STATEMENT OF BASIS AND PURPOSE

FOR AN AMENDMENT TO THE

NATIONAL INTERIM PRIMARY DRINKING WATER REGULATIONS

ON TRIHALOMETHANES

JANUARY 1978

OFFICE OF WATER SUPPLY

CRITERIA AND STANDARDS DIVISION

ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

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I. 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 trihalomethanes (THM) in such water. 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 trihalomethanes and many other organic chemicals in finished drinking water, and furthermore demonstrated that one of them, chloroform, was present in extremely 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 (P. L. 93-523), which directed the

Environmental Protection Agency to conduct a comprehensive study of public water supplies and drinking water sources to determine the nature, extent, sources of, and means of control of contamination by chemicals or other 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 trihalomethanes, 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 (refer to Table 1). The presence of trihalomethanes in finished drinking water was confirmed, and some trend relating non-volatile total organic carbon (NVTOC) of the raw water and the total trihalomethane concentration (TTHM) was postulated. Chloroform occurred invariably in water which had been chlorinated, while it was absent or present at lower concentrations in the raw water. Water samples were collected at the treatment plant in winter and iced for shipment but not dechlorinated. Thus, these values might approximate minima for human exposure in the areas selected. Of the various

Table 1. Analytical Results of Chloroform, Bromoform, Bromodichloromethane, and Dibromochloromethane and Trihalomethane in Water Supplies from NORS and NOMS

Concentrations in mg/liter

	NORS	NOMS			
		Phase I	Phase II	Phase III	
	Chloroform			Dechlorinated	Terminal
Median	0.021	0.027	0.059	0.022	0.044
Mean	-	0.043	0.083	0.035	0.069
Range	NF-0.311	NF-0.271	NF-0.47	NF-0.20	NF-0.540
	Bromoform				
Median	0.005	LD	LD	LD	LD
Mean	-	0.003	0.004	0.002	0.004
Range	NF-0.092	NF- 0.039	NF-0.280	NF-0.137	NF- 0.190
	Dibromochloromethane				
Median	0.001	LD	0.004	0.002	0.003
Mean	-	0.008	0.012	0.006	0.011
Range	NF-0.100	NF- 0.19	NF-0.290	NF-0.114	NF-0.250
	Bromodichloromethane				
Median	0.006	0.010	0.014	0.006	0.011
Mean	-	0.018	0.018	0.009	0.017
Range	NF-0.116	NF-0.183	NF-0.180	NF-0.072	NF-0.125
Total	Trihalomethane (TTHM)				
Median	0.027	0.045	0.087	0.037	0.074
Mean	0.067	0.068	0.117	0.053	0.100
Range	NF-0.482	NF-0.457	NF-0.784	NF-0.295	NF-0.695

NF = not found
LD = less than detection limit

trihalomethanes, chloroform was found at the highest concentrations (averaging approximately 75 percent of the total THM), 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 the chlorination process, therefore, it can be assumed that the presence of these compounds is not related to the disinfection 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 trihalomethanes 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. It appeared that these compounds resulted from the chlorination of precursors in the raw water.

A more recent study, the National Organics Monitoring Study (NOMS), directed by Section 141.40 of the National Interim Primary Drinking Water Regulations (40 F.R. 59574, December 24, 1975), was aimed not only at determining the presence of trihalomethanes in additional water supplies, but also at determining the seasonal variations in concentration of these substances.

The NOMS sample size was 113 public water systems designated by the Administrator. The study also included analyses for approximately 20 specific synthetic organic chemicals deemed to be candidates of particular concern and analyses of several surrogate group chemical parameters which are indicators of the total amount of organic contamination. Three phases of this study have been completed and the mean, minimum, and maximum values of chloroform and trihalomethanes 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 THM's (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 total trihalomethanes 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.

II. The Role of Chlorination

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

Several studies in addition to those mentioned above, have demonstrated increased trihalomethane 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 of more sensitive and refined analytical techniques. Recent work by Rook (1974, 1977) has provided some insight as to the organic precursors which might be responsible for the formation of the trihalomethanes. Studies by Sontheimer and Kuhn (1977) indicate that the THM's 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 trihalomethanes occur in chlorinated drinking waters, and that the concentrations of the various trihalomethanes are dependent on the type and quantity of organic precursor substances, the amount of chlorine used, and the presence of other halogen ions as well as contact time, temperature and pH.

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

The two chemicals most 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.

EPA is currently involved in studying the health effects of chlorine dioxide in water, utilizing several animal species. 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 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 the hematopoietic effects whereas monkeys were apparently insensitive even at levels as high as 200 mg/l. An upper limit for chlorine dioxide usage has been set 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 Fridlyand and Kagan, 1971). Studies with cats have shown that chlorite, which is an oxidant and can cause anemias, has a deleterious effect on red blood cell survival rate at chlorine dioxide concentrations above 10 mg/l. Therefore a limit of 1.0 mg/l is necessary to prevent potential adverse effects on sensitive individuals, particularly children.

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 studies under extreme conditions with chlorine dioxide byproducts thus far have exhibited minimal mutagenic activity.

Combining ammonia with chlorine to form chloramines has been called the chloramine process, chloramination, and combined residual chlorination. The products of this process are monochloramines, dichloramines or trichloramines (nitrogen trichloride) depending on the pH and the chlorine to ammonia ratio. The production of the latter species is referred to as "breakpoint" chlorination and may contribute to taste and odor problems in the finished water.

Based on the results of numerous investigations, the comparative disinfectant efficiency of chloramines ranks last when compared to ozone, chlorine dioxide, hypochlorous acid (HOCL), and hypochlorite ion (OCl^-) (NAS, 1977). 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 in 1953 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 a disinfectant. Studies by Fair et al., (1947) showed that additional dichloramine is about 60 percent and monochloramine about 22 percent as effective as hypochlorous acid at pH 4.5 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 a 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 health effects of water treatment with chloramine have not been studied in detail.

Although these disinfectants do not produce trihalomethanes, questions have also been raised on both their toxicology and the toxicology of their by-products. Studies are underway to clarify this matter and could result in the designation of maximum permissible levels for certain disinfectants when applied to drinking water. In the meantime, EPA has determined that chlorine dioxide applications should be limited to no more than one milligram per liter which is not uncommon in today's usage and that chloramines should not be used as primary disinfectants.

The use of adsorbents for trihalomethane removal has also introduced some unknown factors. Assuming that the adsorption process is effective for its intended purpose, there is always the possibility that a breakthrough of adsorbed chemicals will occur, that these substances will be adsorbed and subsequently slough off to produce contaminant concentrations intermittently, 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, it is essential that the THM concentrations be reduced but without compromising public health from either infectious disease transmission or from the technology that is used. Outbreaks of infectious waterborne disease have been noted when there have been breakdowns in chlorination. The alternative control methods outlined previously are effective and are also being studied for their possible side effects. As soon as data becomes available EPA will make specific recommendations regarding their use. At the present time the best approach to reduce the organic precursors is to use adsorbents such as GAC. This approach has the benefit of reducing the concentrations of many of the organic chemicals in the water in addition to the precursors to THM and other cholorinated organics. Thus, once the organic chemical concentrations in the water have been reduced, the chemical demand for applied disinfectant will also be reduced, thus human exposure to all disinfectant chemicals, and their degradation products and by-products will be minimized.

III. 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 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 alga eaten in Hawaii, contains an essential oil which is composed largely of bromoform (Burreson, et al. 1976).

Chloroform has been widely used as an anesthetic, 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 F.R. 145026, April 9, 1976). The Environmental Protection Agency has issued a notice of "rebuttable presumption" against continued registration of chloroform-containing pesticides (41 F.R. 14588, April 6, 1976). Thus, in addition to drinking water, exposure to some or all of the trihalomethanes is complicated by other environmental sources, however, exposure from some of those sources is being reduced.

The relative contribution and uptake of chloroform can be estimated for three major sources of human exposure: atmosphere, drinking water, and the food supply. The calculations of human uptake were 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 human adults from all three sources was estimated by multiplying estimated exposure levels times estimated intakes.

Human uptake of chloroform from air, food and drinking water is given in Table 2. Chloroform and trihalomethane uptake from drinking water was estimated by multiplying the chloroform and

trihalomethane concentrations found in drinking water supplies from NCMS data (Table 1) and the average consumption of 2 liters of water per day. One hundred per cent absorption of the amount of chloroform in drinking water was assumed for these calculations. The total chloroform uptake from water was estimated as a mean value of 64 mg per year and a maximum uptake value of 343 mg per year.

In order to determine human uptake of chloroform from foods, the concentrations of chloroform in various foods was multiplied by the average consumption of each food item in North American diets which was multiplied by the average consumption of each food item by human adults in the United States, and one hundred per cent absorption of ingested chloroform was assumed. A calculated maximum value of about 16 mg of chloroform uptake per year and a mean value of 9 mg per year from total food consumed was obtained.

The calculation for the uptake of chloroform by humans from air was based upon the assumption that an average of 63 per cent of chloroform present in ambient air was absorbed after inhalation; the volume of air inhaled by an average adult was taken as 8.1×10^6 liters per year; 0.02 and 10 ppb (by volume) chloroform concentrations in urban air as minimum and maximum values, respectively. The minimum and maximum values for the

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 (0.001-0.540)	9 (2 - 15.97)	20 (0.41 - 204)
Trihalomethanes	85 (0.001-0.784)	-	-

* 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.

uptake of chloroform by an adult were estimated as 0.41 and 204 mg per year respectively. At minimum conditions from all sources of exposure the atmosphere contributes 13 percent of the total chloroform while the drinking water contributes 23 percent and food is most significant. At maximum conditions from all sources water is the major contributor at 61 percent. with air at 36 percent. Under conditions of maximum exposure from the water and minimum exposure from the air, the major contribution by far is drinking water as a source of chloroform uptake, which is estimated to be as much as 97 per cent. Thus, relative contributions of drinking water as a source of chloroform to the total body burden may change from a moderate to a maximum contributor as the annual exposure from water ranges from nil to 343 mg/year and from 204 to 0.41 mg/year in ambient air.

IV. Metabolism

Several reports (Brown, et al., 1974: Labigne & Marchand, 1974; Fry et al., 1972 Paul and Rubinstein, 1963: Taylor et al., 1974) have indicated that chloroform is rapidly absorbed on oral and intraperitoneal administration and subsequently metabolized to carbon dixoide and unidentified metabolites in urine. Species variation in the metabolism of chloroform has been

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

summarized in Table 4. It is noteworthy that the mouse, a species which shows greater sensitivity to the oncogenic effect of (Brown et al. 1974) chloroform (Eschenbrenner & Miller 1945), 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 intraduodenally 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. Non-human primate squirrel monkeys, when given 60 mg/kg of chloroform orally excreted 97 per cent of the dose with 17 per cent as carbon dioxide and 78 per cent as chloroform. Fry et al., (1972) recovered unmetabolized chloroform ranging from 17.8-66.6 percent of a 500 mg dose of chloroform given to human volunteers during an 8 hour time period (equivalent to about 7 mg/kg). Since the metabolism of xenobiotics 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.

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 & Rubatein (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

A related halogenated hydrocarbon, carbon tetrachloride (CCl_4) has been shown (NCI, 1976) to be carcinogenic in Osborne-Mendel rats and in B6C3F1 mice at dosages ranging from 57-160 mg/kg and 1250-2500 mg/kg respectively. Dosages for oncogenic effects of chloroform were 90-200 mg/kg for rats and 138-477 mg/kg for mice. Metabolic similarities between those compounds include the appearance of halide ions in urine and carbon dioxide in breath. Carbon dioxide is one of the major metabolites of chloroform in mice and rats whereas it is a minor one in carbon tetrachloride metabolism. Carbon tetrachloride also is metabolized to chloroform in trace amounts, which may in turn, be biotransformed to carbon dioxide. Carcinogenicity of carbon tetrachloride, however, has been attributed to a free radical (CCl_3) which is postulated as an intermediate in the metabolic processes.

Many carcinogens have been reported to form complexes with proteins, DNA and RNA (Miller & Miller, 1966). In some instances the first stage in chemical carcinogenesis may involve metabolism of the carcinogen to a secondary and more active

compound. In the case of chloroform, Ilett et al., (1973) reported covalent bonding of chloroform metabolite(s) to tissue macromolecules of 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 drug metabolizing enzymes. This is suggestive of the involvement of chloroform metabolism in these processes.

Information regarding the metabolism of bromoform and other haloforms is not available. However, the structural similarities of these haloforms with chloroform indicate that these compounds should also be absorbed by the oral and inhalation routes of exposure and then biotransformed into carbon dioxide and halide ions. Related halogenated hydrocarbons of the dihalomethane series, i.e. 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 chloro isomer.

V. Acute and Chronic Health Effects

Biologic responses on exposure of chloroform to mammals include its effect on the central nervous system resulting in

narcosis, hepatotoxicity, nephrotoxicity, teratogenicity, and carcingenicity. Reported LD_{50}'s are as follows: for rats 300 mg/kg administered orally (DHEW, 1973) and for mice 705 mg/kg (Plaa, et al. 1958).

Acute studies involving single dosage level in animals have been reported by several researchers. Jones et al. (1958) studied the effect of various doses of chloroform fed to mice and made the following observations after 72 hours of exposure:

35 mg/kg -- threshold hepatotoxic effect - minimal midzonal fatty changes
70 mg/kg -- minimal central fatty infiltration
140 mg/kg -- massive fatty infiltration
350 mg/kg -- centrilobular necrosis
1100 mg/kg -- minimum lethal dose

In regard to acute effects on exposure to chloroform and bromoform, species variation has been observed. 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_{LO}	800 (Chloroform) 410 (Bromoform)

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

A. Hepatotoxicity

Plaa et al. (1958) established a dose-response relationship in mice, measuring parameters indicative of hepatotoxicity. ED_{50} values of 1.4 mM/kg (166 mg/kg) were found in mice which received chloroform subcutaneously. The inhalation exposure of chloroform by mice for 4 hours at concentrations ranging from 100-800 ppm resulted in fatty infiltration of the liver at all dose levels. These changes were observed at necropsy after 1 - 3 days of exposure.

Like chloroform, bromoform exposure leads to fatty degeneration and centrilobular necrosis of the liver (von Oettingen, 1953). Dibromochloromethane and dichlorobromomethane may bring about similar responses.

B. Nephrotoxicity

Nephrotoxic effect of chloroform was studied by Plaa and Larson (1965). Median effective doses (ED_{50}) of chloroform in mice were 178 mg/kg as measured by phenolsulfophthalein excretion. Increases in urinary protein and glucose, indices of kidney damage, had an ED_{50} 104 mg/kg for chloroform. Data concerning the nephrotoxic effect of other trihalomethanes are not available.

C. Teratogenicity

Teratogenic response on oral dosing of animals to chloroform were investigated by Thompson et al. (1973). Rats and rabbits were administered chloroform at 126 and 50 mg/kg respectively. No significant fetal deformities were observed. 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 etal. 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). The analysis of the water indicated reduced amounts of chlorinated compounds in the purified water. The study was inconclusive in relating chloroform and other chlorinated organics in tap water to reproductive failures in laboratory animals, since the concentration of chlorinated organics in water was lowest in months when reproductive failure was highest, although there did appear to be small differences in these parameters between the highly purified and tap water. In another study 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 parameters of CD-1 mice. No teratogenic studies on the haloforms other than chloroform were available.

D. Mutagenicity

The trihalomethanes (chloroform, bromodichloromethane, dibromochloromethane and bromoform) were assayed for in vitro mutagenic activity using strains of Salmonella typhimurium (TA100 & TA1535). The assays were conducted in desiccators such that each compound was allowed to volatilize and only the vapor phase came in contact with bacteria on the petri plates. 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 TA100 neither with or without activation nor in TA 1535 without activation; (b) bromodichloromethane was mutagenic in TA100 without activation, with a doubling dose of approximately 25 microliters; (c) dibromochloromethane was mutagenic in TA100 without metabolic activation, with a doubling dose of approximately 3.5 microliters; (d) bromoform was mutagenic in TA100 without metabolic activation, with a doubling dose of approximately 25 microliters, and was also mutagenic in TA1535 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 the Ames test which utilizes Salmonella typhimurium bacteria correlates highly (90 percent) with the in vivo carcinogenicity bioassay. However, for certain chlorinated hydrocarbons the test has been shown to have limitations in detecting gene mutations (Ames et al., 1973), which can be demonstrated in other test systems.

E. 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) revealed hepatomas in female mice (strain A) given repeated dosages ranging from 0.145 to 2.32 mg of chloroform for a period of 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 more recent study (NCI, 1976) linking chloroform with oncogenicity, rats and mice of both sexes were fed doses of chloroform ranging from 90 to 477 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 hydrocarbon, carbon tetrachloride, has been shown as carcinogenic in Osborne Mendel rats and in B6C3F1 mice at dosages ranging from 47 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 histopathological 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, C57Bl, 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

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

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. 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.

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.

VI. Human Health Effects

A. NAS Principles of Toxicological Evaluation.

The NAS (1977) in a recent report entitled 'Drinking Water and Health" identified several principles that are the basis of assessing the irreversible effects of long and continued exposure to carcinogenic substances on humans at low dose rates.

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

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

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 bioeffects on exposure to chloroform are similar to that found in experimental animals. These include the 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 unconsiousness. Liver function tests measured by serum enzyme levels after four days of ingestion indicated very high levels of SGOT, SGPT, and LDH. The authors also noted cerebellar damage 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. (1965). 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 tremor of tongue and fingers.

Lunt (1953) reported on the delayed chloroform poisoning in obstetric patients. Laboratory findings indicated renal dysfunction including: albumin, red blood cells, and pus in the urine. Chloroform exposure to 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.

Limited information is available on the controlled bio-effect studies in humans exposed to chloroform. 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 37 mg/kg/day chloroform ingested for 10 years in a study conducted by Wallace (1959).

B. Epidemiologic Studies.

As of July 1977 there had been 11 different epidemiological studies with additional unpublished reports that investigated the relationship between cancer mortality and morbidity and consituents in drinking water. Two of the studies have been published, three others were submitted for publication as of July 1977, and the remaining studies were unpublished. All of the studies were retrospective in design; nine were correlations using an indirect design, two used a case-control or direct design approach. Two studies utilized cancer morbidity or incidence rather than mortality as a measure of disease frequency. The studies vary in sample size, cancer sites considered, confounding factors selected as variables, parameters selected as indicators of water quality, and statistical analysis.

There are several problems peculiar to these studies which make it difficult to interpret their results: 1) there is a limited amount of water quality data on organics, and the data which exists covers less than a five year time period; and 2) the water quality data is often from geographic areas not conterminous with areas (usually counties) reporting cancer mortality data.

The water quality data on organics is of recent origin and it is not known the extent to which current levels may reflect

past exposures. This is important, since the latent period for most types of cancer induction is measured in decades, not months or years. Comparison of the various study results is difficult because of the different approaches used.

In general, indirect, retrospective epidemiological studies are a useful methodological tool in hypothesis generation. A positive correlation cannot establish causal relationship. However, the results from these studies, when viewed collectively can provide some insight into associations of potential causal relationships which need to be tested further by more highly focused direct methods, such as case-control or cohort studies.

The studies do provide evidence that there is reason for concern. When the evidence from all studies is weighed, the emphasis should 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, the association may be due to the variable considered and the evidence should be viewed more seriously.

A large body of data, provides evidence (both epidemiological and experimental) that the majority of human cancers result from multifactorial causes (Weisburger, 1977)., particularly for cancers of the gastrointestinal and urinary tract. Etiologic factors, such as smoking and its association with lung cancer, that result in increased relative risk greater than 5, were the first to be discovered. The etiologic factors associated with cancers of the gastrointestinal and urinary tract are more difficult to evaluate from epidemiological studies because of the lower incidence and mortality rates and because of the mutifactorial interaction of environmental causes. The increased relative risk of most potential factors associated with gastrointestinal and urinary cancers are probably less than 3. Thus, any correlation in a sound, indirect, retrospective study between drinking water and cancer mortality would most probably be weak as is shown in the studies completed.

A number of epidemiologic studies that have been conducted did not define the water quality parameter by chemical constituents and therefore compared various sources of water supply. One

investigation was performed by Page and Harris (1974). The study involved Louisiana county (parish) cancer mortality rates, 1950-69, for total cancer and selected sites in white males. The parishes were categorized by the percentage of the county population drinking Mississippi River water. The variables controlled were rural-urban characteristics, median income, population density, and proportion of employed population in the petroleum, chemical, and mining industries. An unweighted regression analysis resulted in a positive correlation between drinking water and total cancer (minus cancer of the lung, urinary tract, GI tract, and liver), gastrointestinal organs, and lung cancer mortality. These investigations suggested the possibility that there was an association between the cancer mortality rates and drinking Mississippi River water. As a result serious questions were raised as to the safety of drinking water contaminated by suspected carcinogens, particularly various organic chemicals in the water.

Tarone and Gart (1975) reviewed "The Implications of Cancer-Causing Substances in Mississippi River Water" by

Page and Harris and included an additional variable, the elevation above sea level. By using a weighted regression analysis for four race-sex groups, weak but, 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 white females (WF) for the same sites. Thus, there was a lack of consistency across the four sex-race groups for the aforementioned cancer sites.

Another report by Meinhardt et al. (1975) commenting on the Page and Harris report, looked at the cancer mortality gradient 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. From this study it was pointed out that the controls used might not be representative.

A second report by Page and Harris (1975, 1976) on the "Relation Between Cancer Mortality and Drinking Water in Louisiana" utilized independent variables and cancer sites similar to those in the first study, however, relationships for all four sex-race groups were added. Positive regression

coefficients for the water variable that were statistically significant are as follows:

Total cancer sites:	WM, NWM, NWF
All other than lung:	WM
Urinary Tract:	WM, NWF
Gastrointestinal:	WM, NWM, WF, NWF

DeRouen and Diem (1975) did another analysis of the relationship of cancer mortality in Louisiana and the Mississippi River as the drinking water source. An additional variable, latitude, was included, which divided Louisiana into a northern and southern section. This variable effectively resulted in an ethnic division of the population. The variables urban-rural characterisitcs, median income, employment characteristics, and elevation above sea level included in previous studies (Page and Harris, 1974; Tarone and Gart, 1975; Page and Harris, 1975; Page et al., 1976) were omitted. The water variable was handled differently by the investigators, i.e. population groups studied either obtained none of their water from the Mississippi River, or obtained some or all or from the river. The results are in agreement with the Page and Harris results that show 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 tend to be higher than the southern parishes whose source

of drinking water is not the Mississippi River water 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 slightly higher for the southern parishes with river water than northern parishes for cancer of the urinary tract, gastrointestinal tact, 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 inferences from indirect studies. They concluded that the inconsistencies in the data and failure to see the same relationships for other sex-race groups damages the credibility of the hypothesis.

An analysis was done by McCabe (1975) of EPA using 50 of the 80 cities from the NORS data. Only those 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 were included in the study. The results showed a statistically significant correlation between the chloroform concentrations in the drinking water and the cancer mortality rate by city for total cancer combined.

In a second analysis done by McCabe (1977) using Region V data, correlations between $CHCl_3$ and THM's and total cancer

mortality were not positive. When the same correlations were done using Region V plus NORS data for $CHCl_3$ and THM 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 bordering the Ohio River in which 14 of the counties used the Ohio River as a drinking water source. The results do not show a 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 surface water suppliers) between chloroform concentrations and pancreas cancer mortality in white males. 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.

Another study by Kuzma et al. (1977) considered the 88 counties of Ohio, which were 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. Mortality rates for stomach, bladder, and total cancers were slightly higher for white males and for stomach cancer for white females in counties served by surface water supplies than in counties served by ground water supplies.

Reiches et al. (1976) treated the 88 counties of Ohio by using a different methodology. Correlations between the surface drinking water variable and cancer mortality rates of 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 was significant for white males only.

Although several studies defined the water quality parameter by the chlorination or levels of chloroform, only one study has done an analysis of all trihalomethanes, both collectively and separately. Cantor et al. (1976) studied the correlation of cancer mortality at sixteen anatomical sites with the presence of THM concentration levels in drinking

water for whites. Counties were grouped according to the percent of the county population served by the sampled water supply. In both sexes, there was a gradient of increasing correlation between halomethane concentration and bladder cancer in going from the low to intermediate to high percent served county groups or strata. The correlation was stronger for the brominated THM's 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 weakly 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 the brominated trihalomethanes. A gradient of increasing association was observed between brain cancer mortality in both sexes and 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 drinking from a chlorinated drinking water supply

and combined gastrointestinal and urinary tract cancer mortality rates. Further, there was 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.

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 slightly 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 relatively small.

Salg (1977) also conducted a retrospective study of various cancer mortality rates and drinking water as defined by source of supply and type of treatment in 346 counties in seven states bordering the Ohio River Valley Basin. She looked at mortality rates for white and nonwhite males and females. With weighted regression analyses, surface water usage showed weak but

statistically significant associations with the following: for white males - esophagus, lung, larynx, trachea, 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. Only rectal cancer showed positive correlations across all race-sex groups. It should be noted that the test of significance utilized for this study was $p > 0.10$ or less stringent than all other studies, except for Cantor's study, which used even less stringent criteria for some correlations.

Mah et al. (1977) conducted a retrospective study in the Los Angeles County area. The relationship between cancer mortality and morbidity and the chlorinated drinking water supply was analyzed for white populations only. Results did not reveal any trends and were not significant both for mortality and morbidity cancer rates. The authors point out several methodological problems, including the diluting effect of migration in the highly mobile area covered by this study.

Hogan et al. (1977) also utilized the chemical analysis of the NORS and Region V data sets and applied various statistical procedures to the data in order to determine the appropriateness of the statistical model. Thus, it is not surprising

that 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 a weighted regression analysis were applied.

In summary, many but not all of the studies have found positive correlations between drinking water and various cancer mortality/morbidity rates. It is beyond the scope of this document to evaluate each study in depth, however, it is pertinent to consider the interpretations and conclusions that can be drawn from these retrospective epidemiological studies collectively.

It is also extremely important in the evaluation process to consider the results from other epidemiological studies as they develop hypotheses 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 (1977). Therefore, any epidemiological study that investigates the possible association between bladder cancer and drinking water should either control for the aforementioned variables or analyze 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. (1976); only one study by Kruse (1977) attained smoking history 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 association of specific cancer sites, i.e. Salg-rectum. Several studies which considered only white populations found positive correlation coefficients for both sexes: Buncher (1975) - bladder; Reiches (1976) - stomach; and Cantor (1976) - bladder.

A decreasing level of association from high to low levels of the water quality variable, i.e. chloroform or THM, with cancer mortality rates is an important criteria in evaluating the evidence. This pattern of association should be observed if the difference in mortality rates is due to the water variable. Only a few studies defined the water quality variable by the chloroform concentrations (McCabe, 1975; Buncher, 1975; Cantor et al., 1976; Hogan et al., 1977), and by the THM concentrations (Cantor et al., 1976).

Of particular interest are the correlations of liver and kidney cancer mortality 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. Several of the preliminary studies grouped the cancer sites for the anatomical systems, i.e. gastrointestinal and urinary organs, in order to increase the sample size. Only one of the studies (Cantor, 1976) which considered site-specific cancer mortality showed a positive association between drinking water and cancer of the kidney 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 the no-effect level (Weisburger, 1977).

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, nor can it be disproven. When viewed collectively, the epidemiological studies completed thus far provide sufficient evidence for maintaining a hypothesis that there may be a health risk and that the positive correlations may be due to some association between drinking water and cancer mortality. Only when viewed in conjunction with animal studies, both acute and chronic toxicity studies, is the

evidence evaluated in the appropriate context for policy decision making. Additional direct epidemiological studies may provide evidence regarding the strength of the associations and the possibility of a casual relationship between drinking water and cancer mortality.

VII. Risk Assessment

The establishment of chloroform as an animal carcinogen, plus the epidemiological data and mutagenesis data on THM's, show that a potential human risk exists from the consumption of trihalomethanes, but these data do not quantify the risk. Methods have been developed to estimate quantitatively the size of the risk under the assumption that there is no threshold level for a carcinogen. The state-of-the-art at the present time is such that no experimental tools can accurately define, with any degree of certainty, 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 estimates reports different absolute numbers with a wide degree of variability.

It is generally agreed that it is not possible to project with accuracy risk estimates to absolute numbers of cancers in human population from exposure to a given agent, using statistical extrapolation models with animal data. Given that caveat, it may be useful to apply one or more risk estimation procedures in an attempt to estimate a possible range of impact to affected populations both in the absence of the interim proposed standard and at some alternate standard levels.

The EPA Science Advisory Board (SAB) (1975), using the highest levels of chloroform then reported in drinking water bythe NORS data (0.300 mg/l)

and assuming a maximum daily intake of 4 liters of water for a 70 kg man, attempted to compute an estimated risk. The estimates were based on the Eschenbrenner and Miller (1945) animal data, which are highly speculative since the experimental protocol involved only 5 animals per sex per dose. Using a linear extrapolation of the animal data over more than 2 orders of magnitude of dose from mice to humans at the 0.300 mg/l concentration level, the lifetime incidence of liver tumors in man were estimated in the range of 0 to .001 (95% of confidence limits) or 0 to 100×10^{-5} in a lifetime. This rate may be compared with the lifetime incidence of 260×10^{-5} for malignancy of liver derived from 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. Other models would all 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 risk from chloroform ingestion via tap water. Using a margin of safety of 5000 applied to the minimum effect animal

dose, the "safe" level was calculated to be 0.02 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 actual slope of the dose response curve 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 maximum 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 maximum dose level of 0.01 mg/kg/day.

In the National Academy of Sciences (1977) report on "Drinking Water and Health," life-time risks were estimated from the NCI animal data. For concentrations of 10 ppb exposure the number of excess cases of cancers computed to one for every 50,000 exposed persons assuming a risk of 2×10^{-5} and 2 liters per day of water consumed. If the U.S. population using chlorinated water is assumed to be approximately 160 million people this translates into 3,200 excess lifetime deaths from cancer or 45.7 cases per year.

For a concentration of chloroform at 1 ug/liter the estimated lifetime cancer risk would fall at approximately 3.7×10^{-7} at the upper 95% confidence limits.

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. The standardized mortality rates in the U.S. for white males and females combined are 52.5 per million per year for liver carcinoma and 29.2 per million per year for kidney carcinoma.

Based on his risk estimates, Tardiff (1976) calculated that the percent of the cancer mortality rates attributable to chloroform in drinking water would be 1.60% and 1.44% for liver and kidney cancer incidence per year 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.

EPA's Carcinogen Assessment Group's (CAG) risk estimations for chloroform exposure are shown in Table 7. The risks were computed for several exposure levels and were extrapolated from data from the National Cancer Institute (NCI 1976) bioassay with the male rat and female mouse. Human exposure from drinking water was computed using a weighted average of chloroform concentrations in drinking water for 160 million people whose drinking water supplies are chlorinated.

ACTION	TOTAL TUMORS PER YEAR	TOTAL TUMORS PER YEAR REDUCED BY ACTIONS
NONE	23.1*-207.0**	---------
CITIES GREATER THAN 50,000 REDUCE TO:		
100 ugm/l	18.6-166.6	4.5-40.4
50 ugm/l	15.6-140.1	7.5-66.9
10 ugm/l	9.6-85.6	13.5-121.4
CITIES GREATER THAN 75,000 REDUCE TO:		
100 ug/l	19.6-175.3	3.5-31.7
50 ug/l	17.3-155.4	5.8-51.6
10 ug/l	12.1-108.5	11.0-98.5

Risks extrapolated from NCI bioassay data *male rate and **female mouse.

In the absence of a THM standard the CAG statistical risk model would predict from 23 to 207 total tumors per year in the exposed human population, depending which animal data (rat or mouse) is utilized as the base.

Computations of estimated human risk and risk reduction at various levels of control were made for the total population in cities larger than 75,000 which are affected by this regulation.

A standard of 100 ug/l would reduce the annual risk according to the statistical model to 19 to 175 total tumors; a standard of 50 ug/l would reduce the risk to 17 to 155 total tumors; a standard of 10 ug/l would reduce the risk to 12 to 108 tumors.

Given that it is not possible to project with certainty or accuracy from risk estimates based on animal data to absolute numbers of cancers in a human population, such extrapolations are useful in attempting to quantify a range of possible impacts of alternate standards.

It should be noted, however, that these average exposure levels which refer to chloroform alone and do not consider the risk from other contaminants in the impacted population are overestimates of the risk in light of the facts that: 1) the computations are based upon lifetime exposure, while in actuality the proposed interim standard is a temporary, phased standard which will be reduced in the future and therefore, the lifetime exposure values would be less, 2) the interim standard clearly calls for

maximum reductions obtainable using available technology thus indicating a lower average exposure. They may be underestimated since the risk estimates are based upon toxicity exposure data from chloroform, which is only a portion of the total THM's and other contaminants found in drinking water. Therefore the magnitude of the contribution to the risk of the other THM's (bromohalomethanes), which in some cases consists of a substantial portion of the THM's, and the many other possible contaminants is unknown.

VIII. Summary

The occurrence of trihalomethanes in drinking water supplies of various communities across the United States has been documented. Chloroform was found at concentrations ranging from 0.001-0.540 mg/l and trihalomethane potential concentrations as high as 0.784 mg/l have been detected. The concentration of THM increased on treatment of raw water supplies with chlorine in the process of disinfection and subsequent preparation of water for drinking purposes. The THM concentrations may also be indicative of the presence of other undefined chemicals that are produced in water during chlorination.

Besides the presence of chloroform in drinking water humans are exposed to chloroform from air and food. An analysis of the relative contribution of chloroform in drinking water as compared with air and food exposures considered various relative levels of exposures. Depending upon the ranges of chloroform concentrations that have been detected in air, food and water (which is a function of location, urbanization and industrialization), drinking water may contribute from zero to more than 90% of the total dietary intake.

Chloroform has been shown to be rapidly absorbed on oral and intraperitoneal administration and subsequently metabolized to carbon dioxide and unidentified metabolites in urine. 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.

Biological responses on exposure of chloroform to mammals include its effect on the central nervous system resulting in narcosis, hepatotoxicity, nephrotoxicity, teratogenicity, and carcinogenicity. These responses are discernible in mammals on exposure to high levels of chloroform ranging from 30-350 mg/kg; the intensity of response was dependent upon the dose. Although less toxicological information is available for brominated trihalomethanes, mutagenicity and carcinogenicity have been detected in some test systems. Physiological chemical activity should be greater for the brominated THM's than for chloroform.

Exposure to the low levels of trihalomethanes presently found in drinking water supplies may not manifest detectable responses in populations. It is the prolonged human exposure to trihalomethanes that should be a matter of major concern. Prolonged administration of chloroform at relatively high dose levels (100-138 mg/kg)

to animals, specifically rats and mice, manifested oncogenic effects. The oncogenic effect was not observed at a lower dose level (17 mg/kg). Assuming that methods do not exist to establish a non-threshold level for long-term effects for carcinogenesis (NAS, 1977), the preceeding data do not imply that a safe level of exposure can be established.

Epidemiological evidence is inconclusive, although positive correlations have been found in several studies. There have been 11 retrospective studies that have investigated some aspect of a relationship between cancer mortality or morbidity and use of drinking water. 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 association 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 hypothesis 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), Robert Tardiff of EPA, and the Carcinogen Assessment Group (CAG) using four different models have estimated the cancer risks associated with the exposure from chloroform in drinking water. The exposure to THM's from air and food have not been included in these computations. The total cancer risk estimates associated with the MCL at the 0.1 mg/l level range from the NAS estimated lifetime risk of 4×10^{-5} to the CAG's estimate of 2×10^{-4} using somewhat different assumptions. These risks are similar to the lifetime estimated risks of other known carcinogenic standards: e.g. for vinyl chloride emissions (about 10^{-5}) and ionizing radiation exposure to the general public (about 10^{-5}).

On the basis of the available toxicological data summarized in the above 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 may prove to be a human carcinogen. Epidemiological studies also imply 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.

IX. Selected Maximum Contaminant Levels (MCL's)

Since it is evident from the foregoing that a risk to the public exists from exposure to the trihalomethanes in drinking water, the 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 (P.L. 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 through a phased approach, along with monitoring requirements, is the most effective and conservative approach to regulate the levels of trihalomethanes 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 and possibly other synthetic organic contaminants.

Since it is known that chlorination of water is primarily responsible for the relatively high levels of trihalomethanes

in drinking water, modifications in the chlorination process, the substitution of other disinfectants, and the use of adsorbents to remove precursor chemicals are possible approaches for control. The optimal approach would be to reduce organic precursor concentrations by adsorbents or other means prior to addition of the disinfectant.

Use of a chlorine residual in a less active form such as combined chlorine or chloramine will significantly reduce trihalomethane formation, however, chloramines are much less potent disinfectants than free chlorine and therefore it would not always be appropriate to adopt this approach. 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 bio-effects and toxicology of these disinfectants and their by-products are being clarified by the studies underway. In the meantime the application of chlorine dioxide should be limited to 1 milligram per liter.

The National Organics Monitoring Survey found that the mean total trihalomethane (THM) concentrations in the

drinking water systems evaluated were approximately 0.068, 0.117, 0.053 and 0.100 mg/l for Phase I, 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 calculated risk estimates for chloroform from various studies do 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 interacts 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 trihalomethanes are 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 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 risk estimates would result in larger numbers of excess cancer cases.

The reduction of the total trihalomethanes to the MCL level of 0.10 mg/l would reduce the unnecessary and excessive

exposure to these potential human carcinogens, mutagens, and chronic toxicants and may result in the reduction of excess cases of cancer. 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 there is a benefit achieved by reducing the health risks to exposure, EPA has decided to set the MCL at 0.10 mg/l as an initial step in a phased, regulatory approach. As more data becomes available from implementation experience standards will become more restrictive in the future. In the meantime EPA will take steps as necessary on a case by case basis to provide adequate protection for the delivery of safe drinking water to the public.

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