks before mating, during gestation and until the pups were weaned. Five litters were studied at each concentration. Measurement of water intake during gestation indicated that chloral intake was 21.3 and 204.8 mg/kg/day for the 0.06 and 0.6 mg/mℓ groups, respectively. No effects were noted on the total litter weight, number of pups delivered, gestation length, the number of stillborn pups, gross pup malformations or maternal weight gain. However, it is clear that a maximal tolerated dose was not tested. In addition, evaluation for skeletal defects or soft tissue defects not other than those apparent during gross examination was not conducted. On the day of birth (day 0), the litters were culled to eight pups. During the pre-weaning period, drinking solutions were available to the pups. Behavioral testing of pups was conducted from days 1-17, with a screen test completed on day 17, and passive avoidance learning tested on days 23 and 24. No effects were noted on the following behaviors: righting reflex, forelimb placing, forepaw grasping, rooting reflex, eye opening, auditory startle, bar holding, cliff drop and screen test. Results of a passive avoidance learning test showed a significant impairment of retention of the task in mice exposed to 0.6 mg/mℓ perinatally. Because the preweaning mice had access to the chloral hydrate containing drinking water, it is not clear if the observed behavioral effect was a result of <u>in utero</u> or postnatal exposure. No effects on passive avoidance learning were observed at 0.06 mg/mℓ.

6.5. OTHER REPRODUCTIVE EFFECTS

Sperm abnormalities were not observed in groups of eight mice given 5 daily intraperitoneal injections of chloral hydrate at up to 2500 mg/kg (Bruce and Heddle, 1979). The sperm were examined 35 days after the last injection.

Borzelleca and Carchman (1982) treated male ICR Swiss albino mice with intratesticular injections of chloral hydrate at 10-900 mg/kg, followed by an intratesticular injection of tritiated thymidine 3.5 hours later. After 0.5 hours, the mice were sacrificed, and the amount of newly synthesized DNA was determined. The results indicated that doses $\geq$75 mg/kg caused a significant inhibition of DNA synthesis, with synthesis 30% of control values at 75 mg/kg and 3% of control values at 300 mg/kg. Seiler (1977) found no effects on testicular DNA synthesis in mice treated orally with chloral hydrate.

6.6. SUMMARY

Inhalation studies of chloral are limited to abstracts of Russian studies (Biostov et al., 1970; Pavlova, 1975) that reported adverse effects but did not report the frequency or duration of exposure.

Oral toxicity studies of chloral consist of a series of 90-day studies in which mice were provided with drinking water containing chloral at 0.07 or 0.7 mg/mℓ (Sanders et al., 1982; Kauffmann et al., 1982; Kallman et al., 1984). The most sensitive endpoint of toxicity in male mice was liver toxicity (Sanders et al., 1982), while the most sensitive endpoint in female mice was immunotoxicity (Kauffmann et al., 1982). Both effects were observed at 0.07 mg/mℓ, a dose of 16 mg/kg/day in males and 18 mg/kg/day in females. No effects on behavior were observed in male mice, although body temperature was found to be depressed at both concentrations (Kallman et al., 1984).

Chloral hydrate has been used as a sedative for humans. Adverse effects that have been reported at therapeutic doses (0.5-2 g) include epigastric distress, nausea, vomiting, allergic skin reactions, eosinophilia, leukopenia and interactions with a number of drugs (Harvey, 1975). At higher doses, chloral hydrate has been reported to cause cardiac arrhythmias (Bowyer and Glasser, 1980; Wiseman and Hampel, 1978).

Chloral hydrate is lethal to humans at a dose of ~10 g (Harvey, 1975). An oral LD_{50} of 479 mg/kg has been reported in adult rats (Goldenthal, 1971). Kallman et al. (1984) reported an ED_{50} of 84.5 mg chloral/kg for disruption of a screen test in male mice 5 minutes after the mice were treated by gavage with chloral hydrate.

A single dose oral study reported a dose-related increase in liver tumors in mice examined 48-92 weeks after they were treated with chloral hydrate at 5 or 10 μg/g (Rijhsinghani et al., 1986). The increase was statistically significant only at 10 μg/g. A nonstatistically significant increase in skin tumor incidences was observed in mice given 2 weekly applications of chloral hydrate followed by 18 weekly applications of croton oil. Studies of DNA effects have reported positive results in mutation assays and assays of aneuploidizing activity, and chloral hydrate was found to decrease testicular DNA synthesis in an intratesticular injection study using mice (Borzelleca and Carchman, 1982).

Chloral hydrate exposure did not result in any changes in litter parameters or in any gross malformations in offspring of mice provided with drinking water containing chloral hydrate at 0.06 or 0.6 mg chloral/mℓ from 3 weeks before mating through weaning (Kallman et al., 1984). At 0.6 mg/mℓ, an impairment of retention of an avoidance learning task was

observed in 24-day-old mice. Because pups had access to the chloral hydrate dosing solution, it is not clear if the effect was a result of *in utero* or postnatal exposure.

7. EXISTING GUIDELINES AND STANDARDS

U.S. EPA (1987b) has proposed an RQ of 5000 for chloral. No other pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits were located in the available literature as cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the carcinogenicity of chloral following inhalation exposure were not located in the available literature cited in Appendix A.

8.1.2. Oral. In a study by Rijhsinghani et al. (1986), a dose-related increase in liver tumor incidence was observed in mice sacrificed 48-92 weeks after being given a single gavage dose of chloral hydrate at 0, 5 or 10 μg/g. Liver tumors were significantly ($p<0.05$) increased only at 10 μg/g.

8.1.3. Other Routes. In a 2-stage skin carcinogenicity study, Roe and Salaman (1955) found a nonsignificant increase in skin tumors in mice given 2 weekly treatments of chloral hydrate, followed by 18 weekly applications of croton oil.

8.1.4. Weight of Evidence. There are no human data indicating that chloral is a carcinogen. The Rijhsinghani et al. (1986) mouse bioassay study is inadequate for quantitative assessment. Mice were treated only once and few mice were at risk for tumor development. Despite these limitations, the Rijhsinghani et al. (1986) gavage study in mice provides limited evidence that chloral may be a carcinogen. In this study, high-dose animals showed a significant increase in numbers of hepatic nodules and 2/3 carcinomas occurred much earlier than the two carcinomas in the control group. Positive results in mutagenicity assays also suggest the presence of genotoxic activity which may be consistent with carcinogenic mechanisms. In addition, TCA, a metabolite of chloral, has been shown to be carcinogenic (Herren-Freund, 1986). Chloral and TCA are the metabolites suggested to be involved in the carcinogenicity of trichloroethylene (U.S. EPA, 1987c). Using the EPA Guidelines for Carcinogen Risk Assessment, the positive

albeit less than ideal bioassay response in male mice together with indications of genotoxicity and knowledge of metabolites which are by bioassay shown to be carcinogenic, combined with a lack of chronic human data places chloral in weight of evidence Group C.

8.1.5. Quantitative Risk Estimates. The only positive carcinogenicity study of chloral available is the single dose study by Rijhsinghani et al. (1986). This study has too many limitations to support a reasonable derivation of a carcinogenic potency estimate as discussed in Section 8.1.4. An examination of the Herren-Freund (1986) dose-response data in the mouse liver together with the Rijhsinghani (1986) mouse liver responses and approximations with percent TCA produced as a metabolite of chloral might yield a basis for quantitative assessment. This analysis, however, is outside of the scope of this document.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposures. Lack of data concerning the toxicity of chloral hydrate following inhalation exposure precludes the derivation of subchronic and chronic inhalation RfDs.

8.2.2. Oral Exposures.

8.2.2.1. LESS THAN LIFETIME EXPOSURES -- The data concerning the subchronic oral toxicity of chloral are limited to a series of 90-day studies in which mice were provided with drinking water containing chloral hydrate at 0, 0.07 or 0.7 mg/mℓ (Sanders et al., 1982; Kauffmann et al., 1982; Kallman et al., 1984). Measurement of water intake indicated that male mice consumed averages of 16 or 160 mg chloral hydrate/kg/day and female mice consumed an average of 18 or 173 mg chloral hydrate/kg/day. Female mice were not studied in the Kallman et al. (1984) 90-day study. In the Sanders et al. (1982) study, a significant dose-related increase in relative liver

weights was observed in male but not female mice. Serum SGOT and LDH activity were significantly increased in high-dose males, and increased microsomal cytochrome b5 content and aminopyrine N-demethylase and aniline hydroxylase activities were significantly increased in males at both doses. In high-dose females, aniline hydroxylase activity was increased, while liver nonprotein sulfhydryl and cytochrome b5 levels were decreased. No significant changes were noted in low-dose females.

Kauffmann et al. (1982) studied the immune status of mice treated with chloral hydrate. The only significant effect noted was a significant depression in the number of antibody-forming cells (AFC) produced against sheep RBC on day 4 after immunization in female mice at both concentrations. However, this reflects data expressed as AFC/spleen when results were expressed as AFC/10^6 cells only the high dose was significantly different than controls. Other measures of humoral immunity were not affected. The authors did state that the AFC test was the most sensitive indicator.

Kallman et al. (1984) did not observe any effects on the behavior of male mice treated with chloral hydrate in the drinking water. Body temperature was significantly reduced on days 45 and 91 at 160 mg/kg/day and on day 91 at 16 mg/kg/day. In a behavioral teratology study (Kallman et al., 1984), no effects were noted in mice from dams treated at 21.3 mg chloral/kg/day from 3 weeks before mating through weaning, while passive avoidance learning was significantly affected in mice from dams treated at 204.8 mg/kg/day.

The results of these studies indicate that the liver is the most sensitive target of chloral toxicity in male mice, while the immune system may be the most sensitive endpoint in female mice. Liver effects in male mice provided with drinking water containing chloral hydrate at 0.07 mg chloral hydrate/mℓ, resulted in the lowest LOAEL of 16 mg/kg/day. While increases

in liver weight and associated increases in enzyme activity are not necessarily indicative of an adverse effect, the absence of confirmatory histopathological data makes it difficult to rule out an adverse effect. This dose is well below the dose of 204.8 mg/kg/day that resulted in behavioral effects in mice exposed in utero and postnatally.

A subchronic oral RfD of 0.02 mg chloral hydrate/kg/day or 1 mg/day for a 70 kg human, may be derived from the lowest LOAEL of 16 mg chloral/kg/day by dividing the LOAEL by an uncertainty factor of 1000, 10 to extrapolate from animals to humans, 10 to estimate a NOEL from a LOAEL and 10 to protect sensitive individuals. While this document is intended to develop an RfD for chloral per se, it is not considered appropriate to convert the dose to an equivalent chloral concentration. Since chloral rapidly is converted to chloral hydrate in an aqueous environment, expression of the dose as chloral hydrate is considered appropriate.

Confidence in this RfD is low. The limited studies available did not identify a FEL, NOAEL or NOEL. The effects observed were marginal and histopathological examinations were not completed. In addition, the metabolism of chloral is known to differ between mice and humans.

8.2.2.2. CHRONIC EXPOSURES -- Chronic oral studies of chloral were not available. A chronic oral RfD of 0.002 mg chloral hydrate/kg/day or 0.1 mg/day for a 70 kg human can be derived by dividing the subchronic oral RfD by an additional uncertainty factor of 10 to extrapolate from subchronic exposure.

Confidence in this RfD is low because it is based on a 90-day mouse study that did not define a NOEL or NOAEL and did not include histopathological examinations. In addition, there are no supporting studies, and it is known that the metabolism of chloral in mice is different from that in humans.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The toxicity of chloral was discussed in Chapter 6. The only data suitable for the derivation of an RQ are the drinking water studies, which are summarized in Table 9-1. In the study by Sanders et al. (1982), effects on the liver were observed in male mice treated with chloral hydrate in the drinking water at a dose of 16 mg chloral/kg/day for 90 days. In female mice treated at 173 mg/kg/day for 90 days, immune system effects were observed (Kauffmann et al., 1982). Kallman et al. (1984) found an impairment in retention of a passive avoidance task in the offspring of mice treated with chloral hydrate in the drinking water at 204.8 mg chloral/kg/day from 3 weeks before mating through weaning. Because the offspring and dams had access to the drinking water containing chloral, it is not clear if the observed effect was a result of pre- or postnatal exposure.

The derivations of CS and RQ values are presented in Table 9-2. Possible developmental behavioral effects in mice (an RV_e of 9) were observed at a human MED of 1078 mg/day, which corresponds to an RV_d of 1 (Kallman et al., 1984). Multiplying the RV_e by the RV_d, a CS of 7 is calculated. This value is not adjusted for duration because the entire period of gestation and neonatal development was encompassed by the exposure protocol. Other portions of this study illustrated that behavioral effects were not seen in adult animals at similar exposures. Higher CS values are calculated from the 90-day drinking water study. The liver effects in male mice (Sanders et al., 1982) and the immune system effects in female mice (Kauffmann et al., 1982) occurred at human MEDs of 8.8 and 87, respectively, which correspond to RV_ds of 4.1 and 2.6. The liver effects in male mice

TABLE 9-1

Toxicity Summary for Chloral (>99% Purity) Administered to Mice in Drinking Water

Sex	Number at Start	Average Weight (kg)	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
M	140 total	0.034[b]	0.07 mg/ℓ drinking water for 90 days	16[c]	1.26	Increased liver weights, SGOT and LDH, increased hepatic microsomal aminopyrine N-demethylase and aniline hydroxylase activity	Sanders et al., 1982
M	11	0.031[b]	0.7 mg/ℓ drinking water for 90 days	160[c]	12.1	Increased liver weights, and increases in serum SGOT and LDH, increased hepatic microsomal aminopyrine N-demethylase and aniline hydroxylase activity	Sanders et al., 1982
F	12	0.026[b]	0.07 mg/ℓ drinking water for 90 days	173[c]	12.4	Decrease in the number of antibody-forming cells per 10^6 cells	Kauffmann et al., 1982
F	5	0.03[d]	0.60 mg/mℓ drinking water 3 weeks before mating through weaning	204.8[c]	15.4	Impairment in retention of a passive avoidance task in offspring	Kallman et al., 1984

[a]Calculated by multiplying the animal transformed dose by the cube root of the ratio of the animal body weight to the reference human body weight (70 kg).

[b]Estimated from growth curves in the study

[c]Dosage estimated by investigators

[d]Reference mouse body weight (U.S. EPA, 1985c)

TABLE 9-2

Composite Scores for Chloral from Oral Studies in Mice

Animal Dose (mg/kg/day)	Chronic Human MED* (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
16	8.82*	4.1	Liver toxicity - increased weight, enzyme induction	4	16.4	1000	Sanders et al., 1982
160	85.4	2.6	increases in serum SGOT and LDH	6	15.6	100	Sanders et al., 1982
18	8/*	2.6	Decrease in the number of antibody-forming cells	5	13	1000	Kauffman et al., 1982
204.8	1078	1	Behavioral changes in off-spring	7	7	1000	Kallman et al., 1984

*The dose was divided by an uncertainty factor of 10 to approximate chronic exposure.

correspond to an RV_e of 4, and the immune system effects to an RV_e of 5. The severity of the liver effects was increased at the high dose in male mice at this dose level (160 mg/kg/day), the associates MED is 85.4. The increases in the serum enzymes SGUT and LDN suggests cellular necrosis resulting in an RV_e of 6. Mutiplying by the RV_d of 26 results in a CS of 15.6 which also corresponds to an RQ of 1000.

The CS of 16.4 derived from the liver effects in male mice observed in the 90-day study (Sanders et al., 1982) corresponding to an RQ of 1000 is selected to represent the toxicity of chloral and is presented in Table 9-3.

9.2. BASED ON CARCINOGENICITY

Rijhsinghani et al. (1986) found a dose-related significant increase in liver tumor incidence in mice sacrificed 48-92 weeks after being given a single gavage dose of chloral hydrate at 0, 5 or 10 μg/g. In a study by Roe and Salaman (1955), a nonsignificant increase in skin tumors in mice was observed in a 2-stage carcinogenicity study.

There are no human data indicating that chloral is a carcinogen. The Rijhsinghani et al. (1986) mouse bioassay study is inadequate for quantitative assessment. Mice were treated only once and few mice were at risk for tumor development. Despite these limitations, the Rijhsinghani et al. (1986) gavage study in mice provides limited evidence that chloral may be a carcinogen. In this study, high-dose animals showed a significant increase in numbers of hepatic nodules and 2/3 carcinomas occurred much earlier than the two carcinomas in the control group. Positive results in mutagenicity assays also suggest the presence of genotoxic activity which may be consistent with carcinogenic mechanisms. In addition, TCA, a metabolite of chloral, has been shown to be carcinogenic (Henen-Feund, 1986). Chloral and TCA are the metabolites suggested to be involved in the carcinogenicity of trichloroethylene (U.S. EPA, 1987c). Using the EPA

TABLE 9-3

Chloral
Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	8.82 mg/day
Effect:	liver toxicity - decreased liver weight and enzyme induction
Reference:	Sanders et al., 1982
RV_d:	4.1
RV_e:	4
Composite Score:	16.4
RQ:	1000

*Equivalent human dose

Guidelines for Carcinogen Risk Assessment, the positive albeit less than ideal bioassay response in male mice together with indications of genotoxicity and knowledge of metabolites which are by bioassay shown to be carcinogenic, combined with a lack of chronic human data places chloral in weight of evidence Group C. Because the best available data are inadequate to calculate a potency factor, chloral is assigned a Potency Group of 2. Chloral, with an EPA Group of C and a Potency Group of 2, corresponds to a Hazard Ranking of LOW, which is assigned an RQ of 100.

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APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB

These searches were conducted in October 1987, and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

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Grayson, M. and D. Eckroth, Ed. 1978-1984. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

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Jaber, H.M., W.R. Mabey, A.T. Lieu, T.W. Chou and H.L. Johnson. 1984. Data acquisition for environmental transport and fate screening for compounds of interest to the Office of Solid Waste. EPA 600/6-84-010. NTIS PB84-243906. SRI International, Menlo Park, CA.

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Sax, I.N. 1984. Dangerous Properties of Industrial Materials, 6th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1987. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1986. Report on Status Report in the Special Review Program, Registration Standards Program and the Data Call in Programs. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

USITC (U.S. International Trade Commission). 1986. Synthetic Organic Chemicals. U.S. Production and Sales, 1985, USITC Publ. 1892, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

Summary Table for Chloral

	Species	Exposure	Effect	RfD or q_1*	Reference
Inhalation Exposure					
Subchronic	ID	ID	ID	ID	ID
Chronic	ID	ID	ID	ID	ID
Oral Exposure					
Subchronic	mouse, male	0.07 mg/mℓ in the drinking water for 90 days (16 mg/kg/day)	increase in relative liver weights, increase in serum SGOT and LDH activity	1 mg/day	Sanders et al., 1982
Chronic	mouse, male	0.07 mg/mℓ in the drinking water for 90 days (16 mg/kg/day)	increase in relative liver weights, increase in serum SGOT and LDH activity	0.1 mg/day	Sanders et al., 1982
REPORTABLE QUANTITIES					
Based on chronic toxicity:		1000 pounds			Sanders et al., 1982
Based on carcinogenicity:		100 pounds			Sanders et al., 1982

ID = Insufficient data