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Ambient Water Quality Criteria for Chloroform

AMBIENT WATER QUALITY CRITERIA FOR

CHLOROFORM

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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CRITERIA DOCUMENT

CHLOROFORM

CRITERIA

Aquatic Life

The available data for chloroform indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 28,900 µg/l, and would occur at lower concentrations among species that are more sensitive than the three tested species. Twenty-seven-day LC_{50} values indicate that chronic toxicity occurs at concentrations as low as 1,240 µg/l, and could occur at lower concentration among species or other life stages that are sensitive than the earliest life cycle stage of the rainbow trout.

The data base for saltwater species is limited to one test and no statement can be made concerning acute or chronic toxicity.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of chloroform through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentrations should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 1.90 µg/l, 0.19 µg/l, and 0.019 µg/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 157 µg/l, 15.7 µg/l, and 1.57 µg/l, respectively.

INTRODUCTION

Chloroform ($CHCl_3$) was first employed as an anesthetic agent in 1847. Only a small amount was necessary to induce narcosis, and its action was more complete than ether. Today, it has been replaced by other anesthetics with more desirable properties; but it is used widely as a chemical solvent and as an intermediate in the production of refrigerants, plastics, and pharmaceuticals (U.S. EPA, 1975). Current annual production of chloroform approaches 120,000 metric tons (U.S. EPA, 1977).

Chloroform ($CHCl_3$; molecular weight 119.39), at ordinary temperatures and pressures, is a clear, colorless, volatile liquid with a pleasant, etheric, nonirritating odor and sweet taste (Hardie, 1964; Windholz, 1976). It has a boiling point range of 61-62°C, a melting point of -63.5°C, and is nonflammable. There is no flash point (Hardie, 1964; Windholz, 1976). Chloroform is slightly soluble in water (7.42×10^6 μg/l of water at 25°C). It is miscible with alcohol, benzene, ether, petroleum ether, carbon tetrachloride, carbon disulfide, and oils (Windholz, 1976). Chloroform is highly refractive and has a vapor pressure of 200 mm Hg at 25°C (Irish, 1962; Windholz, 1976). Because of its volatile nature, chloroform has the potential for evaporation to the air from pollution sources or from the water column.

At ambient environmental temperatures, chloroform is thermostable and resists decomposition (Hardie, 1964). However, slow decomposition occurs following prolonged exposure to sunlight and in darkness when air is present (Hardie, 1964). Chloroform has the potential to react with, and thereby deplete, the ozone layer; studies have shown that phosgene is a decomposition

product of ozone and chloroform (Hardie, 1964). There is no appreciable decomposition of chloroform at ambient temperatures in water, even in the presence of sunlight (Hardie, 1964). Aqueous degradation of chloroform is accelerated in the presence of aerated waters and metals, such as iron, with hydrogen peroxide representing a reaction product (Hardie, 1964).

Chloroform appears to be ubiquitous in the environment in trace amounts, and discharges into the environment result largely from chlorination of water and wastewater (U.S. EPA, 1975).

REFERENCES

Hardie, D.W.F. 1964. Chlorocarbons and Chlorohydrocarbons: Chloroform. In: D.F. Kirk and D.E. Othmer (eds.), Encyclopedia of Chemical Technology. 2nd ed. John Wiley and Sons, Inc., New York.

Irish, D.D. 1962. Aliphatic Halogenated Hydrocarbons. In: Industrial Hygiene and Toxicology. 2nd ed. John Wiley and Sons, Inc., New York.

U.S. EPA. 1975. Development document for interim final effluent limitations guidelines and new source performance standards for the significant organic products segment of the organic chemical manufacturing point source category. EPA 440/1-75-045. U.S. Environ. Prot. Agency, Washington, D.C.

U.S. EPA. 1977. Determination of sources of selected chemicals in water and amounts from these sources. Area 1. Task 2. Draft final report. Contract No. 68-01-3852. U.S. Environ. Prot. Agency, Washington, D.C.

Windholz, M. (ed.) 1976. The Merck Index. 9th ed. Merck and Co., Inc., Rahway, New Jersey.

Aquatic Life Toxicology*

INTRODUCTION

Chloroform has been most commonly tested under static conditions with no measurement of the concentrations of chloroform to which the organisms are exposed. Consequently, the acute toxicity data base will probably underestimate the toxicity because concentrations in static tests are likely to diminish during the progress of the exposure as a result of loss from water to air.

EFFECTS

Acute Toxicity

A 48-hour static test with *Daphnia magna* resulted in an LC_{50} of 28,900 µg/l (Table 1). Bentley, et al. (1975) compared the toxicity of chloroform to rainbow trout and to bluegill and found (Table 1) that the trout was more sensitive. All 96-hour LC_{50} values for freshwater fish, using static methods and unmeasured concentrations, were between 43,800 and 115,000 µg/l.

Only one appropriate acute test has been reported on the toxicity of chloroform to saltwater aquatic life. Bentley, et al. (1975) conducted a static test with pink shrimp and determined a 96-hour LC_{50} value of 81,500 µg/l (Table 1).

Chronic Toxicity

No chronic effects of chloroform on freshwater or saltwater species are available other than those in Table 3.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

Residues

After a 14-day exposure (U.S. EPA, 1978) to radiolabeled chloroform, the bluegill bioconcentrated chloroform by a factor of 6 times (Table 2) and the tissue half-life was less than 1 day. This degree of bioconcentration and short biological half-life suggest that residues of chloroform would not be an environmental hazard to consumers of aquatic life.

Miscellaneous

Most of these data are compiled from short exposures of minutes to a few hours in duration (Table 3). With stickleback, goldfish, and orangespotted sunfish, anesthetization or death occurred at concentrations between 97,000 and 296,640 µg/l. Birge, et al. (1979) conducted flow-through tests with measured chloroform concentrations in closed systems. Exposures of rainbow trout began within 20 minutes after fertilization and ended eight days after hatching. There was no additional mortality between the fourth and eighth days after hatching. The 27-day LC_{50} values for soft and hard water were 2,030 and 1,240 µg/l, respectively. There was a 40 percent incidence of teratogenesis in the embryos at hatching.

Summary

Two freshwater fish and one invertebrate species have been acutely tested under standard conditions and 50 percent effect concentrations were between 28,900 and 115,000 µg/l. Embryo-larval tests with rainbow trout at two levels of hardness provided 27-day LC_{50} values of 2,030 and 1,240 µg/l. There was a 40 percent occurrence of teratogenesis after a 23-day exposure of rainbow trout embryos. The equilibrium bioconcentration factor for the bluegill was 6, which indicates that residues should not be a problem in the aquatic ecosystem.

Only one test has been conducted with chloroform and saltwater organisms. The 96-hour LC_{50} for the pink shrimp was 81,500 µg/l.

CRITERIA

The available data for chloroform indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 28,900 µg/l, and would occur at lower concentrations among species that are more sensitive than the three tested species. Twenty-seven-day LC_{50} values indicate that chronic toxicity occurs at concentrations as low as 1,240 µg/l, and could occur at lower concentrations among species or other life stages that are more sensitive than the earliest life cycle stage of the rainbow trout.

The data base for saltwater species is limited to one test and no statement can be made concerning acute and chronic toxicity.

Table 1. Acute values for chloroform

Species	Method*	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
		FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	S, U	28,900	28,900	U.S. EPA, 1978
Rainbow trout, *Salmo gairdneri*	S, U	66,800	-	Bentley, et al. 1975
Rainbow trout, *Salmo gairdneri*	S, U	43,800	54,000	Bentley, et al. 1975
Bluegill, *Lepomis macrochirus*	S, U	115,000	-	Bentley, et al. 1975
Bluegill, *Lepomis macrochirus*	S, U	100,000	110,000	Bentley, et al. 1975
		SALTWATER SPECIES		
Pink shrimp, *Penaeus duorarum*	S, U	81,500	81,500	Bentley, et al. 1975

* S = static, U = unmeasured

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Residues for chloroform (U.S. EPA, 1978)

Species	Tissue	Bioconcentration Factor	Duration (days)
	FRESHWATER SPECIES		
Bluegill, *Lepomis macrochirus*	whole body	6	14

Table 3. Other data for chloroform

Species	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES		
Rainbow trout (embryo-larval), *Salmo gairdneri*	27 days	LC50 at 50 mg/l hardness	2,030	Birge, et al. 1979
Rainbow trout (embryo-larval), *Salmo gairdneri*	27 days	LC50 at 200 mg/l hardness	1,240	Birge, et al. 1979
Rainbow trout (embryo), *Salmo gairdneri*	23 days	40% teratogenesis	10,600	Birge, et al. 1979
Orangespotted sunfish, *Lepomis humilis*	1 hr	Death	106,890-152,700	Clayberg, 1917
Goldfish, *Carassius auratus*	30-60 min	50% anesthetized	97,000-167,000	Cherkin & Catchpool, 1964
Threespine stickleback, *Gasterosteus aculeatus*	90 min	Anesthesia with recovery	207,648*	Jones, 1947a
Ninespine stickleback, *Pungitius pungitius*	-	Avoidance	148,320-296,640*	Jones, 1947b

* Corrected from vol/vol to µg/l.

REFERENCES

Bentley, R.E., et al. 1975. Acute toxicity of chloroform to bluegill (Lepomis macrochirus), rainbow trout, (Salmo gairdneri), and pink shrimp (Penaeus durorarum). Contract No. WA-6-99-1414-B. U.S. Environ. Prot. Agency.

Birge, W.J., et al. 1979. Toxicity of organic chemicals to embryo-larval stages of fish. EPA-560/11-79-007. U.S. Environ. Prot. Agency.

Cherkin, A. and J.F. Catchpool. 1964. Temperature dependence of anesthesia in goldfish. Science. 144: 1460.

Clayberg, H.D. 1917. Effect of ether and chloroform on certain fishes. Biol. Bull. 32: 234.

Jones, J.R.E. 1947a. The oxygen consumption of Gasterosteus aculeatus L. to toxic solutions. Exp. Biol. 23: 298.

Jones, J.R.E. 1947b. The reactions of Pygosteus pungitius L. to toxic solutions. Jour. Exp. Biol. 24: 110.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency, Contract No. 68-01-4646.

Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

In an 80-city study, chloroform was found in all finished drinking water supplies produced from raw water which had been chlorinated (Symons, et al. 1975). Chloroform usually was found in the highest concentration among the four trihalomethanes usually detected. In finished drinking water supplies, the respective levels of chloroform, bromodichloromethane, dibromochloromethane, and bromoform ranged from less than 0.1 µg/l to 311 µg/l, undetected up to 116 µg/l, undetected up to 100 µg/l, and undetected up to 92 µg/l. The highest concentrations of total trihalomethanes were found in finished drinking water supplies for which surface water was used as the source; the source water was chlorinated and the free chlorine residual from this chlorination was greater than 0.4 mg/l. Total trihalomethane concentrations were generally related to the organic content of the raw water when sufficient chlorine was added to create a chlorine residual. Analysis of the raw source waters showed only minor contributions to the chloroform levels of the finished drinking waters, thereby inferring the production of chloroform in the chlorination process.

In its Statement of Basis and Purpose for an Amendment to the National Interim Primary Drinking Water Regulations for Trihalomethanes, 1978, the U.S. EPA (1978b) reviewed the latest data on chloroform exposure from drinking water. Data derived from the National Organics Monitoring Study (NOMS) (U.S. EPA, 1977) noted

that with an average per capita consumption figure of 2 liters per day and 100 percent body absorption of chloroform, a total chloroform uptake from water was estimated to be a mean value of 61 mg/year and maximum value of 343 mg/year. The corresponding NOMS mean and maximum chloroform concentrations for drinking water were 0.083 mg/l and 0.47 mg/l.

Additional evidence of chloroform production as a result of chlorination practices in water renovation was provided by Bellar, et al. (1974). Chloroform concentrations in the influent and effluent of the Cincinnati, Ohio sewage treatment plant where chlorination was practiced were 9.3 µg/l and 12.1 µg/l, respectively.

Much higher levels of chloroform have been found in wastewater effluents and also as the result of accidental industrial spills. Wastewater effluents from rubber and chemical companies in the Louisville, Kentucky area have had chloroform levels as high as 22,000 µg/l (National Academy of Sciences (NAS), 1978a). An accidental spill into the Mississippi River was studied in detail by Neely, et al. (1976); the damage involved the rupturing of two barge tanks and the release of 1.75 million pounds ($0.79 \times 10^{+6}$ kg) of chloroform. Numerous spills have been detected in the upper Ohio River (Thomas, 1979), and levels of 50 µg/l persisted for five days in March 1978. Both of these rivers serve as raw water sources for finished drinking water supplies, and it is obvious that these incidences contributed abnormally high exposure of chloroform to the human population.

Ingestion from Food

McConnell, et al. (1975) reviewed the incidence, significance, and movement of chlorinated hydrocarbons in the food chain. They concluded that chloroform is widely distributed in the environment and is present in fish, water birds, marine mammals, and various foods.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seems to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States was analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

A measured steady-state bioconcentration factor of 6 was obtained for chloroform using bluegills (U.S. EPA, 1978a). Similar bluegills contained an average of 4.8 percent lipids (Johnson,

1980). An adjustment factor of 3.0/4.8 = 0.625 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for chloroform and the edible portions of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 6 x 0.625 = 3.75.

In food, the typical range of chloroform was 1 to 30 µg/kg. The highest concentration noted was in Cheshire cheese, at 33 µg/kg. It was concluded that chloroform levels in food would not be acutely toxic to humans. Pearson and McConnell (1975) also reviewed the incidence of chlorinated hydrocarbons in various marine organisms and water birds and found that the concentrations of chloroform in edible fish and marine organisms ranged from 3 to 180 µg/kg.

Potrepka (1976) estimated that the consumption of products such as bread derived from chloroform-treated (as a fumigant) grains would contribute 0.56 µg of chloroform per day to the adult human diet. This number was derived assuming: (1) consumption of 140 g of bread per day, (2) a chloroform level of 0.4 µg/g in the bread where chloroform was used as the grain fumigant, and (3) chloroform comprises only one percent of total fumigant use in the United States.

Inhalation

The National Academy of Sciences (NAS, 1978a) provided data on the occurrence of six halomethanes in the air. The general background tropospheric concentration of chloroform ranged from

9.8×10^{-5} to 19.6×10^{-5} mg/m^3, with higher concentrations in marine air; lower levels were normally found in continental air samples. Over urban areas, there can be higher concentrations of carbon tetrachloride, chloroform, and methylene chloride. Bayonne, N.J. had the highest measured ambient air concentration of chloroform at 0.073 mg/m^3. Automobile exhausts have been implicated in high urban area chloroform concentrations. Typically, automobile exhausts have chloroform levels of 0.027 mg/m^3. The concentration of chloroform in indoor air rarely exceeds 4.9×10^{-4} mg/m^3.

Dermal

At one time, chloroform was administered as an anesthetic by absorption through the skin. The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) has stated the potential danger of percutaneous chloroform poisoning. Today, dermal exposure is rare and is applicable to the small segment of the population engaged in the manufacture and use of chloroform and its products.

PHARMACOKINETICS

Absorption

Chloroform is well absorbed via the respiratory system (49 to 77 percent). In an early study by Lehman and Hasegawa (1910), chloroform required 80 to 100 minutes to reach equilibrium between blood concentration and inhaled air concentration. Chloroform absorption from the gastrointestinal tract approximates 100 percent (Fry, et al. 1972).

Inhalation studies of $CHCl_3$ in experimental animals have been summarized by von Oettingen (1955). At an exposure level of 8,000

ppm of $CHCl_3$, mice were dead within three hours, and at 12,500 ppm, animals died within two hours. At high levels of exposure, anesthesia occurred within a few minutes, indicating rapid absorption and distribution via the respiratory system. Gastrointestinal absorption was slower, but lethal tissue levels could be attained within minutes to a few hours, depending on the dose. Fry, et al. (1972) reported that gastrointestinal absorption approximates 100 percent.

Distribution

Being a lipid soluble compound, $CHCl_3$ passes readily through cell membranes (primarily by simple diffusion) and easily reaches the central nervous system to produce narcosis, an effect common to most of the halogenated hydrocarbon solvents (Cornish, 1975). Cohen and Hood (1969) demonstrated the long-term retention of $CHCl_3$ in body fat, with increased levels occurring in liver during the post-exposure period. Thus, there is redistribution of $CHCl_3$ in body tissues as it slowly builds up in fatty tissues during the post-exposure period.

Metabolism

As early as 1964, Van Dyke, et al. (1964) demonstrated that labeled CO_2 appeared in expired air less than an hour after an injection of ^{14}C-labeled chloroform. This amounted to 4 to 5 percent of the total dose being exhaled as CO_2 over the subsequent 12 hours and about 2 percent exhaled as other labeled metabolites. This represents considerable metabolism of a relatively inert chemical solvent. Other unidentified metabolites also were reported in the urine during this early study. The chloride ion (^{36}Cl) also has

been found in the urine of rats after the intraperitoneal dose of labeled $CHCl_3$.

It has been suggested that the formation of CO_2 results from the degradation of $CHCl_3$ to methylene chloride (CH_2Cl_2) and thence to formaldehyde, formic acid, and CO_2 (Rubenstein and Kanics, 1964). However, the formation of CH_2Cl_2 has not been well established.

Scholler (1970) reported that the hepatotoxicity of chloroform was markedly enhanced by phenobarbital, a known inducer of the mixed function oxidase (MFO) system. Conversely a decrease in hepatotoxicity of $CHCl_3$ occurred in animals pretreated with SKF 525-A, an inhibitor of the MFO enzyme system (Gopinath and Ford, 1975). Chloroform metabolism depleted liver glutathione, and this depletion was stimulated by liver microsomal enzyme inducers, such as phenobarbital (Ilett, et al. 1973). These authors also reported that after phenobarbital treatment there was an increased biliary excretion of labeled metabolites of $^{14}CHCl_3$ in the bile of rats.

The formation of a chemically reactive $CHCl_3$ metabolite, which may bind covalently to tissue macromolecules, has been reported by several investigators (Ilett, et al. 1973; Uehleke and Werner, 1975). Covalent binding in both liver and kidney was increased following microsomal enzyme induction. In vitro studies (Ilett, et al. 1973) indicated that the formation of $CHCl_3$ metabolites capable of covalent binding is NADPH-dependent and inhibited by carbon monoxide. There is a suggestion that a different or additional pathway of metabolism also may operate in the kidney, since there is a

minimal requirement for NADPH and no requirement for O_2 in the *in vitro* microsomal system.

Recent reports have shown the *in vitro* formation of a systemic metabolite of chloroform (2-oxothiazolidine-4-carboxylic acid) during incubation with liver microsomes (Pohl, et al. 1977). This compound is readily formed by the reaction of cysteine and phosgene, raising again the suggestion of phosgene as an intermediate in the metabolism of chloroform. Pohl (1979) suggested the initial formation of unstable trichloromethanol via the cytochrome P450 system, spontaneous elimination of HCl to yield the reactive phosgene which binds with cysteine and other tissue macromolecules. The author also reported data indicating that deuterium (D)-labeled chloroform ($CDCl_3$) was less toxic and less readily metabolized than $CHCl_3$, suggesting that the cleavage of the C-H bond is the rate-limiting step in the process resulting in the hepatotoxicity of chloroform. Free radical formation also has been proposed as a metabolic pathway of $CHCl_3$ which would lead to reactive intermediates (Smuckler, 1976; Reynolds, 1977; Royer, et al. 1978).

As a result of these studies, it is quite apparent that the microsomal enzyme system plays an important role in the metabolism and toxicity of chloroform. However, several pathways and intermediates have been proposed as the relevant ones. Additional clarification at the molecular level is still necessary to determine the operative *in vivo* pathways involved in the metabolism of chloroform in animals and in man.

Excretion

Fry, et al. (1972) studied a group of adult humans who ingested capsules containing 500 mg of ^{14}C-labeled chloroform. More than 96 percent of the administered isotope was exhaled within 8 hours. Unchanged chloroform was excreted by this route with an efficiency of 18 to 67 percent. Less than one percent of the isotope appeared in the urine. Those people with a higher fat content exhaled less unchanged chloroform in the 8-hour period and presumably more CO_2. A kinetic analysis of Fry's data on two people by Chiou (1975) showed that, extrapolated to infinite time, the fraction metabolized to CO_2 is 46 percent for a male and 58 percent for a female, and the rest is exhaled as chloroform. The half-life of chloroform in the blood and in expired air is approximately 1.5 hours.

EFFECTS

Acute, Subacute, and Chronic Toxicity

Human exposure to chloroform may be via inhalation, ingestion, or by cutaneous contact (Gonzales, et al. 1954; Schroeder, 1965). The first reported case of death as a result of chloroform anesthesia-induced liver damage occurred in 1894 (Guthrie, 1894). Toxic effects include local irritation (hyperemia, erythemia, moisture loss) at the site of skin absorption (Malten, et al. 1968), central nervous system depression, gastrointestinal irritation (Challen, et al. 1958), hepatic and renal damage, and possible cardiac sensitization to adrenalin (Fuhner, 1923; Althausen and Thoenes, 1932; Cullen, et al. 1940).

Chloroform is considered to be moderately toxic. It is several times more potent than carbon tetrachloride as a depressant of

the central nervous system when inhaled, but clinical experience suggests that it is less toxic than carbon tetrachloride when taken orally. The ingestion of 263 g has been possible, although ingestion of much smaller amounts has produced serious illness. The mean lethal dose is approximately 44 g (Gosselin, et al. 1976).

The National Institute for Occupational Safety and Health (NIOSH) Criteria Document (1974) contains a tabulation of the effects of chronic chloroform exposure on humans. One 33-year-old male, who habitually had inhaled chloroform for 12 years, was noted to have the psychiatric and neurologic symptoms of depression, loss of appetite, hallucination, ataxia, and dysarthria. Other symptoms from habitual use are moodiness, mental and physical sluggishness, nausea, rheumatic pain, and delirium.

Most human toxicological data have resulted from the use of chloroform as a general anesthetic in operations. Delayed chloroform poisoning has often occurred after delivery in obstetrical cases. The delayed toxic effects were usually preceded by a latent period ranging from a few hours to one day. Initially drowsiness, restlessness, jaundice, and vomiting occurred, followed by fever, elevated pulse rate, liver enlargement, abdominal tenderness, delirium, coma, and abnormal findings in liver and kidney function tests were also reported. Death often ensued, three to ten days post partum. Autopsy reports generally described the liver as having a bright yellowish color, fatty infiltration with necrosis was found. Other hepatotoxic effects have been reviewed (NIOSH, 1974). Numerous animal studies have shown that chloroform causes fatty infiltration and necrosis of the liver. None of these studies

involved long-term exposures to low concentrations. However, these studies show that hepatotoxic effects of chloroform can occur as the result of ingestion, inhalation, or intravenous administration (NIOSH, 1974). Although the causes of death in most cases of chloroform poisoning have been attributed to necrosis of the liver, there also has been evidence at autopsy of renal damage, including albumin and red blood cells in urine, elevated blood urea, an 18 percent decrease in prothrombin after surgery, and fatty degeneration.

A case of pulmonary toxicity resulting from an intentional intravenous injection of chloroform has been reported (Timms and Moser, 1975). Chloroform poisoning has resulted in symptoms similar to those of marked hemolytic anemia. Chloroform has induced hemolysis of human erythrocytes _in vitro_ (Belifore and Zimmerman, 1970).

Malten, et al. (1968) reported that chloroform exposure ultimately results in an injury to only the horny layer of skin in humans, and that the skin often responds with the formation of a temporary protective barrier.

There have been few studies of industrial worker exposure. Challen, et al. (1958) reported a study of workers in a confectionary firm in England that manufactured medicinal lozenges. In 1950, the workers began to complain of chloroform vapor given off during the production of the lozenges. These workers were placed on a reduced work week to alleviate their complaints of lassitude, flatulence, water brash (British term indicative of symptoms of dyspepsia), dry mouth, thirst, depression, irritability, and frequent and

"scalding" micturition. This action was not successful and the employees refused to work on that particular process. In 1954, a new team of operators was engaged and in 1955, a system of exhaust ventilation was installed, after which manufacturing proceeded without interruption.

Clinical investigations of three different groups of workers in this manufacturing plant were performed by Challen, et al. (1958). One group of eight employees was termed the "long service operators." These were people who refused to continue in the lozenge department after they experienced the previously described symptoms. This group of workers, when exposed to chloroform vapor in concentrations ranging from 376 to 1,158 mg/m^3, had been observed staggering about the work area. After terminating work in the lozenge department, the "long service operators" reported experiencing nausea after even short exposures to chloroform.

A second group of nine employees, termed the "short service operators," were the replacements for the "long service operators." Two of these nine employees did not report unpleasant experiences from chloroform exposure. Among the other seven, five reported dryness of the mouth and throat at work; two were subject to lassitude in the evening; one complained of lassitude and flatulence at work; and the experiences of two others were similar to those of the "long service operators." The "short service operators" worked in locations where the chloroform concentrations ranged from 112 to 347 mg/m^3.

A third group of five employees who worked in other departments of the firm served as controls and exhibited no symptoms.

Tests of liver function (thymol turbidity, thymol flocculation, direct van den Bergh, and indirect serum bilirubin), clinical examinations, and urinary urobilinogen failed to show significant differences among the three groups of workers.

Bomski, et al. (1967) reported on liver injury from chloroform exposure among workers in a pharmaceutical factory in Poland. The study included the entire group of 295 workers who were exposed to chloroform in the course of production. Of these, 68 were exposed to chloroform for 1 to 4 years and still were in contact with chloroform, 39 had chloroform contact at one time, but were no longer exposed, 23 had viral hepatitis with icterus two to three years earlier and were designated as posticterus controls and were working in a germ-free area, and 165 worked in a germ-free area with no history of viral hepatitis. Blood pressure, blood morphology, urinalysis, blood albumin, serum protein, thymol turbidity, zinc sulfate turbidity, urobilinogen, SGOT, and SGPT were measured in all; the "Takata-Ara" sulfate (colorimetric) test was also performed. A complete medical history was taken. Sixty of the people were hospitalized for determination of BSP clearance and urinary urobilinogen.

The air in the production room was sampled, and chloroform concentrations were determined with the Grabowicz method. The concentration of chloroform ranged from 9.8 to 1,002 mg/m^3. No other concentration measurements were reported, nor was there any mention of the frequency of sampling.

The authors compared the frequency of viral hepatitis and jaundice among a group of inhabitants of the city, 18 years of age

and older, with that of the same 68 pharmaceutical workers who were exposed to chloroform. The results showed that in 1960, 0.35 percent of city inhabitants had viral hepatitis, while 16.67 percent of the chloroform-exposed workers had viral hepatitis. In 1961, the frequency of viral hepatitis for city inhabitants was 0.22 percent, and the frequency among the chloroform workers was 7.50 percent. In 1962, the frequency of viral hepatitis was 0.38 percent for city inhabitants and 4.4 percent for workers exposed to chloroform. The authors suspected that the toxic liver changes occurring as a result of exposure to chloroform promoted a viral infection in such cases, but they did not give information on the incidence of viral hepatitis among the other groups of plant workers. This information might have helped resolve questions about sanitary practices and facilities in the plant.

The majority of the workers who were in contact with chloroform during the investigation period covered in this study complained of headache, nausea, belching, and loss of appetite. Among the 68 workers using chloroform, 19 cases of splenomegaly were found; none was found in the controls.

The frequency of enlarged livers (17 of 68) among workers exposed to chloroform exceeded the frequency of enlarged livers in two of the other groups (5 of 39 and 2 of 23). Livers were judged to be enlarged if they extended at least 1 cm beyond the rib arch in the midclavicular line. The upper margin was apparently not measured. In 3 of the 17 chloroform workers with enlargement of the liver, toxic hepatitis was diagnosed on the basis of elevated serum enzyme activities and elevated serum gamma globulin,

but the measured amounts of these serum constituents in these 3 workers were not reported. In the remaining 14 cases of liver enlargement, fatty liver was diagnosed.

Intraperitoneally-injected chloroform can be nephrotoxic in mice (Klaassen and Plaa, 1967a). The acute LD_{50} value for male mice was 1,800 mg/kg body weight; for females, 1,900 mg/kg body weight. Male mice demonstrated renal dysfunction at 116 mg/kg body weight, but females did not exhibit renal dysfunction at any time during or after exposure to even a lethal dose of chloroform.

Intragastric administration of 250 mg of chloroform/kg body weight to rats showed gross pathological changes in both renal and hepatic tissues (Torkelson, et al. 1976). The intragastric LD_{50} for chloroform was 2,000 mg/kg body weight, with most deaths occurring from 2 to 4 hours.

Rats, guinea pigs, and rabbits received repeated exposure to chloroform vapor at 85 ppm, 50 ppm, and 25 ppm (415, 244, and 122 mg/m^3, respectively) for 7 hours per day, 5 days per week for up to 203 days. Dogs were similarly exposed to a chloroform concentration of 122 mg/m^3. The results of these studies are reported in Table 1.

The effects of chloroform on kidney and liver function in mongrel dogs have been reported (Klaassen and Plaa, 1967b). Male and female dogs received intraperitoneal injections of chloroform in corn oil. The 24-hour LD_{50} was estimated to be 1,483 mg/kg body weight using the "up and down" method of Browning (1937).

Toxic effects by dermal administration have been demonstrated in both humans and other mammals. Torkelson, et al. (1976) reported

TABLE 1

Effects of Chloroform Inhalation on Four Laboratory Animal Species*

Animal	Sex	Concentration (mg/m^3)	Effects
Rats:	Male	415	Pneumonia, renal symptoms, hepatic degradation
	Female	415	Renal & hepatic pathology
Guinea Pigs:	Male	415	No effects
	Female	415	Pneumonitis
Rabbits:	Male	415	Pneumonitis, hepatic necrosis
	Female	415	Hepatic, renal pathology
Rats:	Male	244	Symptoms less severe than reported at 415 mg/m^3
	Female	244	Less affected than males
Guinea Pigs:	Male	244	Normal
	Female	244	Normal
Rabbits:	Male	244	Normal
	Female	244	Normal
Dogs:	Male	122	Normal
	Female	122	Microscopic changes in kidney

*Source: Torkelson, et al. 1976

on adverse effects in the rabbit. One to two 24-hour applications, by a cotton pad bandaged on the shaven belly of rabbits, produced a slight hyperemia with moderate necrosis and a resulting eschar formation. Healing appeared to be delayed on the site and on abraded areas treated in the same way. Single applications as low as 1,000 mg/kg of body weight for 24 hours under an impermeable plastic cuff resulted in degenerative changes in the kidney tubules. Chloroform dropped into the eyes of rabbits produced slight injury which required one week to heal.

Synergism and/or Antagonism

In male rats, chloroform has been demonstrated to be hepatotoxic. Experiments have elucidated the role of microsomal amidopyrine N-demethylase activity in the hepatotoxic response (Gopinath and Ford, 1975). Pretreatment with phenobarbitone sodium or phenylbutazone, from 1 hour to 14 days prior to single oral doses of chloroform, induced this enzyme and potentiated the hepatotoxic effects of chloroform, i.e., necrotized cells, up to 1,000 percent over control values. On histological examination, degenerative cells were also apparent. Pretreatment with sodium diethyldithiocarbamate and carbon disulfide has been shown to protect against liver damage, with no necrotized regions apparent histologically.

Pretreatment with alcohols, barbiturates, and other chemicals such as DDT increased the toxic effects of chloroform, apparently by lowering the threshold for its necrotic action. Studies by Ilett, et al. (1973) indicate that this synergistic effect may be related to enhanced tissue binding.

Kutob and Kutob (1961) found that ethanol pretreatment of mice increased the toxic effects of chloroform on the liver. McLean (1970) demonstrated the potentiating effects of other agents. Phenobarbital and DDT increased the liver hydroxylating enzyme activity, and the toxicity of chloroform was more than doubled by the pretreatment with these chemicals as measured by the LD_{50}.

Animals on high fat or protein-poor diets are more susceptible to hepatotoxicity from chloroform, whereas diets high in carbohydrates and proteins have a protective effect (von Oettingen, 1964).

Teratogenicity

In 1974, Schwetz, et al. demonstrated the effects of repeated exposures to chloroform on rat embryos and fetal development. Pregnant Sprague-Dawley rats were exposed to airborne chloroform at 147, 489, and 1,466 mg/m^3 for 7 hours per day on days 6 to 15 of gestation. Pregnant rats exposed to 489 mg/m^3 showed a significant increased incidence of fetal abnormalities compared with controls. There were significantly increased incidences of acaudia (no tails), imperforate anus, subcutaneous edema, missing ribs, and delayed sternebrae ossification. Rats exposed to 147 mg/m^3 showed significantly increased incidences of delayed skull ossification and wavy ribs, but exhibited no other deleterious effects compared with controls.

Thompson, et al. (1974) reports in a range-finding study on rats, oral doses of chloroform (126 mg/kg/day and greater) produced dose-related maternal toxicity. Doses of 316 mg/kg/day and greater caused acute toxic nephrosis and hepatitis and death of dams, as well as fetotoxicity. Results of the Thompson, et al.

(1974) study in the rabbit suggest this species to be more sensitive to the effects of chloroform, in that oral doses of 100 mg/kg/day or higher were toxic to both the dam and fetus.

In these teratology studies, the occurrence of adverse clinical effects in the females of both species and of hepatotoxicity in the rabbit indicates that maximum tolerated doses of chloroform were used. At levels toxic to the mother, only mild fetal toxicity in the form of reduced birth weights was observed. Dose levels as high as 126 mg/kg/day in the rat and 50 mg/kg/day in the rabbit were neither embryocidal nor teratogenic.

The occurence of fetal anomalies (Schwetz, et al. 1974) following exposure of pregnant rats to chloroform by inhalation, and the absence of effects following oral exposure (Thompson, et al. 1974) may be attributed to the difference in routes of administration. Blood concentrations and tissue distribution of chloroform in maternal and fetal compartments would undoubtedly be affected by the route and duration of maternal exposure which differed in the two studies, i.e., continuous exposure seven hours daily in the inhalation study compared with one or two short periods of exposure per day in the oral study.

Mutagenicity

Chloroform, tested by the histidine-revertant mutation system employing *Salmonella typhimurium* tester strains, was found to be negative. The other trihalomethanes formed by chlorination of drinking water were positive in such tests (Simmon, et al. 1977).

Carcinogenicity

Eschenbrenner and Miller (1945) studied the effect of repeated oral doses of chloroform on the induction of hepatomas in mice. A graded series of necrotizing and nonnecrotizing doses of chloroform was administered. Three-month-old strain A mice which had an incidence of spontaneous hepatomas of less than one percent at 16 months were given intragastric doses of chloroform in olive oil solutions at 5 ml/kg body weight. The chloroform content of the solutions varied so that the chloroform doses were 1.6, 0.8, 0.4, 0.2, or 0.1 ml/kg, respectively (2,373, 1,187, 593, 297, 148 mg/kg).

The presence or absence of liver necrosis was determined by microscopic examination of liver sections taken 24 hours after administration of a single dose of chloroform. The livers of animals receiving doses of 297 and 148 mg/kg of chloroform showed no necrosis. However, with these doses, necrotic areas were observed in the kidneys of males, but not of females. This sex difference of renal necrotic lesions was observed at all concentrations. No sex difference was observed for liver necrosis. Twenty-four hours after a single dose of 593 mg/kg or more of chloroform, there was extensive necrosis of liver cells around the central veins. Thirty doses were given at four-day intervals to test for any carcinogenic effect. (This was the schedule under which a hepatoma incidence of 100 percent was obtained when carbon tetrachloride was used). Hepatomas were found only in animals that received necrotizing doses of chloroform (at least 593 mg/kg) and which were killed one month after the last dose. These were seen only in female mice,

which could reflect the lower tolerance to chloroform for males, i.e., the males might have died earlier of renal necrosis, before onset of malignant changes. The authors suggested that necrosis was a prerequisite to tumor induction.

In 1976, the National Cancer Institute (NCI) released its Report on Carcinogenesis Bioassay of Chloroform. This study followed the protocol that had been developed for testing a series of chemicals by the Carcinogenesis Bioassay Program of the Division of Cancer Cause and Prevention. The work was carried out under contract with the Hazelton Laboratories of America, Inc.

A carcinogenesis bioassay of USP grade chloroform was conducted using male Osborne-Mendel rats and both male and female $B6C3F_1$ mice. Chloroform was administered orally (by gavage) in corn oil to 50 animals of each sex and at two dose levels 5 times per week for 78 weeks. Rats were started on the test at 52 days of age and killed after 111 weeks. The dose levels for males were 90 and 180 mg/kg body weight. Female rats were started at 125 and 250 mg/kg, reduced to 90 and 180 mg/kg after 22 weeks, with an average level of 100 and 200 mg/kg for the study. A decrease in survival rate and weight gain was evident for all treated groups. The most significant observation ($p = .0016$) was kidney epithelial tumors in male rats with incidences of: 0 percent in controls, 8 percent in the low-dose groups, and 24 percent in the high-dose groups (Table 2). An increase in thyroid tumors was also observed in treated female rats, but this finding was not considered statistically significant.

TABLE 2

Statistically Significant Tumor Incidence in Rats*

	Males			
	Controls			
	Colony	Matched	Low Dose	High Dose
Kidney epithelial tumors/animals	0/99	0/19	90 mg/kg 4/50 (8%)	180 mg/kg 12/50 (24%)
p value	0.0000	0.0016		

*Source: NCI, 1976

The epithelial tumors varied from circumscribed, well-differentiated tubular-cell adenomas to highly pleomorphic, poorly differentiated carcinomas which had invaded and metastasized. The cells in adenomas were relatively uniform and polygonal, with abundant eosinophilic cytoplasm. Nuclei were central or basal in location, with minimal atypia and little increase in mitotic index. Most carcinomas were very large and replaced a considerable portion of the renal parenchyma. They were infiltrated surrounding normal tissues and were poorly circumscribed. These cells assumed the form of irregular sheets, nests, and tubular arrangements with varying degrees of anaplasia and increased nuclear/cytoplasmic ratio. The nests of cells were often surrounded by a delicate fibrovascular stroma, and central necrosis was sometimes present in the more anaplastic neoplasms. A papillary glandular pattern was rarely observed.

Mice were started on test at 35 days and killed after 92 to 93 weeks. Initial dose levels were 100 and 200 mg/kg for males and 200 and 400 mg/kg for female mice. These levels were increased after 18 weeks to 150/300 and 250/500 mg/kg, respectively, so that the average levels were 138 and 277 mg/kg for male and 238 and 477 mg/kg for female mice. Survival rates and weight gains were comparable for all groups except high dose females which had a decreased survival. Highly significant increases ($p = .001$) in hepatocellular carcinoma were observed in both sexes of mice with incidences of 98 percent and 95 percent for males and females at the high dose, and 36 and 80 percent for males and females at the low dose (Table 3). This compares with six percent in both matched and colony control

TABLE 3

Hepatocellular Carcinoma Incidence in Mice*

	Controls			
	Colony	Matched	Low Dose	High Dose
Male	5/77 (6%)	1/18 (6%)	138 mg/kg 18/50 (36%)	277 mg/kg 44/45 (98%)
Female	1/80[a] (1%)	0/20 (0%)	238 mg/kg 36/45[a] (80%)	477 mg/kg 39/41 (95%)

*Source: NCI, 1976

[a]Data used for calculation of cancer risk in Criteria Formulation section of this document.

males, zero percent in matched control females, and one percent in colony control females. Nodular hyperplasia of the liver was observed in many low dose male mice that had not developed hepatocellular carcinoma.

The incidence of hepatocellular carcinoma is significantly elevated in both sexes of mice. A high incidence of these tumors was observed in all treated groups, and the difference was determined to be statistically significant at the $p < 0.001$ level. The lesions were observed in animals which died as early as 54 weeks following initial exposure. The increase in lesion development observed is due to the occurrence of a specific type of tumor, hepatocellular carcinoma. The tumors varied from those composed of well-differentiated hepatocytes with a relatively uniform arrangement, to those which were very anaplastic and poorly differentiated with numerous mitotic figures. Various types of hepatocellular carcinomas described in the literature were seen, including those with an orderly cord-like arrangement of neoplastic cells, those with a pseudoglandular pattern resembling adenocarcinoma, and those composed of sheets of highly anaplastic cells with little tendency to form a cord or gland-like arrangement. The diagnosis of hepatocellular carcinoma was based primarily on histologic characteristics of the neoplasm. Hepatocellular carcinomas were found to have metastasized to the lung in two low-dose males and two high-dose females, and to the kidney in a high-dose male.

A search of the literature has not revealed long-term followup studies on industrially-exposed populations. It is expected that there would be a long latency period. A survey of plant workers who

had been exposed for only a few years would not be expected to show a significant increase in cancer.

When data on chloroform concentrations became available from the U.S. EPA's surveys of drinking water, a correlation was noted with cancer death rates for all sites in the survey (McCabe, 1975). Fifty cities, where at least 70 percent of the population was served by the water sampled, had chloroform concentrations measured in 1975 that could be compared with cancer mortality in 1969-71. A statistically significant correlation was reported between the age, sex, and race-adjusted death rate for total cancer and chloroform levels.

Epidemiology studies of cancer frequency for trihalomethanes, of which chloroform is a primary chemical species, began to appear in 1974. EPA asked a number of research groups to evaluate whether there was a relationship between cancer rates and chloroform and other trihalomethanes (THM) in water supplies. Most of the EPA requested studies used indirect evidence of the presence of THM in water supplies while two others used direct measurements of chloroform and other THM.

This type of study has been extended by Cantor, et al. (1977) who looked at the association between each of 16 cancer rates in whites, by sex and levels of trihalomethanes separated into chloroform and nonchloroform components. Exposure information came from the National Organics Reconnaissance Survey and the U.S. EPA Region V Survey of 1975. Seventy-six counties, in which more than 50 percent of the population was served by the sampled and assayed water supply, were included in the study. The most consistent finding

was an association between bladder cancer mortality rates and trihalomethane levels. The association was observed in both sexes and showed a gradient of increasing degree of correlation when counties were grouped by percentage of the county population served by the water supply. The correlations noted were stronger with the brominated trihalomethanes than with chloroform.

Hogan, et al. (1977) used approximately the same data base and applied various statistical procedures to the data in order to determine the appropriateness of the statistical model. The results were similar to previous studies showing positive correlation between rectal-intestinal and bladder cancer mortality rates and chloroform levels in drinking water, when a weighted regression analysis was applied.

Given the number of existing epidemiology studies, the EPA asked the National Research Council to review the studies. The National Academy of Sciences (NAS, 1978b) provided such a review of 10 epidemiology studies, including the ones previously mentioned. It is useful to quote from their summary and conclusions:

> The studies that the subcommittee reviewed were divided into two groups: those in which nonspecific measures of exposures to putative carcinogens in water (e.g., the use of surface water vs. ground water) were examined and those in which water quality was characterized by measurements of trihalomethane (THM) concentrations. The subcommittee gave greater weight to the conclusions of the latter group of studies because crude measures of exposure, which lead to the comparisons of cancer between surface water users and ground water users, must be of limited value. They do not permit the quantitation of exposure to contaminants in water consumed, which is needed to determine dose-response relationships between THM concentrations and cancer frequencies and to estimate the effects of reducing THM concentrations.

The conclusions drawn in the second group of studies, in which many cancer sites were examined, suggest that higher concentrations of THMs in drinking water may be associated with an increased frequency of cancer of the bladder. The results do not establish causality, and the quantitative estimates of increased or decreased risk are extremely crude. The effects of certain potentially important confounding factors, such as cigarette smoking, have not been determined.

CRITERION FORMULATION

Existing Guidelines and Standards

The Occupational Safety and Health Administration (OSHA) limit for chloroform in work place air is 50 ppm, or 244 mg/m^3. This is a "ceiling value" for a maximum 10-minute exposure that at no time should be exceeded. NIOSH recommended a criterion of 10 ppm (48.9 mg/m^3) in 1974. This criterion was applied to a time-weighted exposure for as high as 10 hours per day and a 40-hour work week. Following the National Cancer Institute (NCI) study of chloroform, NIOSH on June 9, 1976, reduced this allowable time-weighted average exposure criterion to 2 ppm (9.8 mg/m^3).

Based on available health information, a safe level of airborne exposure to halogenated agents could not be defined. Since a safe level of occupational exposure to halogenated anesthetic agents could not be established by either animal or human investigations, NIOSH recommended that airborne exposure be limited to levels no greater than the lowest level detectable using the recommended sampling and analysis techniques (NIOSH, 1977). At the present, chloroform is not usually used as an anesthetic; this use is included in the criterion and is limited to 2 ppm or 9.8 mg/m^3.

If a procedure that converts this air limit to a water limit is employed, the equivalent exposure in water would be 34.9 mg/l (Stokinger and Woodward, 1958). In this method, complete absorption from inhalation and ingestion is assumed. The inhalation absorption may be closer to 50 percent and the equivalent water exposure would then be 17.4 mg/l. The occupational limits apply to the healthy working-age population, and even then if exposure level

is half the limit, comprehensive medical surveillance is required. To use the occupational limit as a guide for the general population, an application factor of 100 can be used. Thus, an equivalent level in water would be 174 µg/l. It must be remembered that the occupational limit for chloroform is based on the lowest level detectable in air using NIOSH recommended analytical techniques and does not necessarily represent a level adequate to protect man.

In general, the use of inhalation data assumes an 8-hour day, time-weighted average, occupational exposure in the working place with workers inhaling the toxic substance throughout such a period. Exposures for the general population should be considerably less. Such worker-exposure inhalation standards are inappropriate for the general population since they presume an exposure limited to an eight-hour day, an age bracket of the population that excludes the very young and the very old, and a healthy worker prior to exposure. Ingestion data are far superior to inhalation data when the risks associated with the food and water of the aquatic environment are being considered.

Following the NCI study of chloroform, the Food and Drug Administration took action to halt the use of chloroform in drug products, cosmetic products, and food contact materials (41 FR 15026, 15029). The EPA has issued a notice of "rebuttable presumption" against continued registration of chloroform-containi .g pesticides (41 FR 14588).

The EPA has also proposed an amendment which would add to the National Interim Primary Drinking Water Regulations a section on the control of organic halogenated chemical contaminants in

drinking water (43 FR 5756). The proposed limit for total trihalomethanes, which includes chloroform, is 100 µg/l. This limit was set largely on the basis of technological and economic feasibility. Originally the limit will apply only to water supplies serving greater than 75,000 consumers; this is intended to provide an orderly upgrading of drinking water treatment in the country. The basis and purpose of the regulation are discussed in a paper by the Office of Drinking Water issued in January, 1978 (U.S. EPA, 1978b). This document contains a number of estimates of cancer risk attributable to the presence of chloroform in drinking water. One of these, performed by NAS, using a linear non-threshold extrapolation from animal data, estimated that the lifetime risk would fall between 1.5×10^{-7} and 17×10^{-7} µg/$CHCl_3$/l of water consumed daily depending upon the data set employed. The upper 95 percent confidence estimates would range between 3×10^{-7} and 22×10^{-7} µg/l/day.

Current Levels of Exposure

The National Academy of Science (NAS, 1978a) assembled data based on human exposure to chloroform. Their calculations of human uptake are based on fluid intake, respiratory volume, and food consumption data for "reference man" as compiled by the International Commission for Radiological Protection. Table 4 from the NAS report is reproduced to show their estimates of chloroform uptake from fluids. Table 5 presents the data on relative human uptake from the three sources.

According to the NAS report the uptake of chloroform from the atmosphere at minimum levels of exposure is about 10 times greater

TABLE 4

Chloroform Uptake From Fluids (mg/yr) Assuming 100 Percent Absorption[a,*]

Exposure	Fluid	Adult Man			Adult Woman			Child (5-14 Yr)		Child (10 Yr)
		Min. Fluid Intake	Max. Fluid Intake	Refer. Man Intake	Min. Fluid Intake	Max. Fluid Intake	Refer. Man Intake	Min. Fluid Intake	Max. Fluid Intake	Refer. Man Intake
Minimum Concentration Exposure (0.0001 mg/l)	Tap Water	0.016	0.027	0.005	0.016	0.027	0.004	0.020	0.029	0.007
	Other[b]	0.012	0.053	0.055	0.012	0.053	0.040			0.027
	Total Fluid	0.037	0.088	0.071	0.037	0.088	0.051	0.036	0.061	0.051
Median Concentration Exposure (0.021 mg/l)	Tap Water	3.44	5.59	1.15	3.44	5.59	0.77	4.14	6.06	1.53
	Other[b]	2.45	11.1	11.5	2.45	11.1	8.43			5.75
	Total Fluid	7.57	18.4	14.9	7.67	18.4	10.7	7.67	12.8	10.7
Maximum Concentration Exposure (0.366 mg/l)	Tap Water	60.0	97.5	20.1	60.0	97.5	13.4			26.7
	Other[b]	42.7	194	200	42.7	194	147	72.1	106	100
	Total Fluid	134	321	261	134	321	187	134	223	187

[a]Calculated by multiplying the exposure concentration (µg/l) x fluid intake (l/yr) for minimum and maximum intakes, and dividing by 1000 µg/mg = mg/yr.

[b]Includes water based drinks, such as tea, coffee, soft drinks, beer, cider, wine.

*Source: NAS, 1978a

TABLE 5

Relative Human Uptake of Carbon Tetrachloride (CCl_4) and Chloroform ($CHCl_3$) from Environmental Sources (mg/year)*

	At Minimum Exposure Levels[a]					
	Adult Man		Adult Woman		Child	
Source	CCl_4	$CHCl_3$	CCl_4	$CHCl_3$	CCl_4	$CHCl_3$
Fluid Intake	0.73	0.037	0.73	0.037	0.73	0.036
Atmosphere	3.60	0.41	3.30	0.37	2.40	0.27
Food Supply	0.21	0.21	0.21	0.21	0.21	0.21
Total	4.54	0.66	4.24	0.62	3.34	0.52

	At Typical Exposure Levels[b]					
	Adult Man		Adult Woman		Child	
Source	CCl_4	$CHCl_3$	CCl_4	$CHCl_3$	CCl_4	$CHCl_3$
Fluid Intake	1.78	14.90	1.28	10.70	1.28	10.70
Atmosphere	4.80	5.20	4.40	4.70	3.20	3.40
Food Supply	1.12	2.17	1.12	2.17	1.12	2.17
Total	7.70	22.27	6.80	17.57	5.60	16.27

TABLE 5 (Continued)

	At Maximum Exposure Levels[c]					
	Adult Man		Adult Woman		Child	
Source	CCl_4	$CHCl_3$	CCl_4	$CHCl_3$	CCl_4	$CHCl_3$
Fluid Intake	4.05	321	4.05	321	1.83	223
Atmosphere	618	474	567	434	405	310
Food Supply	7.33	16.4	7.33	16.4	7.33	16.4
Total	629	811	578	771	414	549

*Source: NAS, 1978a

(a) Minimum conditions of all variables assumed: Minimum exposure-minimum intake for fluids; minimum exposure-minimum absorption for atmosphere; and minimum exposure-minimum intake for food supplies.

(b) Typical conditions of all variables assumed. For CCl_4: 0.0025 mg/l-reference man intake for fluids; average of typical minimum and maximum absorption for atmosphere; and average exposure and intake for food supplies. For $CHCl_3$: median exposure-reference man intake for fluids; average of typical minimum and maximum absorption for atmosphere; and average exposure and intake for food supplies.

(c) Maximum conditions of all variables assumed: maximum exposure intake for fluids; maximum exposure-maximum absorption for atmosphere; and maximum exposure-maximum intake for food supplies.

than from fluids. At maximum exposure levels, the chloroform uptake from fluids is slightly less than that from the atmosphere. At typical exposure levels, however, the human uptake from fluids is 2 to 3 times greater than from the atmosphere, with slight variation by sex and age noted.

In its Statement of Basis and Purpose for an Amendment to the National Interim Primary Drinking Water Regulations on Trihalomethanes, the U.S. EPA (1978b) estimated the total human exposure to chloroform (Table 6). The estimates have basic assumptions that are comparable to those used by the NAS (1978a), are based on newer values for chloroform content in drinking water from NOMS data, and provide estimates for human adults only.

The two exposure estimates, NAS (1978a) and the U.S. EPA (1978b) demonstrate that chloroform intake from ingesting water is likely to range from a modest to predominant percentage of total exposure with a simple minimum, mean and maximum exposure scenario.

	% total exposure from water (U.S. EPA)	% total exposure from water (NAS)
Minimum Exposure	23%	6%
Mean Exposure	69%	67%
Maximum Exposure	61%	40%

Basis and Derivation of Criteria

Chloroform has several adverse effects on the human body. Safe levels of chloroform in water necessary to avoid some of these effects would be difficult to establish because adequate studies have not been conducted. The most serious effect to consider is

TABLE 6

Uptake of Chloroform for the Adult Human from Air, Water, and Food*

Source	Adult mg/yr	Percent uptake
	Maximum Conditions	
Atmosphere	204	36
Water	343	61
Food Supply	16	3
Total	563	100.00
	Minimum Conditions	
Atmosphere	0.41	13
Water	0.73	23
Food Supply	2.00	64
Total	3.14	100.00
	Mean Conditions	
Atmosphere	20.0	22
Water	64.0	69
Food Supply	9.00	10
Total	93	101.00

*Source: U.S. EPA, 1978b

the cancer-causing potential of the chemical. Current knowledge leads to the conclusion that carcinogenesis is a non-threshold, nonreversible process. The non-threshold concept implies that many tumors will be produced at high doses, but any dose, no matter how small, will have the probability of causing cancer. Even small carcinogenic risks have a serious impact on society when the exposed population is large, because it is likely that some cancers will be caused by chloroform. The nonreversible concept implies that once the tumor growth process has started, growth will continue and may metastasize and involve other organs until death ensues.

Chloroform has been shown to induce cancer in two species of experimental animals. This conclusion is neither confirmed nor denied by the results of numerous epidemiology studies now available, although from a public health point of view, a suspicion of a qualitative weight of evidence for confirmation probably exists.

The available information on total human exposure to chloroform from air, water, and food sources suggests that drinking water contributes from 6 to 69 percent of the total exposure. Studies in which water quality was characterized by measurements of THM concentrations suggest that higher trihalomethanes (THM) concentrations in drinking water may be associated with an increased frequency of cancer of the bladder. The results do not establish causality, and the estimates of increased or decreased risk are extremely crude.

It is therefore proposed that the total risk for carcinogenic response be allocated to the ambient water exposure conditions of

ingesting 2 liters/day of water and consuming 6.5 grams of potentially contaminated fish products.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Chloroform is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of chloroform in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases, and in order to assist the Agency and states in the possible future development of water quality regulations, the concentrations of chloroform corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5}, for example, indicates a probability of one additional case of cancer for every 100,000 people exposed; a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7}, as shown in the following table.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 grams of fish and shellfish (2)	0.019 µg/l	0.19 µg/l	1.90 µg/l
Consumption of fish and shellfish only.	1.57 µg/l	15.7 µg/l	157 µg/l

(1) Calculated by applying a linearized multistage model, as discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice which announced the availability of this document, to the animal bioassay data presented in Appendix I and in Table 3. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Approximately 1 percent of the chloroform exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 3.75-fold. The remaining 99 percent of chloroform exposure results from drinking water.

Concentration levels were derived by assuming a lifetime exposure to various amounts of chloroform: (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding chloroform concentrations; and (2) occurring solely from consumption of aquatic life grown in the waters

containing the corresponding chloroform concentrations. Although total exposure information for chloroform is discussed and an estimate of the contributions from other sources of exposure can be made, these data will not be factored into ambient water quality criteria formulation until additional analysis can be made. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

REFERENCES

Althausen, T.L. and E. Thoenes. 1932. Influence on carbohydrate metabolism of experimentally induced hepatic changes. Arch. Int. Med. 50: 257.

American Conference of Governmental Industrial Hygienists. 1977. TLVs: Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1977. Cincinnati, Ohio.

Belifore, F. and H.J. Zimmerman. 1970. Cytotoxicity of chlorinated hydrocarbons *in vitro*. Observations on chloroform-induced hemolysis. Proc. Soc. Exp. Biol. Med. 134: 61.

Bellar, T.A., et al. 1974. The occurrence of organohalides in chlorinated drinking water. Jour. Am. Water Works Assoc. 66: 703.

Bomski, H., et al. 1967. Toxic damage of the liver by chloroform in chemical industrial workers. Arch. Gewerbepathol. Gewerbehyg. 24: 127.

Browning, E. 1937. Toxicity of organic solvents. Gr. Br. Med. Res. Coun. Rep. Ind. Health Res. Board., London. 80: 128.

Cantor, K.P., et al. 1977. Association of cancer mortality rates and trihalomethane level in municipal drinking water supplies. Am. Jour. Epidemiol. 106: 230. (Abst.)

Challen, P.J., et al. 1958. Chronic chloroform intoxication. Br. Jour. Ind. Med. 15: 243.

Chiou, W.L. 1975. Quantitation of hepatic and pulmonary first-pass effect and its implications in pharmacokinetic study. I. Pharmacokinetics of chloroform in man. Jour. Pharmaco. Biopharmaceu. 3: 193.

Cohen, E.N. and N. Hood. 1969. Application of low temperature autoradiography to studies of the uptake and metabolism of volatile anesthetics in the mouse. Jour. Chloroform Anesthesiol. 30: 306.

Cornish, H.H. 1975. Solvents and Vapors. In: L. Casarett and J. Doull (eds.) Toxicology, the Basic Science of Poisons. MacMillan Publ. Co., Inc., p. 503.

Cullen, S.C., et al. 1940. Anesthesia and liver injury. Jour. Am. Med. Assoc.

Eschenbrenner, A.B. and E. Miller. 1945. Induction of hepatomas in mice by repeated oral administration of chloroform, with observations on sex differences. Jour. Natl. Cancer Inst. 5: 251.

Fry, B.J., et al. 1972. Pulmonary elimination of chloroform and its metabolites in man. Arch. Int. Pharmacodyn. 196: 98.

Fuhner, H. 1923. Relative potencies of chloroform and carbon tetrachloride. Arch. Exp. Pathol. Pharmakol. 97: 86.

Gonzales, T.A., et al. 1954. Legal Medicine - Pathologic Toxicology, Volatile Aliphatic Compounds, 2nd ed. Appleton-Century Crafts, New York. p. 795.

Gopinath, C. and C. Ford. 1975. The role of microsomal hydroxylases in the modification of chloroform hepatotoxicity in rats. Br. Jour. Exp. Pathol. 56: 442.

Gosselin, R.E., et al. 1976. Clinical Toxicology of Commercial Products. Williams and Wilkins, Baltimore, Maryland.

Guthrie, L.B. 1894. On some fatal after-effects of chloroform on children. Lancet. 1: 193.

Hogan, M.D., et al. 1977. Association between chloroform levels in finished drinking water supplies and various site-specific cancer mortality rates. NIEHS report. (Draft)

Ilett, K.F., et al. 1973. Chloroform toxicity in mice: Correlation of renal and hepatic necrosis with covalent binding of metabolites to tissue macromolecules. Exp. Mol. Pathol. 19: 215.

Johnson, K. 1980. Memorandum to D.W. Kuehl. U.S. EPA. March 10.

Kopfler, F.C., et al. 1976. GC/MS Determination of Volatiles for the National Organics Reconnaissance Survey (NORS) of Drinking Water. In: L.H. Keith (ed.) Identification and Analysis or Organic Pollutants in Water. Ann Arbor Science Pub., Inc., Michigan.

Klaassen, C.D. and G.L. Plaa. 1967a. Susceptibility of male and female mice to the nephrotoxic and hepatotoxic properties of chlorinated hydrocarbons. Proc. Soc. Exp. Biol. Med. 124: 1163.

Klaassen, C.D. and G. Plaa. 1967b. Relative effects of various chlorinated hydrocarbons on liver and kidney function in dogs. Toxicol. Appl. Pharmacol. 10: 119.

Kutob, S.D. and G.L. Kutob. 1961. The effect of acute ethanol intoxication on chloroform-induced liver damage. Jour. Pharmacol. Exp. Ther. 135: 245.

Lehman, K.B. and Hasegawa. 1910. Studies of the absorption of chlorinated hydrocarbons in animals and humans. Archiv fuer Hygiene. 72: 327.

Malten, K.E., et al. 1968. Horny layer injury by solvents. Berufsdermatosen. 16: 135.

McCabe, L.J. 1975. Association between trihalomethanes in drinking water (NORS data) and mortality. U.S. Environ. Prot. Agency. (Draft)

McConnell, G., et al. 1975. Chlorinated hydrocarbons and the environment. Endeavour. 34: 13.

McLean, A.E.M. 1970. The effect of protein deficiency and microsomal enzyme induction by DDT and phenobarbitone on the acute toxicity of chloroform and pyrrolizidine alkaloid retrorsine. Br. Jour. Exp. Pathol. 51: 317.

National Academy of Sciences/National Research Council. 1978a. Nonfluorinated halomethanes in the environment. Environ. Stud. Board, Washington, D.C.

National Academy of Sciences/National Research Council. 1978b. Epidemilogical studies of cancer frequency and certain organic constitutents of drinking water. A review of recent literature for U.S. Environ. Prot. Agency.

National Cancer Institute. 1976. Report on carcinogenesis bioassay of chloroform. Natl. Tech. Inf. Serv. PB-264018. Springfield, Virginia.

National Institute for Occupational Safety and Health. 1974. Criteria for a recommended standard - occupation exposure to chloroform. Publ. No. (NIOSH) 75: 114. Dep. Health Edu. Welfare, Washington, D.C.

National Institute for Occupational Safety and Health. 1977. Criteria for a recommended standard - occupational exposure to waste anesthetic gases and vapors. Publ. No. (NIOSH) 77-140. Dep. Health Edu. Welfare, Washington, D.C.

Neely, W.B., et al. 1976. Mathematical models predict concentration-time profiles resulting from chemical spill in a river. Environ. Sci. Tech. 10: 72.

Pearson, C.R. and G. McConnell. 1975. Chlorinated C_1 and C_2 hydrocarbons in the marine environment. Proc. R. Soc. London. 189: 305.

Pohl, L.R. 1979. Biochemical toxicology of chloroform. Rev. Biochem. Toxicol. 1: 79.

Pohl, L.R., et al. 1977. Phosgene: A metabolite of chloroform. Biochem. Biophys. Res. Commun. 79: 684.

Potrepka, R.F. 1976. Risk of chloroform. Off. Pestic. Criter. Eval. Div., U.S. Environ. Prot. Agency, Washington, D.C.

Reynolds, E.S. 1977. Liver endoplasmic reticulum: Target site of halomethane metabolism. Adv. Exp. Med. Biol. 84: 117.

Royer, J.L., et al. 1978. Spin-trapping of the trichloromethyl radical produced during enzymic NADPH oxidation in the presence of carbon tetrachloride or bromotrichloromethane. Biochem. Biophys. Acta. 539: 402.

Rubenstein D. and L. Kanics. 1964. The conversion of carbon tetrachloride and chloroform to carbon dioxide by rat liver homogenates. Can. Jour. Biochem. 42: 1577.

Scholler, K.L. 1970. Modification of the effect of chloroform on the rat liver. Br. Jour. Anaesth. 42: 603.

Schroeder, H.G. 1965. Acute and delayed chloroform poisoning: A case report. Br. Jour. Anaesth. 37: 972.

Schwetz, B.A., et al. 1974. Embryo and fetotoxicity of inhaled chloroform in rats. Toxicol. Appl. Pharmacol. 28: 442.

Simmon, J.M., et al. 1977. Mutagenic Activity of Chemicals Identified in Drinking Water. In: D. Scott, et al. (ed.) Progress in Genetic Toxicology. Elsevier/North Holland Biomedical Press, New York.

Smuckler, E. A. 1976. Structural and functional changes in acute liver injury. Environ. Health Perspect. 15: 13.

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3.

Stokinger, H.E. and R.L. Woodward. 1958. Toxicological methods for establishing drinking water standards. Jour. Am. Water Works Assoc. 50: 515.

Symons, J.M., et al. 1975. National organics reconnaissance survey for halogenated organics. Jour. Am. Water Works Assoc. 67: 634.

Thomas, R.F., et al. 1979. Monitoring of trihalomethanes and other purgeable compounds in a water supply vulnerable to industrial contamination. 178th American Chemical Society Meeting, Division of Environmental Chemistry, September, 1979, Pap. No. 19. (Abst.)

Thompson, D.J., et al. 1974. Teratology studies on orally administered chloroform in the rat and rabbit. Toxicol. Appl. Pharmacol. 29: 348.

Timms, R.M. and K.M. Moser. 1975. Toxicity secondary to intravenously administered chloroform in humans. Arch. Int. Med. 135.

Torkelson, T.R., et al. 1976. The toxicity of chloroform as determined by single and repeated exposure of laboratory animals. Am. Ind. Hyg. Assoc. Jour. 37: 697.

Uehleke, H. and T. Werner. 1975. A comparative study on the irreversible bindings of labelled halomethane, trichlorofluoromethane, chloroform, and carbon tetrachloride to hepatic protein and lipids *in vitro* and *in vivo*. Arch. Toxicol. 34: 289.

U.S. EPA. 1977. National Organic Monitoring Survey. Tech. Supp. Div. Off. of Water Supply, Cincinnati, Ohio.

U.S. EPA. 1978a. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646.

U.S. EPA. 1978b. Statement of basis and purpose for an amendment to the national interim primary drinking water regulations on trihalomethanes. Off. of Water Supply, Washington, D.C.

U.S. EPA. 1980. Seafood consumption data analysis. Stanford Research Institute International. Menlo Park, California. Task 11, Final Report. Contract No. 68-01-3887.

Van Dyke, R.A., et al. 1964. Metabolism of volatile anesthetics to $^{14}CO_2$ and chloride. Biochem. Pharmacol. 13: 1239.

von Oettingen, W.F. 1955. The halogenated hydrocarbons, toxicity and potential dangers. U.S. Dep. Health Edu. and Welfare. U.S. Gov. Printing Office, Washington, D.C.

von Oettingen, W.F. 1964. The Hydrocarbons of Industrial and Toxicological Importance. Elsevier Publ. Co., New York.

APPENDIX I

Derivation of Criterion for Chloroform

The NCI (1976) bioassay with female mice given a time-weighted average dose of chloroform at 238 or 477 mg/kg by stomach tube 5 times per week for 78 weeks is used to derive the water quality criterion. The treatment induced hepatocellular carcinomas in the tested animals and controls as outlined in the table below. Assuming that the fish bioaccumulation factor is 3.75, the parameters of the extrapolation model are:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	0/20
238 x 5/7 = 170	36/45
477 x 5/7 = 341	39/41

le = 546 days
Le = 644 days
L = 644 days

w = 0.030 kg
R = 3.75 l/kg

With these parameters the carcinogenic potency for humans, q_1^*, is 0.18272 (mg/kg/day^{-1}). The result is that the water concentration should be less than 1.90 µg/l in order to keep the individual lifetime risk below 10^{-5}.

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