ATTACHMENT 7

STATEMENT OF BASIS AND PURPOSE
FOR AN AMENDMENT TO THE
NATIONAL INTERIM PRIMARY [DRINKING WATER REGULATIONS]
ON TRIHALOMETHANES

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OFFICE OF DRINKING WATER
CRITERIA AND STANDARDS DIVISION
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I. Summary

The trihalomethanes (THMs) are a family of organic compounds, named as derivatives of methane, where three of the four hydrogen atoms are substituted by a halogen atom. Although halogens can include fluorine, chlorine, bromine and iodine, only chlorine and bromine substituents are now considered for the purpose of this regulation. THMs in drinking water are produced by the action of the chlorine added for disinfection or oxidation, with the naturally occurring organic precursors (e.g., humic or fulvic acids) commonly found in source waters.

THMs are commonly found in drinking water supplies throughout the United States. Chloroform has been found at concentrations ranging from 0.001-0.540 mg/l and (TTHM) potential concentrations as high as 0.784 mg/l have been detected. The concentrations of TTHM increase when raw water supplies are treated with chlorine for disinfection and other purposes. TTHM concentrations are indicative of the presence of other halogenated and oxidized organic chemicals that are produced in water during chlorination.

People are also exposed to chloroform in the air they breathe and the food they eat. Analyses of the relative contribution of chloroform in drinking water, air and food exposures assumed various levels of exposure based on monitoring studies. Drinking water may contribute from zero to more than 90% of the total body burden.

Chloroform has been shown to be rapidly absorbed on oral and intraperitoneal administration and subsequently metabolized to carbon dioxide, chloride ion, phosgene, and other unidentified metabolites. The metabolic profile of chloroform in animal species such as mice, rats, and monkeys is indicated in Table 4 and is qualitatively similar to that in man.

Mammalian responses to chloroform exposure include: central nervous system depression, hepatotoxicity, nephrotoxicity, teratogenicity, and carcinogenicity. These responses are discernible in mammals after oral and inhalation exposures to high levels of chloroform ranging from 30-350 mg/kg; the intensity of response is dependent upon the dose. Although less toxicological information is available for the brominated THMs, mutagenicity and carcinogenicity have been detected in some test systems. Physiological chemical activity should be greater for the brominated THMs than for chloroform.

Although short-term toxic responses to THMs in drinking water are not documented, the potential effects of chronic exposures to THMs should be a matter of concern. Prolonged administration of chloroform at relatively high dose levels (100-138 mg/kg) to rats and mice, manifested oncogenic effects. Oncogenic effects were not observed at the lowest dose level (17 mg/kg) in three experiments. Since methods

do not now exist to establish a threshold no effect level of exposure to carcinogens, the preceeding data do not imply that a "safe" level of exposure can be established for humans.

Human epidemiological evidence is inconclusive, although positive correlations with some sites have been found in several studies. There have been 18 retrospective studies shown in Table 7 that have investigated some aspect of a relationship between cancer mortality or morbidity and drinking water variables. Due to various limitations in the epidemiological methods, in the water quality data, and problems with the individual studies, the present evidence cannot lead to a firm conclusion that there is an associaton between contaminants in drinking water and cancer mortality/morbidity. Causal relationships cannot be proven on the basis of results from epidemiological studies. The evidence from these studies thus far is incomplete and the trends and patterns of association have not been fully developed. When viewed collectively, however, the epidemiological studies provide sufficient evidence for maintaining the hypotheses that there may be a potential health risk, and that the positive correlations may be reflecting a causal association between constituents of drinking water and cancer mortality.

Preliminary risk assessments made by the Science Advisory Board (SAB), the National Academy of Sciences (NAS), Tardiff, and EPA's Carcinogen Assessment Group (CAG)

using different models have estimated the incremental risks associated with the exposure from chloroform in drinking water. The exposure to THMs from air and food have not been included in these computations. The risk estimates associated with the MCL at the 0.10 mg/l level are essentially the same from the NAS and CAG computations (3.4×10^{-4} and 4×10^{-4}) assuming two liters of water at 0.10 mg/l chloroform consumed daily for 70 years.

On the basis of the available toxicological data summarized in the following report, chloroform has been shown to be a carcinogen in rodents (mice and rats) at high dose levels. Since its metabolic pattern in animals is qualitatively similar to that in man, it should be suspected of being a human carcinogen. Epidemiological studies also suggest a human risk. Therefore, because a potential human health risk does exist, levels of chloroform in drinking water should be reduced as much as is technologically and economically feasible, using methods that will not compromise protection from waterborne infectious disease transmission.

Although documentation of their toxicity is not so well established, other THMs should be suspected of posing similar risks. Because the treatment process that can reduce drinking water levels of chloroform have about the same effectiveness in reducing levels of the other THMs, the proposed regulation is addressed to these substances, as well.

II. INTRODUCTION

The extent and significance of organic chemical contamination of drinking water or drinking water sources first came to public attention in 1972, when a report, "Industrial Pollution of the Lower Mississippi River in Louisiana" was published (EPA, 1972). While this report did not include quantification of the pollutants found, and was directed toward locating industrial discharges responsible for the pollution, the report did include analyses of finished (treated) drinking water and provided evidence of the presence of THMs. Subsequently, a more thorough examination of finished drinking water in the New Orleans area was carried out, using the most sophisticated analytical methods available (EPA, 1974). This latter study confirmed the presence of THMs and many other organic chemicals in finished drinking water, and furthermore it demonstrated that one of them, chloroform, was present in high relative concentrations.

The findings in New Orleans promoted other studies, primarily for the purpose of determining how widespread and serious the organic chemical contamination of drinking water was. Impetus was added by the passage of the Safe Drinking Water Act (PL 93-523), which directed the EPA to conduct a comprehensive study of public water supplies and drinking water sources to determine the nature, extent, sources,

and means of control of contamination by substances suspected of being carcinogenic. The National Organics Reconnaissance Survey of Halogenated Organics (NORS) (Symons, et al., 1975), or "80 City Study", was aimed primarily at determining the extent of the presence of four THMs, chloroform, bromodichloromethane, dibromochloromethane and bromoform, along with carbon tetrachloride and 1,2-dichloroethane, and at determining what effect raw water source and water treatment practices had on the formation of these compounds (Table 1). The presence of THMs in finished drinking water was confirmed, and some trend relating non-volatile total organic carbon (NVTOC) of the raw water and the total trihalomethane (TTHM) was postulated. Chloroform occurred invariably in water which had been chlorinated, while it was absent or present at much lower concentrations in the raw water. Water samples were collected at the treatment plant in winter and iced for shipment but not dechlorinated. Thus, those values might approximate minima for human exposure in the areas selected. Of the various THMs, chloroform was found at the highest concentrations (averaging approximately 75 percent of the TTHM), with progressively less bromodichloromethane, dibromochloromethane and bromoform being detected.. In some cases chloroform was found at concentrations greater than 0.300 mg/l; (the highest value found was 0.540 mg/l). Carbon tetrachloride

and 1,2-dichloroethane were found at very low concentrations. The concentration of these two components did not increase after chlorination; therefore, it can be assumed that these compounds are not related to the chlorination process.

A Joint Federal/State Survey of Organics and Inorganics in 83 Selected Drinking Water Supplies, carried out by EPA's Region V (Chicago) provided additional evidence of the ubiquitous nature of chloroform and other THMs in chlorinated drinking water (EPA, 1975). Two conclusions reached in that study were that raw water relatively free of organic matter results in finished water that is relatively free of chloroform and related halogenated compounds, and that there is a correlation in some instances between the concentrations of chloroform, bromodichloromethane, dibromochloromethane and bromoform in finished water and the amount of organic matter found in raw water.

The National Organics Monitoring Survey (NOMS), directed by Section 141.40 of the National Interim Primary Drinking Water Regulations (40 FR 59574, December 24, 1975), was aimed not only at determining the presence of THMs in additional water supplies, but also at determining the seasonal variations in concentration of these substances.

The NOMS sampling included 113 public water systems designated by the Administrator, and also included analyses

for approximately 20 specific synthetic organic chemicals deemed to be candidates of particular concern as well as analyses of several surrogate group chemical parameters which are indicators of the total amount of organic contamination. Three phases of this study were completed and the mean, minimum, and maximum values of chloroform and THMs in drinking water are reported in Table 1. Phase I analyses in the NOMS were conducted similarly to the NORS. Phase II analyses were performed after the THM-producing reactions were allowed to run to completion. Phase III analyses were conducted on both dechlorinated samples and on samples that were allowed to run to completion (terminal). Again chloroform was found at the highest concentrations in most cases, however, in a few cases bromoform was found to be the highest concentration of the THMs (0.280 mg/l). The mean concentrations of chloroform were 0.043 mg/l, 0.083 mg/l, 0.035 mg/l, and 0.069 mg/l for Phase I, II, III (dechlorinated) and III (terminal), respectively; the mean concentrations for TTHMs were 0.068 mg/l, 0.117 mg/l, 0.053 mg/l and 0.100 mg/l for Phase I, II, III (dechlorinated) and III (terminal), respectively.

III. The Role of Chlorine and Other Disinfectants

All available evidence indicates that chlorination of drinking water containing naturally occurring organic chemicals is the major factor in the formation of halogenated organic chemicals, particularly the THMs in finished drinking water. Chlorinated organic compounds, however, can also be introduced into drinking water from industrial outfalls, urban and rural runoff, rainfall, through polluted air, or from the chlorination in sewage and industrial wastewater.

Several studies in addition to those mentioned above, have demonstrated increased THM concentrations in drinking water. Work by J. J. Rook (1974) in the Netherlands, and the studies by Bellar, Lichtenberg and Kroner (1974), showed that chloroform and other halogenated methanes are formed during the water chlorination process. It should be noted that these findings came as a result of the development and application of more sensitive and refined analytical techniques. Recent work by Rook (1974, 1977) has provided some insight into the organic precursors which might be responsible for the formation of the THMs. Studies by Sontheimer and Kuhn (1977) indicate that the THMs may represent only a portion of the total halogenated products of chlorination of water. Bunn et al. (1975), have demonstrated that hypochlorite in the presence of bromide and iodide ions but not

fluoride will react with natural organic matter to produce all ten possible trihalogenated methanes.

It can be concluded from the above studies and others that the THMs occur in chlorinated drinking waters, and that the concentrations of the various THMs are dependent on the type and quality of organic precursor substances, the amount of chlorine used, and the presence of other halogen ions as well as contact time, temperature and pH.

A number of methods are available for reducing levels of THMs in drinking water. These options include modifications of current treatment practices, such as moving the point of chlorination, the use of alternative disinfectants such as chlorine dioxide, chloramines, or ozone, and various methods that will reduce organic precursor concentrations such as use of adsorbents like granular activated carbon (GAC).

Two chemicals often mentioned as alternative disinfectants, chlorine dioxide and ozone, are both well known as effective disinfectants and chemical oxidants, and some history of their practical use in water treatment has been accumulated particularly in Europe, but also in the United States.

Chlorine dioxide is usually prepared at the water plant by the reaction of chlorine (either as gas or as sodium hypochlorite) with sodium chlorite. Unless an excess of chlorine is used, there will be unreacted sodium chlorite

left over from the reaction. When chlorine dioxide reacts with organic matter in the water, one of the reaction products is the chlorite ion. Thus, whenever chlorine dioxide is used to treat water, the presence of chlorite ion in the treated water can be expected.

EPA is studying the health effects of chlorine dioxide in water, utilizing several animal species as well as human volunteers. Studies of the toxicology of chlorine dioxide and chlorite ion in drinking water reveal considerable variations. These compounds have been reported to affect the hematopoietic systems such as oxidative changes in hemoglobins and and hemolysis of red blood cells. Other bioeffects observed include gastrointestinal disturbances. The preliminary results indicate species variability in biological manifestations. Cats and African green monkeys appear to lie at the extreme ends of the spectrum from among the species studied; cats are very sensitive to hematopoietic effects whereas monkeys were apparently insensitive even at levels as high as 400 mg/l (Bull, 1979). An upper limit for chlorine dioxide by-product exposure is being considered primarily because of the lack of data concerning the safety of this material, and particularly its decomposition products, at higher concentrations (Musil et al., 1963 and Fridyland and Kagan, 1971. Studies with cats have shown that chlorite, which is oxidant that can cause anemias, has

a deleterious effect on red blood cell survival rate at chlorine dioxide concentrations above 10 mg/l. Preliminary studies in a small human population did not demonstrate substantial blood chemistry changes, except possibly in one person known to be deficient in glucose-6-phosphotase dehydrogenase. Lack of sufficient health effects data on human toxicity for ClO_2 and its by-products prevents establishment of an MCL at this time, however, work in progress is expected to provide much additional information within the coming year. In the meantime, EPA recommends that monitoring be conducted when chlorine dioxide is used, and that residual oxidant should not exceed 0.5 mg/l as ClO_2.

A preliminary study concerning ozonation of 29 organic compounds potentially present in water supply sources indicated the formation of a number of products (Cotruvo, Simmon, Spanggord, 1976, 1977). These reaction mixtures were assayed for mutagenic activity employing 1) five strains of Salmonella typhimurium (Ames Salmonella/microsome assay); and 2) mitotic recombination in the yeast Saccharomyces cerevisiae D3. After very extensive ozonation in water some of the organic compounds exhibited mutagenic activity in these systems. Similar more recent studies under extreme conditions with chlorine dioxide by-products did not exhibit mutagenic activity (SRI Report).

Combining ammonia with chlorine to form chloramines has been called the chloramine process, chloramination, and combined residual chlorination. The products of this process are monochloramine, dichloramine or trichloramines (nitrogen trichloride) depending on the pH and the chlorine to ammonia ratio. The production of the latter species may contribute to taste and odor problems in the finished water; however, chloramination does not reduce the formation of THMs.

Based on the results of numerous investigations, the comparative disinfectant efficiency of chloramines ranks last when compared to ozone, chlorine dioxide, hypochlorous acid acid (HOCL), and hypochlorite ion (OCl^-) (NAS, 1977, 1979). Early studies by Butterfield and Waties (1944, 1946, 1948) demonstrated that chloramines required approximately a 100-fold increase in contact time to inactivate coliform bacteria and enteric pathogens as compared to free available chlorine at pH 9.5. This work was later confirmed by Kabler (1953) and by Clarke et al., (1962).

Results with cysts of Entamoeba histolytica and viruses also confirm the decreased effectiveness of chloramines as disinfectants. Studies by Fair, et al., (1947) showed that additional dichloramine is about 60 percent and monochloroamine about 22 percent as effective as hypochlorous acid at pH 4.5 against cysts of E. histolytica. Kelly and Sanderson

(1960) found that chloramines in the concentration of 1 mg/l at 25° C required 3 hours at pH 6, or 6 to 8 hours at pH 10 to achieve 99.7 percent inactivation of polio virus. With 0.5 mg/l free chlorine at pH 7.8, by comparison, inactivation of 99.99 percent of polio virus can be achieved in approximately 15 minutes (Liu and McGrowan, 1973). Chloramine treatment finds its widest application in maintenance of chlorine residuals in the distributing systems. The human health effects of consuming water treated with chloramine have not been studied in detail.

Although all of these disinfectants can reduce THM formation, questions have been raised on both their toxicity and the toxicity of their by-products. Studies are underway to clarify these matters, and could result in the designation of maximum permissible levels for certain disinfectants applied to drinking water.

The use of adsorbents for THM removal has also introduced some unknown factors. Assuming that the adsorption process is effective for its intended purpose, there is the possibility that a breakthrough of some of the adsorbed chemicals may occur, that these substances will be adsorbed and subsequently slough off to produce intermittent contamination, or that bacteria and/or toxins will be added to the water from growth on the adsorbent. All of these potential effects are controllable in practice, and EPA

encourages the use of GAC to purify contaminated waters and to control THM precursors.

Thus, THM concentrations should be reduced, but without compromising public health from either increased risk of infectious disease transmission or from the chemicals that are used. Outbreaks of infectious waterborne disease have been noted when chlorination systems have been improperly operated. The alternative control methods outlined previously are effective, and are also being studied for their possible side effects. As soon as data become available, EPA will make specific recommendations regarding their use. At the present time, the best approach to reduce THMs in finished water is to reduce precursors prior to chlorination, such as with GAC. This approach has the benefit of reducing the concentration of many other organic chemicals in the water as well as to the precursors to THM and other chlorinated organics. Thus, once the organic chemical concentrations in the water have been reduced, the chemical demand for applied disinfectant will be reduced. Thus, human exposure to all disinfectant chemicals and their degradation products and by-products will be minimized. This is the intent of the regulation controlling THMs.

IV. Sources of Trihalomethane Exposure

McConnell et al. (1975), have reported that chloroform occurs in many common foods and that while some halogenated compounds in food may result from manufacturing, canning and pest control practices, chloroform may be introduced as the result of geochemical processes. Chlorinated compounds are the halogenated species most prevalent in food, but at least one food, Limu Kohu, a seaweed or algae eaten in Hawaii, contains an essential oil which is composed largely of bromoform (Burreson, et al. 1975).

Chloroform was widely used as an anesthetic in the past, and, until recently, was a common ingredient in dentifrices and cough preparations. The Food and Drug Administration has taken action to halt the use of chloroform in drug products, cosmetic products, and food-contact articles (41 FR 145026, April 9, 1976). EPA has issued a notice of "rebuttable presumption against registration" of chloroform-containing pesticides (41 FR 14588, April 6, 1976). Thus, in addition to drinking water, exposure to some or all of the THMs is complicated by other environmental sources, however, exposure from some of these sources is being reduced.

The relative human chloroform exposures can be estimated for three major sources of human exposure: atmosphere, drinking water, and the food supply. The uptake calculations are based on the fluid intake, respiratory volume, and

food consumption data for "reference man" as compiled by the International Commission on Radiological Protection. The combined uptake for adults from all three sources was derived by multiplying estimated exposure levels by the estimated annual intakes and combining the results [ODW protocol].

Human uptake of chloroform from air, food and drinking water is given in Table 2. Chloroform and TTHM uptake from drinking water was estimated by multiplying the chloroform and THM concentrations from NOMS data (Table 1) by the average consumption of 2 liters of water per day for the 70 kg adult male, by 365. One hundred per cent absorption of the amount of chloroform in drinking water is assumed for these calculations. The total chloroform uptake from water was estimated as a mean value of 64 mg per year. The maximum uptake value may be 394 mg per year.

To determine uptake of chloroform from foods, the concentration of chloroform in each food item in North American diets was multiplied by the average annual consumption of that food item by adults in the United States (NAS, 1977), and the results were combined again; one hundred per cent absorption of ingested chloroform was assumed. A calculated maximum value of about 16 mg of chloroform uptake per year from total food and a mean value of 9 mg based on ODW assumptions was obtained.

Table 2. Human Uptake of Chloroform and Trihalomethanes from Drinking Water, Food and Air

	Exposure Levels mg/year		
Chemical	Drinking Water Mean (Range)	Food Mean (Range)	Air* Mean (Range)
Chloroform	64 (0.73-343)	9 (2 - 15.97)	20 (0.41 - 204)
Trihalomethanes	85 (0.73 - 572)		

* Calculated from data supplied by Strategies and Air Standards Division, Office of Air Quality Planning and Standards. Environmental Protection Agency, Research Triangle Park. The air samples were collected both from the rural and industrial areas during the years 1974 - 76. The mean value was derived from the concentrations obtained from urban industrialized areas, the minimum value from the rural area and the maximum value from an urban industrialized area.

The calculation for the uptake of chloroform by humans from ambient air was based upon the assumptions that 63 percent of inhaled chloroform is absorbed, (NAS, 1977); the volume of air inhaled by an average adult is 8.1×10^6 liters per year; and 0.02 and 10 ppb (by volume) are the respective minimum and maximum chloroform concentrations in urban air. The minimum and maximum values for the annual uptake of chloroform by an adult were estimated at 0.41 and 204 mg, respectively. Assuming minimum exposures from all sources, the atmosphere contributes 12 percent of the total chloroform, the drinking water contributes 23 percent, and food is most significant (65%). Assuming maximum exposures from all sources, drinking water is the major contributor at 61 percent, with air at 36 percent. Thus, the relative contribution of drinking water to the total body burden of chloroform may range from a moderate to a maximum contributor as the annual exposure from water ranges from nil to 394 mg/year, and from 204 to 0.73 mg/year in ambient air (Table 3).

Table 3. 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
	Max-Water Min-Air	
Atmosphere	0.41	1
Water	343.00	97
Food Supply	9.00	2
Total	352.41	100.00

V. Metabolism

Several reports (Brown, et al., 1974; Labigne & Marchand, 1974; Fry et al., 1972; Paul and Rubenstein, 1963; Taylor et al., 1974) have indicated that chloroform is rapidly absorbed on oral and intraperitoneal administration and subsequently metabolized to carbon dioxide and unidentified metabolites in urine. Species variation in the metabolism of chloroform has been summarized in Table 4. It is noteworthy that the mouse, a species which shows greater sensitivity to the oncogenic effect of chloroform (Eschenbrenner & Miller, 1945; Brown et al. 1974) metabolized chloroform extensively to carbon dioxide (80%) and unidentified metabolites (3%) from an oral dose of 60 mg/kg. Rats also metabolize chloroform to carbon dioxide but to a lesser extent (66%). In another report, Paul and Rubinstein (1963) recovered 4 percent carbon dioxide after administering 1484 mg/kg chloroform intradoudenally to rats. The discrepancy in these two results may be dose related.

Dose related differences in the metabolism of compounds are known and have recently been reported for the carcinogen vinyl chloride. Squirrel monkeys, when given 60 mg/kg of chloroform orally, excreted 97 percent of the dose, with 17 percent as carbon dioxide and 78 percent as chloroform. Fry, et al. (1972), recovered unmetabolized chloroform ranging from 17.8-66.6 percent of a 500 mg dose

Table 4. Disposition of Chloroform - Species Variation

ANIMAL SPECIES	SEX	STRAIN	DOSE mg/ kg	METABOLISM (PERCENT) $CHCl_3$	CO_2	URINE FECES	TOTAL EXCRETION	REFERENCES
MOUSE	M	CBA CF/LP C57	60 po	6	80	3	93*	Brown et al (1974)
RAT	M	Sprague Dawley	60 po	20	66	7	93	Brown et al 1974
RAT	-	—	1484 id	70				Paul & Rubstein (1963)
RAT	M	Sprague Dawley	4710 ip		0.39			
MONKEY	M	Squirrel	60 po	78	17	2	97	Brown et al (1974)

*Includes radioactivity in carcas.
Po = Orally
id = intradeudenally
ip = intraperitoneal

of chloroform given to human volunteers during an 8 hour time period (equivalent to about 7 mg/kg). Since the metabolism of chemicals is also dependent on age and sex, the widespread variation in the quantitative disposition of chloroform in human subjects may be due to the experimental protocols wherein subjects ranging from 18-50 years of age were used. Individual variability in the non-homogenous human population is a major factor.

Metabolic similarities between carbon tetrachloride and chloroform include the appearance of halide ions in urine and carbon dioxide in breath. A related chemical, carbon tetrachloride, is a common contaminant of the chlorine used in water disinfection. Carbon tetrachloride also is metabolized to chloroform in trace amounts, which may in turn, be biotransformed to carbon dioxide. Both chloroform and carbon tetrachloride are proven animal carcinogens (see below). However, this is mentioned because of possible metabolic production of proximal carcinogens. Toxicity of carbon tetrachloride, however, has been attributed to a free radical (CCl_3) which is postulated as a metabolic intermediate. Chloroform appears to be metabolized to form phosgene (Krishna, 1979).

Many carcinogens have been reported to form complexes with proteins, DNA and RNA (Miller & Miller, 1966). In the case of chloroform, Ilett et al., (1973) reported covalent bonding of chloroform metabolite(s) to tissue macromolecules in mice. The covalent bonding increased or decreased when the animals were pretreated with phenobarbital or piperonyl butoxide, agents which stimulate or inhibit the metabolism of foreign compounds by mixed function oxidase enzymes. This is suggestive of the involvement of chloroform metabolism in these processes. These results may be interpreted to mean that the potency of an ingested chemical will be dependent upon its rate of metabolism to the active form.

Information regarding the metabolism of bromoform and other haloforms is not available. However, the structural similarities of these haloforms with chloroform indicate that they should also be absorbed by the oral and inhalation routes of exposure and then metabolized into carbon dioxide and halide ions. Related halogenated hydrocarbons of the dihalomethane series (e.g., dichloromethane, dibromomethane and bromochloromethane) have been reported (Kubic et al. 1974) to be metabolized to carbon monoxide; the rate of metabolism of dibromomethane was higher than that of the dichloromethane.

VI. Acute and Chronic Health Effects in Animals

Mammalian responses to chloroform include effects on: the central nervous system, hepatotoxicity, nephrotoxicity, teratogenicity, and carcinogenicity. Reported oral LD_{50} values are as follows: for rats, 300 mg/kg (DHEW, 1978); and for mice, 705 mg/kg (Plaa, et al., 1958).

Jones, et al. (1958), reported the effect of various oral doses of chloroform on mice 72 hours after exposure:

35 mg/kg -- threshold hepatotoxic effect - minimal midzonal fatty changes

70 mg/kg -- minimal hepatic central fatty infiltration

140 mg/kg -- massive hepatic fatty infiltration

350 mg/kg -- hepatic centrilobular necrosis

1100 mg/kg -- minimum lethal dose

Acute effects of exposure to chloroform and bromoform vary among species. Reported lethal doses for chloroform and bromoform are:

Species	Subcutaneous Lethal Dose	Values in mg/kg
Mouse	LD_{50}	704 (Chloroform) 1820 (Bromoform)
Rabbit	LD_{50}	800 (Chloroform) 410 (Bromoform)

Data on the acute toxicity of dibromochloromethane and dichlorobromomethane are not available.

Hasegawa (1910) reported dizziness and light intoxication during 20-minute exposures to chloroform concentrations of 4300-5100 ppm. Repeated exposures up to six days to concentrations as low as 920 ppm for 7 minutes resulted in symptoms of central nervous system depression (Lehman & Schmidt-Kehn, 1936). Additional important information has been submitted to EPA and is discussed below.

Effects of acute and subchronic chloroform exposure on cholinergic parameters in mouse brain were studied by Vocci, et al., (1977). Male Swiss Webster ICR mice were gavaged with single doses of chloroform (30 and 300 mg/kg) and sacrificed 15 minutes after administration of chloroform. In another experiment, the mice were gavaged with 14 or 90 daily doses of chloroform (3 or 30 mg/kg) and sacrificed 18 hours after the last administration. Neither of the above dosage regimens had any effect on in vitro [^{3}H] choline uptake in synaptosomes. In another study (ibid) of biosynthesis of acetylcholine in mouse brain, chloroform (30 mg/kg) significantly decreased the [^{3}H] acetylcholine synthesis (57% of control). Administration of chloroform (3 mg/kg) for 14 days produced a reduction in [^{3}H] acetylcholine (57% of control) (Vocci, Personal Communication, April 1979).

Chloroform, dichlorobromomethane, chlorodibromomethane and bromoform, at concentrations of 8×10^{-4} M did not

alter the update of norepinephrine or dopamine into brain synaptosomes in vitro (Vocci, Personal Communication, April 1979).

D. Teratogenicity

Teratogenic responses to oral dosing of animals with chloroform were investigated. Rats and rabbits were administered chloroform at 126 and 50 mg/kg respectively. No significant fetal deformities were observed (Thompson et al. (1973). Inhalation of chloroform by Sprague Dawley rats at 30, 100 and 300 ppm for 7 hours a day, on days 6 through 15 of gestation revealed significant fetal abnormalities including: acaudia, imperforate anus, subcutaneous edema, missing ribs and delayed skull ossification (Schwetz et al. 1974).

In an attempt to explain reproductive failure in laboratory animals, i.e., mice and rabbits, McKinney et al. (1976) conducted a study using CD-1 mice wherein groups of mice were given tap water and purified tap water (passed through a Corning 3508 ORC and a Corning 3508 B demineralizer), respectively. Analysis indicated reduced amounts of chlorinated compounds in the purified water. The study could not relate chloroform and other chlorinated organics in tap water to reproductive failures in laboratory animals, since the concentrations of chlorinated organics in water were lowest in those months that reproductive failure was

highest, although there did appear to be small, non-significant differences in this parameter between the highly purified and tap water. In a reevaluation involving the effect of Durham tap water and purified tap water as in the above study, Chernoff (1977) did not find striking differences in the reproductive success of CD-1 mice. No teratogenic studies on haloforms other than chloroform were available.

E. Mutagenicity

The THMs (chloroform, bromodichloromethane, dibromochloromethane, dibromochloromethane and bromoform) were assayed in vitro for mutagenic activity using strains of Salmonella typhimurium (TA 100 & TA 1535). The assays were conducted in desiccators to allow each compound to volatilize so that only the vapor phase came in contact with bacteria on the petri dishes. The activation system was tested and found not to be required for the bromohalomethanes since they were positive in the absence of activation. The results obtained were as follows: (a) chloroform was not mutagenic in TA 100 with or without activation, nor in TA 1535 without activation; (b) bromodichloromethane was mutagenic in TA 100 without activation, with a doubling dose of approximately 25 microliters; (c) dibromochloromethane was mutagenic in TA 100 without metabolic activation, with a doubling dose of approximately 3.5 microliters; (d) bromoform was mutagenic in TA 100 without metabolic activation,

with a doubling dose of approximately 25 microliters, and was also mutagenic in TA 1535 with metabolic activation, with a doubling dose of approximately 100 microliters (Tardiff, 1976). All three compounds demonstrating mutagenic activity did so in a dose-response mode. For certain classes of compounds, except for many chlorinated hydrocarbons (Ames, 1973) the Ames test which utilizes Salmonella typhimurium bacteria correlates highly (90 percent) with the in vivo carcinogenicity bioassay.

F. Carcinogenicity

Prolonged administration of chloroform at relatively high dose levels to animals, specifically mice and rats, manifested oncogenic effects. The investigation conducted by Eschenbrenner and Miller (1945) produced hepatomas in female mice (strain A) given repeated dosages ranging from 0.145 to 2.32 mg of chloroform for a period of only four months. Minimum doses of 593 mg/kg chloroform per day (total of 30 doses) produced tumors in all of the surviving animals.

In a recent bioassay (NCI, 1976) linking chloroform with oncogenicity, rats and mice of both sexes were fed doses of chloroform ranging from 90 to 200 (rats), and 138-477 (mice) mg/kg. In this study, the lowest dose for observed carcinogenic effect (kidney epithelial tumors) in male rats was 100 mg/kg and for mice 138 mg/kg administered to the animals for

a total period of 78 weeks. A related halogenated hydorcarbon, carbon tetrachloride, was carcinogenic in Osborne Mendel rats and in B6C3F1 mice at dosages ranging from 57 to 160 mg/kg and 1250 to 2500 mg/kg, respectively. The incidence of hepatocellular tumors formed in these animals at both dose levels almost approached one hundred percent (Table 5). The percent survival in mice treated with chloroform and carbon tetrachloride is depicted in Table 6. Almost all the animals on treatment with carbon tetrachloride died between 91-92 weeks whereas with chloroform treatment at both dose levels, 73 and 46 percent of the animals survived. Miklashevskii et al. (1966) fed chloroform to rats at 0.4 mg/kg apparently for 5 months and detected no histopathlogical abnormalities after this treatment. A recent study on the carcinogenic effect of chloroform at dose levels of 17 mg/kg/day and 60 mg/kg/day was conducted by Roe (1976), utilizing the rat (Sprague-Dawley), the beagle dog and four strains of mice (ICC Swiss, C57B1, CVA and CF/1). Comparison with the NCI study (1976) indicates that the number of animals and the duration of the experiment were essentially similar; the major differences were the dosages, which were lower than in the NCI study, and the vehicle, which was toothpaste. The only finding of neoplasia was an excess of tumors of the renal cortex in the male ICI-Swiss mice at a dose level of 60 mg/kg/day.

Table 5. Comparison of Hepatocellular Carcinoma Incidence in Chloroform and Carbon Tetrachloride-Treated Mice

Animal Group		Chloroform	Carbon Tetrachloride
Males	Controls	5/77	5/77
	Low Dose	18/50	49/49
	High Dose	44/45	47/48
Females	Controls	1/80	1/80
	Low Dose	36/45	40/40
	High Dose	39/41	43/45

Table 6. Comparison of Survival of Chloroform and Carbon Tetrachloride - Treated Mice

		Chloroform			Carbon Tetrachloride		
Animal Group		Initial No.	78 Weeks	90 Weeks	Initial No.	78 Weeks	91-92 Weeks
Males	Controls	77	53	38	77	53	38
	Low Dose	50	43	37	50	11	0
	High Dose	50	41	35	50	2	0
Females	Controls	80	71	65	80	71	65
	Low Dose	50	43	36	50	10	0
	High Dose	50	36	11	50	4	1

However, animals fed 17 mg/kg/day of chloroform showed no incidence of renal carcinoma.

Some renal tumors were also seen in control animals in a later study. The negative results observed in the dog experiment may be explained on the basis that either the animals were not exposed for a suitable length of time (i.e. duration of life span) or that an insufficient number of animals were tested, or that this species may not have been responsive to the oncogenic effect of chloroform. The negative results of the rat study may be explained on the basis of lack of strain sensitivity. Based on the extrapolation from the NCI study, the dose was too low to produce an effect in so few animals (Cueto, NCI, 1979).

Much less information is available on the carcinogenicity of bromohalomethanes. Preliminary results from the strain A mouse pulmonary tumor induction technique (Theiss et al., 1977) indicated that bromoform produced a positive pulmonary adenoma response while chloroform did not. Other studies (Poirier, et al., 1975) indicated that in several instances brominated compounds exhibited more carcinogenic activity than their chlorinated analogs in the pulmonary adenoma bioassay.

VII. Human Health Effects

A. NAS Principles of Toxicological Evaluation

The recent NAS (1977) report entitled "Drinking Water and Health" identified several principles for assessing the irreversible human effects of long and continued low dose exposure to carcinogenic substances.

Principle 1: Effects in animals, properly qualified, are applicable to man.

Principle 2: Methods do not now exist to establish a threshold for long-term effects of toxic agents.

Principle 3: The exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible carcinogenic hazards in man.

Principle 4: Materials should be assessed in terms of human risk, rather than as "safe" or "unsafe".

On the basis of studies in animals and human toxicological data the NAS (1977) has recommended that strict criteria should be applied for establishing exposure limits to chloroform.

The National Institute for Occupational Safety and Health has recommended that the occupational exposure to chloroform should not exceed 2 ppm determined as time-weighted average exposure for up to a 10 hour work day.

The human health effects as observed in accidental, habitual, and occupational exposures appear to indicate that the effects produced by exposure to chloroform are similar to those found in experimental animals. These include effects on the central nervous system, liver, and kidney.

The symptoms observed (Storms, 1973) in a 14 year old patient following an accidental exposure to an unknown amount of chloroform included cyanosis, difficulty in breathing and unconsciousness. Liver function tests measured by serum enzyme levels four days after ingestion indicated high levels of SGOT, SGPT, and LDH. The authors also noted damage to the cerebellum characterized by an instability of gait and a slight tremor on finger-to-nose testing. The symptoms disappeared in two weeks.

Several cases of habitual chloroform use have also been recorded by Heilbrunn et al. (1945). A case study of interest was a 33 year old male who had habitually inhaled chloroform for 12 years. The subject showed psychiatric and neurological symptoms including restlessness, hallucinations, convulsions, dysarthria, ataxia, and tremors of the tongue and fingers.

Lunt (1953) reported that delayed chloroform poisoning in obstetric patients, anaesthetized with chloroform is characterized by renal dysfunction as indicated by: albumin, red blood cells, and pus in the urine. Chloroform exposure

of humans by inhalation was studied by Lehman and Schmidt-Kehl (1936). Ten different concentrations of chloroform were used and the chloroform concentrations were determined by the alkaline hydrolysis method. Exposure at concentrations of 7 ppm for 7 minutes and at all higher levels up to 3000 ppm caused symptoms of central nervous system depression.

Desalva et al. (1975) studied the effects of chloroform in humans; the subjects were given dentifrice containing 3.4% chloroform and mouthwash with 0.43% chloroform for 1 to 5 years. No hepatotoxic effects were observed at estimated daily ingestion of 0.3 to 0.96 mg/kg chloroform. Reversible hepatotoxic effects were manifested at 23 to 27 mg/kg/day chloroform ingested for 10 years in a study conducted by Wallace (1959).

B. Epidemiologic Studies

By August 1979, 18 epidemiological studies, and additional unpublished reports discussed possible relationships between cancer mortality and morbidity and drinking water supplies. The results of the studies are shown in Table 7 in the approximate chronological order of completion. The table shows the statistically significant results of analysis by anatomical site. The statistically significant positive results are denoted by "M" for males and "F" to females and the statistically significant negative results are denoted by "-" before the "M" or "F".

Five of the studies were published through August 1979. All of the studies were retrospective in design; sixteen were correlation studies, and four used a case-control approach. Four studies utilized cancer morbidity or incidence rather than mortality as a measure of disease frequency. The studies vary in sample size, cancer sites considered, factors selected as possible explanatory variables, parameters selected as indicators of water quality, and in the statistical techniques used for analysis, so caution must be used in comparing the results of one study with the results of another study.

There are several problems which make the results difficult to interpret: 1) there is limited water quality data on organics and other contaminants in the finished drinking water, and the data which exist cover less than five years; and 2) the water quality data are often from geographic areas other than those (usually counties) reporting cancer mortality data.

The water quality data are recent, and it is not known to what extent they reflect past exposure to THMs. This is important, since the latent period for most types of cancer is measured in decades. Comparison of the various study results is difficult also because of the different approaches used.

In general, retrospective epidemiological studies are a useful methodological tool in hypothesis generation. The results from these studies, when viewed collectively, can provide some insight into the postulation of causal relationships which then need to be tested further, using epidemiological designs such as case-control or cohort studies, for documentation.

When the evidence from all studies is weighed, an emphasis can be placed not only on the statistical significance of single correlation coefficients but on their consistency and patterns. When more than one independent study shows positive associations for site-specific cancers, then the association may not be due to chance alone. When the association is verified by consistent results across all four sex-race groups (white male, non-white male, white female, non-white female), the association is more likely to be used due to the variable considered and the evidence should be viewed more seriously. The studies done so far suggest the appropriateness of concern.

There is much evidence (both epidemiological and experimental) that most human cancers result from a combination of causes (Weisburger, 1977). Etiologic factors (e.g. smoking as a cause of lung cancer, soot as a cause of scrotal cancer in chimney sweeps) that result in increased relative risk

greater than 5, were among the first to be discovered. The etiologic factors associated with cancers of gastrointestinal and urinary tract are more difficult to isolate from epidemiological studies because of the lower incidence and mortality rates, the interaction of environmental causes, and site-specific differences. The increased relative risk of populations exposed to most factors suspected of being associated with gastrointestinal and urinary cancers are less than three. Effects as small as, or smaller than, these, are difficult to detect or quantify.

A number of the epidemiologic studies relating "water quality" to cancer did not define the water quality parameter by chemical constituents but instead compared cancers in persons who used water from different sources. Among the first of these was an investigation by Page, Talbot, and Harris (1974). The study considered Louisiana parish (county) cancer mortality rates for 1950-69, for total cancers and various selected cancer sites, and related these to the percentage of the parish populations drinking water from the Mississippi River, which is known to be contaminated by many organic chemicals (Laseter, 1972). The variables controlled were the rural-urban character of the parish, median income, population density, and proportion of population employed in the petroleum, chemical, and mining

industries. An unweighted regression analysis showed a positive correlation between drinking water and total cancer (excluding cancer of the lung, urinary tract, GI tract, and liver), and then separately for cancer of the gastrointestinal organs and lung cancer. These investigations suggested an association between cancer mortality rates and use of drinking water from the Mississippi.

Meinhardt, et al. (1975), commenting on the Page-Harris report, looked at the cancer mortality gradient by apparent "dose" of river water and concluded that there was a random distribution of high and low cancer mortality rates among the river water consumers along the lengths of the Missouri and Mississippi River systems.

Subsequent reports by Page and Harris (1975, 1976) on the "Relation Between Cancer Mortality and Drinking Water in Louisiana" utilized explanatory variables and cancer sites similar to those in the first study; relationships for all four sex-race groups were considered. Positive regression coefficients for the water variable that were found statistically significant were:

Total cancer sites: WM, NWM, NWF

All other than lung: WM

Urinary Tract: WM, NWF

Gastrointestinal: WM, NWM, WF, NWF

Tarone and Gart (1975) reviewed the Page-Harris work and included an additional variable, elevation above sea level. By using a weighted regression analysis for four race-sex groups, statistically significant, positive correlations were found between the water variable and total cancer and lung cancer mortality for white males (WM), non-white males (NWM), and non-white females (NWF). The correlations were not statistically significant for while females (WF) for the same sites. Thus, there was a lack of consistency across the four sex-race groups for the aforementioned cancer sites.

Vasilenko and Magno (1975) conducted an ecological study in New Jersey and determined the relation between water source and age-adjusted cancer mortality from lung, stomach and urinary tract cancer of white females. Water quality was estimated from the ratio of the number of households served by public systems and private water companies to the number served by individual wells. Positive associations were found for lung and stomach cancer.

DeRouen and Diem (1975) also reviewed the relationship of cancer mortality in Louisiana and the Mississippi River as the drinking water source looking at ethnic variables as a possible confounding factor. By dividing Louisiana into a northern and southern section, they were able to mimic an ethnic division of the population. Many of the variables

(urban-rural characteristics, median income, employment characteristics, and elevation above sea level) included in the previous studies were omitted. The water variable was handled differently by the investigators. Population groups were dichotomized into those who obtained none of the water from the Mississippi River, and those who obtained some or all from the river. The results showe a positive relationship between cancer mortality and drinking water, for gastrointestinal cancer. The cancer mortality rates for southern parishes of Louisiana whose source of drinking water is the Mississippi River are higher than in the southern parishes whose source of drinking water is not the Mississippi River for the following:

Stomach: NWF	Cervix: NWF
Rectum: WM	Lung: NWF
Large Intestine: WF, NWF	Total Cancer: NWF

The cancer mortality rates tend to be higher for the southern parishes with river water use than northern for river water parishes for cancer of the urinary tract, gastrointestinal tract, and the lung.

In another set of analyses and comments, DeRouen and Diem (1975) discuss the problems associated with interpretation of regression coefficients as they relate to the Page and Harris Report, particularly the problem of making interferences from correlational studies. They concluded that

inconsistencies such as the failure to see the same relationships for all sex-race groups reduces the credibility of the hypothesis of a causal relationship between water source and cancer risk.

An analysis was done by McCabe (1975) of EPA using the 50 (of a total of 80) NORS cities with a 1950 population greater than 25,000 and 70 percent or more of the city's population, receiving water comparable to that sampled by EPA. McCabe showed a statistically significant correlation between the chloroform concentrations in the drinking water and the cancer mortality rate by city for all cancers combined.

In a second analysis by McCabe using water quality data from Region V, correlations between chloroform and TTHMs and total cancer mortality were not positive. When the same correlations were done using Region V plus NORS data for chloroform and total trihalogenated methane concentration levels, a positive statistically significant result was obtained.

Several epidemiological studies have been conducted in the Ohio River area. Buncher (1975) conducted a study of 88 counties (in Ohio, bordering the Ohio River) of which 14 used the Ohio River as a drinking water source. Buncher reports no significant relationship with drinking water from the Ohio River and the higher cancer mortality rates. There

was a weak positive correlation between the chloroform concentration in 23 cities and the cancer mortality rate for all cancer sites in white males. Similar results were found in 77 cities (59 with surface water supplies) between chloroform concentrations and pancreatic cancer mortality in white females. For cities that accounted for more than 70 percent of the county population, there was a significant correlation between chloroform concentration and bladder cancer mortality rates for both white males and white females.

As a follow up on the Buncher study, a study by Kuzma, et al. (1977), considered the 88 Ohio counties, classified as either ground water or surface water counties based on the source of the drinking water used by a majority of the county residents. A two-stage analysis was performed and no statistically significant results were shown between the drinking water from the Ohio River and cancer mortality rates. However, rates for stomach, bladder, and total cancers were higher for white males in counties served by surface water supplies (probably chlorinated) than in counties served by ground water supplies (probably not chlorinated).

Reiches, et al. (1976), re-examined the Ohio data using a different methodology. Correlations between the surface drinking water variable and cancer mortality rates for

stomach cancer and total cancers for both white males and females were statistically significant. The correlations between the drinking water variable and cancer mortality rates of the pancreas, bladder, esophagus, gastrointestinal tract, and urinary organs were significant for white males only.

Although several studies defined the water quality parameter by chlorination or levels of chloroform, only one study has considered the relationships of cancer with all THMs, both collectively and separately. Cantor et al. (1978) studied the correlation of cancer mortality at sixteen anatomical sites with the presence of concentration levels for each THM and TTHM in drinking water for whites. Counties were grouped according to the percentage of the county population served by the sampled water supply. In both sexes, there was a positive dose-response gradient of increasing correlation between trihalomethane concentration and bladder cancer. The correlation was stronger for bromoform than with chloroform. There was a negative correlation in white females of stomach cancer with total THM levels. Kidney cancer in white males showed a positive correlation with chloroform levels. Lung cancer in white females showed a positive correlation with THM levels. Among white males non-Hodgkins' lymphoma showed a positive correlation with bromoform. A positive dose-response was observed between

brain cancer mortality (in both sexes) with increasing use of water containing chloroform, but the associations were not strong.

Alavanja, et al. (1976) conducted a retrospective, case-control study of female cancer mortality and its relationship to drinking water chlorination in seven selected New York counties. A statistically significant association was found between a region being served from a chlorinated drinking water supply and combined gastrointestinal and urinary tract cancer mortality rates in that region. There was also a higher mortality for the summed gastrointestinal and urinary cancer in urban areas served by chlorinated surface or ground drinking water supplies than in urban areas served by nonchlorinated supplies, however, the results should be viewed cautiously due to the small numbers in the sample.

Alavanja (1977) expanded this study and included gastrointestinal and urinary cancer deaths. Results showed that males living in the chlorinated water areas of three counties and females living in the chlorinated water areas of two counties were at greater risk of gastrointestinal and urinary tract cancer mortality than individuals living in the non-chlorinated areas. Alavanja (1978) did a second study (shown on Table 7), which expanded the first to nineteen counties in New York and several specific cancer

sites. Statistically significant positive associations were found for males and lung cancer and for females and pancreatic cancer. Statistically significant positive associations were found for both males and females and cancer of the large intestine, combined gastrointestinal, and all cancers.

Kruse (1977) conducted a retrospective, case control study of white males and females in Washington County, Maryland. The relationship between mortality and morbidity from liver (including biliary passages) and kidney cancer in areas supplied by chlorinated public water supplies was analyzed. While there was a higher incidence of liver cancer among the exposed group; i.e., the group which consumed chlorinated drinking water, the correlations were not statistically significant. It should be noted that the sample size was small and that fewer than 50 cases each of liver cancer and kidney cancer were counted.

Salg (1977) also conducted a retrospective study of various cancer mortality rates and drinking water from a variety of sources and receiving different types of treatment in 346 counties in seven states in the Ohio River Valley Basin. She compared mortality rates for white and non-white males and females using weighted regression analyses, surface water usage showed weak but statistically significant associations between chlorinated water supplies (regardless

of source) and the following cancers: for white males - esophagus, respiratory organs, large intestine, rectum, bladder, other urinary organs and lymphosarcoma and reticulosarcoma; for white females - breast and rectum, and for non-white females -esophagus and larynx. Rectal cancer showed positive correlations across all race-sex groups. It should be noted that the test of significance utilized for this study was $p < 0.10$, which is less stringent than that used in other studies.

Mah, et al. (1977), conducted a retrospective study of the white population in the Los Angeles County area of the relationship between cancer mortality and morbidity and the chlorinated drinking water supply. They did not reveal any trends and showed no significant relationships for either cancer mortality or morbidity. The authors pointed out several methodological problems, including the diluting effect of migration into the area covered by this study.

Hogan et al. (1979) also utilized the NORS and Region V data sets and applied various statistical procedures to the data in order to determine the effects of using different statistical models. Their results were similar to previous studies showing a positive correlation between rectal-intestinal and bladder cancer mortality rates and chloroform levels in drinking water when weighted regression analysis were applied. However, as the authors pointed out, "the marked extent to which these results were dependent on (1)

the weighting scheme adopted in the analysis, (2) the presumed appropriateness of the data, and (3) the characteristics of the statistical model, was also clearly illustrated."

Wilkins (1978) conducted a case-control study in Washington County, Maryland and investigated the association between liver, kidney and bladder cancer and chlorinated water source. A positive correlation was found for female liver cancer and male bladder cancer and the chlorinated drinking water source. Due to small numbers of cases the outcome of this study should be viewed with suspicion.

Rafferty (1979) studied associations between drinking water quality in North Carolina communities and cancer mortality rates. The drinking water supplies were characterized by domestic and/or industrial contribution. No significant positive association were found.

Tuthill and Moore (1978) investigated the association between cancer mortality rates and parameters of water quality for Massachusetts community public water supplies. The average annual chlorine dose was one of the independent water characteristics. Simple correlations showed that the average chlorine dose level in the water was negatively associated with female buccal cancer, and positively associated with female esophageal and male respiratory cancers. Occupation, population mobility, and other demographic variables were controlled.

In summary, many but not all of the studies have found positive correlations between some characteristics of drinking water and various cancer mortality/morbidity rates. However, these correlations are dependent upon the selection and appropriateness of the data, the weighting scheme and extrapolation in the analysis, and the characteristics of the statistical model. Because of these dependencies the quantitative, causal interpretation of results generated from an indirect or ecological study should be viewed as tenuous for the primary purpose of generating hypotheses and even questionable in most cases.

It is important in the evaluation process to consider the results from other epidemiological studies as they develop hypothesis of potential causal associations between cancer mortality and other agents. For example, the confounding factors of diet, occupation, and smoking all have been suggested as potential causative agents of bladder cancer, Cole (1972). Therefore, any epidemilogical study that investigates the possible association between bladder cancer and drinking water should be designed to avoid the problems that result in confounding of the data. None of the studies completed thus far have obtained data on or controlled for diet; several studies have attempted to control for occupational exposure (Page and Harris, 1974 and 1975; Cantor, et al., 1978; Tuthill and Moore, 1978);

only the studies by Kruse (1977) and Wilkins (1978) obtained smoking data. Only a few studies considered four sex-race groups (the number of non-whites is too small in some of the geographic areas) and of those studies only a few showed consistent patterns of associaton of specific cancer sites, e.g., Salg (1977)-rectum. Several studies which considered only white populations found positive correlation coefficients for both sexes: Kuzma (1977) - stomach; De Rouen (1975) - intestine, stomach and bladder; Buncher (1975) - bladder; Reiches (1976) - stomach; Cantor (1978) - bladder; Hogan (1979) - intestine and bladder; and Alavanja (1978) - intestine. Only a few studies defined the water quality variable by the chloroform concentrations (McCabe, 1975; Buncher, 1975; Cantor et al., 1977; Hogan et al., 1977; Alvanja, 1978), and by the THM concentrations (Cantor et al. 1977).

Of particular interest are possible correlations of liver and kidney cancer rates with drinking water, since the animal exposure data indicate that hepatocellular carcinomas and hepatic modular hyperplasias have been observed in B6C3F1 strains of mice after life time exposure to chloroform. Several of the preliminary studies grouped the cancer sites for the anatomical systems, e.g., gastrointestinal and urinary organs, in order to increase the sample size. One of the studies (Cantor, 1978) which considered site-specific cancer mortality showed a positive association between

drinking water and cancer of the kidneys in white males. The absence of any positive association between drinking water and liver cancer mortality may be due in part to small sample sizes, very low incidence of the disease, or because the exposure levels of contaminants in trace amounts over a lifetime may be below a no-effect level (Weisburger, 1977). The incremental increase may be too small to measure for statistical significance. On the other hand, many scientists believe that the specific site in which cancer appears in animal tests need not necessarily be the same site in which the cancer is likely to appear in humans.

Thus, the evidence is incomplete and the trends and patterns of association have not been fully developed. As stated previously, a causal relationship cannot be established by correlation studies. When viewed collectively, the epidemiological studies completed thus far provide evidence for maintaining a hypothesis that there may be a health risk and that the positive correlations may be due to an association between some constituents of drinking water and cancer mortality. The animal test data alone provide a firm basis for policy decision making. Additional epidemiological studies may provide evidence regarding the strength of the associations and the possibility of a causal relationship between drinking water and cancer mortality, and thus provide a stronger basis for further regulatory action.

The NAS Epidemiology Subcommittee of the Safe Drinking Water Committee reviewed the first thirteen of the aforementioned eighteen studies. In the report, "Epidemiological Studies of Cancer Frequency and Certain Organic Constituents of Drinking Water -- A Review of Recent Literature Published and Unpublished," September 1978, the Committee reached the following conclusions, which are consistent with EPA. Among the group of studies that characterized water quality by actual measurements, the results 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 positive association found for bladder cancer was small and had a large margin of error; not only statistical, but much more importantly, because of the very nature of the studies.

Further research is being conducted with more definitive analytical studies. A large case-control bladder cancer study with 3,000 cases and 6,000 controls is being conducted by the National Cancer Institute (NCI). Three other case-control colon cancer studies are being conducted in Louisiana, Pennsylvania, and Utah. The results of these studies may provide more solid evidence to answer the question of possible associations between water quality and increased incidence of bladder and colon cancer.

VIII. Mechanism of Toxicity

Biologic responses upon exposure of mammals to chloroform include effects on the central nervous system resulting in narcosis, hepatotoxicity, nephrotoxicity, teratogenicity and carcinogenicity. Elucidation of the mechanism of toxicity of chloroform and related compounds has been attempted by several researchers.

Scholler (1968) and McLean (1970) observed that phenobarbital pretreatment of rats caused an increase in liver necrosis after administration of chloroform. Later, Brown, et al. (1974) reported that exposure of rats to an atmosphere containing chloroform (0.5%) for 2 hour markedly decreases glutathione (GSH) concentration in the liver when the animals have been pretreated with phenobarbital. In an attempt to further elucidate the role of GSH in chloroform-induced hepatotoxicity, Docks and Krishna (1976) injected chloroform into rats pretreated with microsomal enzyme inducers - phenobarbital, 3-methylcholanthrene, acetone and isopropanol. A dose of chloroform as little as 0.2 mg/kg decreased liver GSH levels and caused centrilobular necrosis within 24 hours in phenobarbital pre-treated rats. At a dose of 0.05 ml/kg, chloroform did not decrease liver GSH or cause liver necrosis. When the rats were not pretreated with phenobarbital, a chloroform dose of 0.2 ml/kg caused neither GSH depletion nor necrosis. In this connection, it

is interesting to note that cysteine, which is a precursor of GSH and a common amino acid in one's diet, protected the liver from the hepatotoxicity produced by chloroform. The animals were also protected from the hepatotoxic effect by pretreatment with cystamine, not a precursor of GSH, thus suggestive of a mechanism other than of GSH depletion in the hepatotoxicity of $CHCl_3$.

Earlier reports by Ilett, et al. (1973) suggested the possibility of another mechanism involving the formation of an active metabolite of chloroform responsible for the chloroform-induced hepatotoxicity. This study correlated the renal and hepatic necrosis with covalent binding of chloroform metabolites to tissue macromolecule. Bioactivation of xenobiotics including chloroform, involves mixed function enzymes; the NADPH cytochrome reductase-cytochrome P-450 coupled systems. Sipes, et al. (1972) studied the bioactivation of carbon tetrachloride, chloroform and bromotrichloromethane utilizing ^{14}C-labeled compounds and rat liver microsomes. The covalent binding of radiolabel to microsomal protein was used as a measure of conversion of the compounds to reactive intermediates. The authors concluded that cytochrome P-450 is the site of bioactivation of these three compounds rather than NADPH cytochrome C reductase. CCl_4 bioactivation proceeds by cytochrome P-450 dependent reductive pathways, while $CHCl_3$ activation, proceeds by cytochrome P-450 dependent oxidative pathways.

The isolation and identification of an active metabolite of chloroform supposedly responsible for toxicity was attempted by Pohl and his co-workers (1977). 2-oxithiazolidine-4-carboxylic-acid, an *in vitro* metabolite of chloroform, and presumably formed by the reaction of cysteine and phosgene ($COCl_2$), was isolated and characterized. When the incubation was conducted in an atmosphere of $[^{18}O]\ O_2$, the trapped $COCl_2$ contained $[^{18}O]$. These findings suggest that C-H bond of $CHCl_3$ is oxidized by a cytochrome P-450 mono-oxygenase to produce trichloromethanol which spontaneously dehydrochlorinates to phosgene. The electrophilic phosgene could react with water to form carbon dioxide, a known metabolite of $CHCl_3$ *in vitro* and *in vivo* or with microsomes to yield a covalently bound product. The *in vitro* oxidation of chloroform and its relationship to chloroform toxicity has been further substantiated by the studies wherein deuterated chloroform was used. Pohl and Krishna (1978) reported that $CDCl_3$ was metabolized slower than chloroform suggesting that the cleavage of C-H bond of chloroform is the rate determining step in the enzymatic process. The observation that $CDCl_3$ is less hepatotoxic than $CHCl_3$ indicates that the cleavage of the C-H bond is also the critical step in the process leading to $CHCl_3$ induced hepatotoxicity. The finding that $CDCl_3$ depletes less glutathione in the liver of rats than $CHCl_3$ suggests

the active metabolite phosgene is responsible for the depletion of glutathione.

In the experiments involving the isolation and characterization of metabolites of chloroform, the evidence for the metabolism of chloroform to phosgene *in vitro*, by the oxidative pathway was present. Recent research has indicated the possibility of formation of phosgene *in vivo*. Pohl, et al. (1979), isolated and characterized 2-oxo-thiazolidine-4-carboxylic acid from the liver of rats pretreated with cysteine carboxylic acid after a dose of chloroform and/or deutrated chloroform. In these experiments, deuterated chloroform yielded less amount of metabolite, confirming once again the specificity of the cytochrome P-450 dependent enzymes in the mediation of oxidative dehalogenation of chloroform and its toxicity.

IX. Risk Assessment

The establishment of chloroform as an animal carcinogen, plus the epidemiological data and mutagenesis data on THMs, show that a potential human risk exists from the consumption of THMs, but these data do not quantify the risk. Methods have been developed to estimate the level of risk, based on an assumption that there is no threshold level for the action of a carcinogen. The state-of-the-art at the present time is such that no experimental tools can accurately define the absolute numbers of excess cancer deaths attributable to chloroform in drinking water. Due to the biological variability and a number of assumptions required, each of the risk-estimating procedures leads to a different value. There is wide variation among these estimates and their interpretation.

The EPA Science Advisory Board (SAB)(1975), using the highest levels of chloroform then reported in drinking water by the NORS data (0.300 mg/l) and assuming a maximum daily intake of 4 liters of water for a 70 kg man, attempted to estimate the risk. The estimates were based on the Eschenbrenner and Miller (1945) animal data, which themselves are subject to great variability since the experiments used only 5 animals per sex per dose. Using a linear extrapolation of the animal data over more than 2 orders of magnitude dose from mice to humans at the 0.300 mg/l concentration level, the lifetime incidence of liver tumors in man

were estimated to range from 0 to .001 (95% confidence limits) or 0 to 100 x 10^{-5} in a lifetime. This rate may be compared with the lifetime incidence of 260 x 10^{-5} for malignancy of liver derived from the data of the Third National Cancer Survey (1976). This estimate would range from zero to approximately 40% of the observed incidence of liver cancer in the United States that may be attributable to exposure to chloroform in drinking water at the 0.300 mg/l level. It should be noted that this value is at the upper limit of the confidence interval and the linear non-threshold dose-effect model allows an estimate of maximal risk where a risk has actually been observed. Most other models would yield lower estimates. The SAB, however, also stated that a more reasonable assumption would yield lower estimates of the risk.

Tardiff (1976) using four different models, calculated the maximum risks from chloroform ingestion via tap water. Using a margin of safety of 5000 applied to the minimum effect animal dose, i.e., the Weil conjecture, the "safe" level was calculated to be 0.2 mg/kg/day. Using the log-probit model and the slope recommended by Mantel and Bryan, the conclusion reached was that at a maximum daily dose of 0.01 mg/kg the risk would be between 0.016 and 0.683 cancers per million exposed population per year. Using the identical data, but with the experimental slope of the dose

response curve as found in the mice as opposed to the slope of the one in the previous calculation, the conclusion reached was that a maximum daily dose of 0.01 mg/kg would produce less than one tumor per billion population per lifetime. Using the linear, or one hit model, usually considered to be the most conservative, a risk estimate of between 0.42 and 0.84 cancers per million population per year was calculated to result from a dosage level of 0.01 mg/kg/day. The two step model produced an estimated maximum risk of between 0.267 and 0.283 cancers per million population per year at a dose level of 0.01 mg/kg/day.

In the National Academy of Sciences (1977) report on "Drinking Water and Health," lifetime risks were estimated from the more recent, and much more extensive NCI animal data using a multi-stage model.

For a concentration of chloroform at 1 ug/liter the estimated incremental lifetime cancer risk would fall at approximately 1.7×10^{-6} per microgram per liter at the upper 95% confidence limit, assuming 70 year daily consumption of water at that level. Assuming lifetime exposure at the standard of 0.10 mg/l level in drinking water the incremental risk would be 3.4×10^{-4} assuming two liters of water at 0.10 mg/l consumed daily for 70 years.

In evaluating the risk estimates, it is important to compare the calculated maximum risk with the current cancer

mortality data. Both liver and kidney cancer are rare diseases in the U.S. (< 5 per 100,000 population per year). The standardized mortality rates in the U.S. for white males and females combined are 52.5 per million per year for liver cancer and 29.2 per million per year for kidney carcinoma.

Based on the various risk estimates, Tardiff (1976) calculated that the percent of the annual cancer mortality attributable to chloroform in drinking water could be 1.60% and 1.44% for liver and kidney cancer respectively assuming the maximum exposure levels. Applying these percentages to the actual cancer mortality rates, the number of cancer deaths per year would be 168 from liver carcinoma or 84 from kidney carcinoma; an estimated maximum of 252 cancer deaths per year attributable to chloroform in drinking water.

Reitz, Gehring, and Park (1978) discussed EPA's procedures in estimating risk. They stated that EPA "seriously overestimates the actual potential of chloroform .... (for) two major reasons." These are: (1) The mechanism through which chloroform exerts its toxicity, and (2) reliance on the NCI bioassay protcols which call for high doses of chloroform, and by not conducting studies at lower doses which usually induce relatively less carcinogenicity, there is a likelihood of ignoring a possible detoxification mechanism which protects test animals until they are overwhelmed by very large doses. They also suggest that an experiment

to evaluate the carcinogenicity of chloroform at lower doses must be performed before high/low dose extrapolations can be performed. Definitive data do not exist to prove or to disprove the above claims.

The authors indicated that EPA's proposed standard for THMs of 0.10 mg/l in drinking water supplies was based on the carcinogenic risk estimates. It should be pointed out the EPA's proposed standard for THM was based upon that feasibility of achieving the TTHM concentration in drinking water, as well as the potential adverse health effects.

EPA's Office of Water Planning and Standards and Office of Research and Development with EPA's Carcinogen Assessment Group, developed a risk estimate in the draft document, "Chloroform - The Consent Decree Ambient Water Quality Criteria Document" (1979). The method used assumed consumption of 2 liters/per day of drinking water and 18.7 gm/per day of fish and shellfish. The lifetime risk estimates for excess cancers ranged from 10^{-5}, 10^{-6}, and 10^{-7} with corresponding consumption of 2.1 ug/l, 0.21 ug/l and 0.021 ug/l, respectively. The difference in these risk estimations may be explained by the assumption of daily fish consumption as well as other exposure sources. Without the fish consumption, the equivalent concentrations are 4.8 ug/l and 0.48 ug/l for estimated cancer risk of 1×10^{-5} and 1×10^{-6}, respectively. When this estimate is computed for

the concentration of 0.10 mg/l for levels in drinking water, the incremental risk would be 4.0×10^{-4} assuming two liters of water at 0.10 mg/l was consumed daily for 70 years.

At an assumed lifetime exposure of 2 liters of water per day at 0.10 mg/l chloroform the risk reduction to the impacted population was estimated as a range of approximately 200-500 total cases. It should be noted however, that these average exposure levels in the impacted population may result in overestimates of the risk in light of the facts that: 1) The computations are based upon lifetime exposures. In actuality the proposed interim standard will likely be reduced in the future as technologically feasible, and, therefore, the lifetime exposure values will be less. 2) The interim standard encourages maximum reduction obtainable using current technology. A much lower average exposure is likely in the future because technology will most likely improve and result in greater exposure reductions. On the other hand, these may be underestimated because they are based upon toxicity exposure data from chloroform, which is only a portion of the TTHMs, which are only a portion of the by-products of the chlorination process; therefore, the magnitude of the contribution to the risk of the other THMs, which in some cases contribute significantly to TTHMs, is unknown. The exposure to THMs from air and food have not been included in these computations.

X. Seclected Maximum Contaminant Levels (MCLs)

Since a risk to the public exists from exposure to TTHMs and other chlorination by-products in drinking water, the potential for that risk should be reduced as much as is technologically and economically feasible without increasing the risk of microbiological contamination. This can be accomplished by several means, and the Safe Drinking Water Act (PL 93-523) provides two major regulatory avenues - 1) the establishment of an MCL, or 2) the institution of a treatment requirement.

EPA has determined that the establishment of an MCL in the Interim Primary Drinking Water Regulations, along with monitoring requirements, is the most effective and immediate approach to reducing the levels of THMs in drinking water. The Administrator has determined that monitoring is both technically and economically feasible (refer to "Economic Impact Analysis of a Trihalomethane Regulation for Drinking Water," EPA, 1977). Measures taken to reduce the THM concentrations will concurrently provide the additional benefit of reducing human exposure to the other undefined by-products of chlorination and possibly other synthetic organic contaminants.

Since it is known that chlorination of water is primarily responsible for the relatively high levels of THMs in drinking water, modifications in the chlorination process,

the substitution of other disinfectants, and the use of adsorbents and other technologies to remove precursor chemicals are possible approaches to control. The optimal approach would be to reduce organic precursor concentrations prior to addition of a disinfectant in order to reduce disinfectant demand and minimize all by-products.

Use of a chlorine residual in a less active form such as combined chlorine or chloramine will significantly reduce THM formation; however, chloramines are much less potent disinfectants than free chlorine, and therefore, this approach must only be used after careful consideration, and assurance of maintenance of excellent biological quality. The two chemicals most often mentioned as substitute disinfectants, ozone and chlorine dioxide, are both well known as effective disinfectants and chemical oxidants. The issues of the biological effects and toxicity of these disinfectants and their by-products are being clarified by studies underway. In the meantime, EPA recommended that the residual total oxidant levels after application of chlorine dioxide should be limited to 0.5 milligram per liter.

The National Organics Monitoring Survey found that the mean total trihalomethane (TTHM) concentrations in the drinking water systems evaluated were approximately 0.068, 0.117, 0.053 and 0.100 mg/l for Phase 1, II, III (dechlorinated) and III (terminal) respectively, with the highest levels of 0.784 mg/l in Phase II (refer to Table 1).

It is reasonable to assume that the various calculated risk estimates for chloroform indicate a potential risk to public health. It is possible that a percentage of the total number of liver and/or kidney cancers are attributable to exposure of chloroform in drinking water, although it is most likely that drinking water exposure would interact with a number of other variables such as smoking and diet as effect modifiers in a multifactorial manner. It is also likely that the other by-products of chlorination also present a potential risk.

Thus, based upon a number of risk extrapolations assuming various levels of exposure to chloroform in drinking water, it has been estimated that such exposures may cause an annual excess of cancers in the U.S. population (ranging from 0 to several hundred). At higher levels of exposure of chloroform (> 0.300 mg/l) the cancer risk estimates are even higher.

The reduction of TTHMs to an MCL level of 0.10 mg/l would reduce the unnecessary and excessive exposure to these potential human carcinogens, mutagens, and chronic toxicants, and other effects. At the same time, measures taken to reduce THM levels (such as the use of adsorbents) will concurrently result in reduction of human exposure to other contaminants in drinking water.

Since it is economically and technologically feasible to reduce the THM levels in drinking water, and since benefits

are achieved by reducing the health risks of exposure, EPA has decided to establish the MCL at 0.10 mg/l as the initial feasible step in a phased, regulatory approach. As more data become available from implementation experience, and toxicology and epidemiology, standards are expected to become more restrictive. In the meantime, EPA and the States should continue to take steps as necessary on a case-by-case basis to provide adequate protection for the delivery of safe drinking water to the public, by minimizing the amounts of toxic chemicals in the water.

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