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AN SAB REPORT: REVIEW OF DRINKING WATER HEALTH CRITERIA DOCUMENT

REVIEW OF THE OFFICE OF DRINKING WATER'S HEALTH CRITERIA DOCUMENT ON TRIHALOMETHANES BY THE DRINKING WATER COMMITTEE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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EPA-SAB-DWC-92-011

OFFICE OF
THE ADMINISTRATOR

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Review of Health Criteria Document for Trihalomethanes by the Drinking Water Committee of the Science Advisory Board

Dear Mr. Reilly:

The Science Advisory Board's Drinking Water Committee met in Washington, DC on October 25-26, 1990 to review the Office of Drinking Water's background document **Revised External Draft for the Drinking Water Criteria Document for Trihalomethanes.**

Trihalomethanes (THMs) are by-products of disinfection with chlorine and to some extent with chloramine and ozone (bromoform). The THMs include chloroform, bromoform, bromodichloromethane and dibromochloromethane. In 1979 these substances were regulated in drinking water at a level of 0.10 mg/L. The regulation was based primarily on tumor formation in mouse liver and rat kidney following chronic exposure to chloroform, but health data were not available on brominated THMs at that time. Some new information has been generated and the revised document addresses the issues related to the Maximum Contaminant Level Goal (MCLG) for THMs. The Committee reviewed this document and addressed specific and general issues concerning the toxicity of THMs.

At the meeting, EPA Staff presented to the Committee questions regarding the carcinogenic and non-carcinogenic risk assessments for THMs. The attached report addresses the Committee's responses. Additional issues raised by the Committee during its deliberations are the lack of data on human exposure to THMs, and the concentrations of chloroform in humans. The Health Criteria Document for Trihalomethanes should include a discussion of the pharmacokinetic properties of chloroform and other THMs because it is important to know the dosed target tissues and organs and the rate of elimination from the body. This information when combined with environmental exposure levels encountered by people are critical for assessing risks.

The Committee addressed the following issues:

1. **Does the SAB agree with the selection of the key studies serving as the basis for carcinogenic and non-carcinogenic risk assessments?** The Committee concluded that the studies utilized for estimating carcinogenic risks are the best currently available for deciding whether these chemicals are human carcinogens and for estimating the potency of these chemicals as carcinogens but pointed out that it was far from proven that these studies provide a basis for declaring that they are carcinogens at the concentrations encountered in drinking water. The Committee found that the studies selected for the non-carcinogenic endpoints of THM toxicity were appropriate in general. However, it is suggested that the Condie study be used for the 10-day Health Advisory for bromoform and strong consideration should be given to the chronic National Toxicology Program (NTP) study on bro-moform for determination of the drinking water equivalent level (DWEL).

2. **Studies with chloroform indicate that the vehicle of administration may influence the toxicity exhibited by chloroform. Based on the available data, can the same inference be made with the brominated THMs?** Because hepatic tumors were observed when corn oil was used as the vehicle for chloroform but not when water was the vehicle the Committee recommended that the hepatic carcinogenicity produced by THMs administered in an oil vehicle be disregarded from making quantitative estimates of risk.

3. **The mutagenicity data for the THMs are largely negative or equivocal. Could the THMs collectively or individually be considered epigenetic carcinogens?** A review of the data does not support a contention that these compounds can be considered collectively as epigenetic carcinogens. Tribromomethane and bromodichloromethane have demonstrated sufficient activity in several assays to be considered genotoxic whereas the evidence for chlorodibromomethane and trichloromethane is inconclusive for genotoxicity.

4. **The THM standard applies to the sum of the four predominant THMs. Based on the health effects of the individual THMs, is it reasonable to continue to consider this group as a mixture or would separate assessments be more appropriate for regulations?** The Committee recommends that separate MCL values be calculated for each of the THMs. One reason is because their carcinogenic properties differ significantly in both quantitative and qualitative terms.

5. **Are there any restrictions to using mouse liver tumor data as the basis of quantitative risk assessments?** The Committee recommended that mouse liver tumor induction should be utilized in making the weight-of-evidence judgment that chloroform is a carcinogen. However, these data should not be used for making quantitative assessments of risk. A number of comments are made to support this recommendation.

6. **Is there reason to suspect chloroform acts on the rat kidney through the alpha-2u-globulin mechanism?** Based on published reports alpha-2u-globulin appears to play no role in the etiology of chloroform-induced renal tumors in rats.

7. **Are hepatocellular adenomas and carcinomas the appropriate basis for quantification of carcinogenicity for bromodichloromethane? Would the occurrence of these tumor types be expected if the compound were administered in drinking water? Is the current quantitation applicable to drinking water exposure? Should further research be initiated testing this compound in drinking water?** The Committee concludes that it is inappropriate to consider hepatic tumors as the basis for quantification of carcinogenicity for bromodichloromethane and recommends that EPA utilize renal of intestinal tumors. The data suggest that the intestinal tumors would be more appropriate since they are not commonly seen in rats and the resulting incidence is quite high in males and observed in both sexes. Bromodichloromethane also produces tumors in the rat kidney, a site which is probably independent of vehicle effects whereas hepatic tumors are likely to be seen primarily, if not exclusively, with THMs administered in the presence of a vehicle such as corn oil. Thus, quantitation of carcinogenic risks using hepatic tumors appears not to be applicable to drinking water exposure. Appropriate research has been proposed for studying the pharmacokinetics and metabolism of bromodichloromethane. However, research on defining the mechanism by which the compound induces tumors in non-hepatic target organs appears to be critical.

8. **EPA has classified dibromochloromethane in group C: possible human carcinogen based on liver tumors in mice. Does the SAB agree with the conclusions in light of the flaws of the studies conducted?** The Committee recommends that based on its definitions and criteria for classification of chemicals as carcinogen or non-carcinogens, the EPA classify dibromochloromethane in group C. The gavage error alluded to in the EPA briefing document occurred in a low-dose group only. There was no indication of the intestinal or other tumor types in the high-dose group and no evidence of carcinogenicity in rats.

9. Is the weight-of-evidence classification for bromoform of B2 correct? The Committee noted that the EPA classified bromoform in group B2 based on the incidence of neoplastic lesions of the large intestine in female rats. Classification of a compound as a probable human carcinogen based on the induction of a tumor at a single tumor site at low incidence in a single species is not scientifically defensible. However, the Committee noted that the intestinal tract is not a common tumor site and that bromoform is the one THM that is the most clearly mutagenic. Thus, in using all the available information (both carcinogenic and mutagenic) the Committee supports the classification of bromoform in the B2 category.

In addition the Committee recommends that a section on human exposure and body burden to chloroform be incorporated into the criteria document because it provides direct evidence as to the magnitude and widespread occurrence of chloroform in people.

We appreciate having been given the opportunity to conduct this particular review. We request that the agency respond formally to the scientific advice provided herein, particularly in regard to the Committee's concern about the inclusion of exposure data.

Sincerely,

Raymond C. Loehr, Chair
Executive Committee
Science Advisory Board

Verne Ray, Chair
Drinking Water Committee
Science Advisory Board

Enclosure

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ABSTRACT

The Science Advisory Board's Drinking Water Committee met in Washington, DC on October 25-26, 1990 to review the Office of Drinking Water's document Revised External Draft for the Drinking Water Criteria Document for Trihalomethanes (THM), addressing issues concerning the toxicity of THMs. The 1979 THM regulations were based primarily on tumor formation in mouse liver and rat kidney following chronic exposure to chloroform. Health data were not available on brominated THMs at that time. Some new information has been generated and the revised document addresses the issues related to the Maximum Contaminant Level Goal (MCLG) for THMs.

The Committee addressed the selection of the key studies serving as the basis for carcinogenic and non-carcinogenic risk assessments (The Committee concluded that the studies utilized for estimating carcinogenic risks are the best currently available); the effects of the vehicle of administration on the toxicity exhibited by chloroform (The Committee recommended that the hepatic carcinogenicity produced by THMs administered in an oil vehicle be disregarded from making quantitative estimates of risk); the designation of the THMs collectively or individually as epigenetic carcinogens (The Committee found that the data does not support a contention that these compounds can be considered collectively as epigenetic carcinogens. Tribromomethane and bromodichloromethane have demonstrated sufficient activity in several assays to be considered genotoxic whereas the evidence for chlorodibromomethane and trichloromethane is inconclusive for genotoxicity); The consideration of the four predominant THMs as a group or mixture, opposed to using separate assessments for regulations (The Committee recommends that separate MCL values be calculated for each of the THMs, since their carcinogenic properties differ significantly in both quantitative and qualitative terms); Restrictions to using mouse liver tumor data as the basis of quantitative risk assessments (The Committee recommended that mouse liver tumor induction should be utilized in making the weight-of-evidence judgment that chloroform is a carcinogen); the role of the alpha-2u-globulin mechanism in renal tumor induction (Based on published reports it does not appear to play a role in the etiology of chloroform-induced renal tumors in rats); The use of hepatocellular adenomas and carcinomas as a basis for quantification of carcinogenicity for bromodichloromethane (The Committee found it inappropriate to consider hepatic tumors as the basis for quantification of carcinogenicity for bromodichloromethane and recommends that EPA utilize renal of intestinal tumors); The classification of dibromochloromethane in group C: possible human carcinogen, based on liver tumors in mice (The Committee recommends that the EPA classify dibromochloromethane in group C); The weight-of-evidence classification for bromoform as B2 (The Committee supports the classification of bromoform in the B2 category).

The Committee also recommended that a section on human exposure and body burden to chloroform be incorporated into the criteria document.

KEYWORDS: Trihalomethanes; chlorodibromomethane; dibromochloromethane; trichloromethane; Maximum Contaminant Level Goal (MCLG); renal tumors.

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1. EXECUTIVE SUMMARY

The Science Advisory Board's Drinking Water Committee met in Washington, DC on October 25-26, 1990 to review the Office of Drinking Water's background document *Revised External Draft for the Drinking Water Criteria Document for Trihalomethanes (THM).* Trihalomethanes are by-products of disinfection with chlorine and to some extent with chloramine. The THMs include chloroform, bromoform, bromodichloromethane and dibromo-chloromethane. In 1979, these substances were regulated in drinking water at a level of 0.10 mg/L. The regulation was based primarily on evidence of tumor formation in mouse liver and rat kidney following chronic exposure to chloroform, but health data were not available on brominated THMs at that time. Some new information has been generated since that time and the revised Drinking Water Criteria Document represents a revised draft which would address the issues related to the Maximum Contaminant Level Goal (MCLG) for THMs in drinking water. The Drinking Water Committee reviewed this document and has addressed specific and general issues concerning the toxicity of THMs.

A number of general and specific issues were presented to the Committee for response. In addition, one issue which the Committee raised and which is deficient in the Agency's draft report is discussed at length. It deals with the need to obtain information other than that presented in the Criteria Document concerning human exposure and body burden to THMs which should be incorporated into the document in order to gain information as to the magnitude (i.e., concentrations) and occurrence of chloroform in humans. Further, a consideration of the pharmacokinetic properties of chloroform and other THMs should be discussed because of importance in knowing the dosed target tissues and organs, the rate of elimination form the body and environmental exposure levels encountered by people and other issues which need to be addressed in humans.

General Issues

a. Does the SAB agree with the selection of the key study serving as the basis for carcinogenic and non-carcinogenic risk assessments?

The Committee concluded that the studies utilized for estimating carcinogenic risks with THMs are the best that are currently available for deciding whether these chemicals are human carcinogens and for estimating the potency of these chemicals as carcinogens but pointed out that it was far from proven that these studies provide a basis for declaring that these chemicals are carcinogens at the concentrations they are encountered in drinking water. The Committee found that the studies selected for the non-carcinogenic endpoints of THM toxicity were appropriate in general. One exception was noted. Namely, the Condie study should be used for the 10-day Health Advisory (HA) for bromoform just as it was for bromodichloromethane and dibromochloromethane and strong consideration should be

given to the chronic NTP study on bromoform for determination of the drinking water equivalent level (DWEL) for this compound.

b. Studies with chloroform indicate that the vehicle of administration may influence the toxicity exhibited by chloroform. Based on the available data, can the same inference be made with the brominated THMs?

Because hepatic tumors were observed when corn oil was used as the vehicle for chloroform but not when water, the more relevant vehicle, was used, the Committee recommended that the hepatic carcinogenicity produced by THMs administered in an oil vehicle be disregarded from making quantitative estimates of risk.

c. The mutagenicity data for the THMs are largely negative or equivocal. Could the THMs collectively or individually be considered as epigenetic carcinogens?

A review of the data does not support a contention that these compounds can be considered collectively as epigenetic carcinogens. Tribromomethane and bromodichloromethane have demonstrated sufficient activity in several assays to be considered genotoxic whereas the evidence for chlorodibromomethane and trichloromethane is inconclusive for genotoxicity. A discussion is presented dealing with differences in methodology which influence interpretation of results. Further, reference is made to studies which suggest that THM concentrations that may have provoked mutagenic responses were orders of magnitude higher than those found in drinking water.

d. The THM standard applies to the sum of the four predominant THMs. Based on the health effects of the individual THMs, is it reasonable to continue to consider this group as a mixture or would separate assessments be more appropriate for regulation?

The Drinking Water Committee recommends that separate MCL values be calculated for each of the THMs. One reason for this recommendation is because their carcinogenic properties differ significantly in both quantitative and qualitative terms.

e. Are there any restrictions to using mouse liver tumor data as the basis of quantitative risk assessments?

The Committee recommended that mouse liver tumor induction should be utilized in making the weight-of-evidence judgment that chloroform is a carcinogen. However, these data should not be used for making quantitative assessments of risk. A number of individual comments are made in order to support this recommendation.

f. Is there reason to suspect chloroform acts on the rat kidney through the alpha-2u-globulin mechanism?

The alpha-2u-globulin appears to play no role in the etiology of chloroform-induced renal tumors in rats.

g. Are hepatocellular adenomas and carcinomas the appropriate basis for quantification of carcinogenicity for bromodichloromethane? Would the occurrence of these tumor types be expected if the compound were administered in drinking water? Is the current quantitation applicable to drinking water exposure? Should further research be initiated testing this compound in drinking water?

The Committee concludes that it is inappropriate to consider the induction of hepatic tumors as the basis for quantification of carcinogenicity for bromodichloromethane. The Committee recommends that EPA utilize renal or intestinal tumors to estimate the carcinogenic risks for humans. The data reviewed suggests that the induction of intestinal tumors would be more appropriate since a site is involved where tumors are not commonly seen in rats and the resulting incidence is quite high in males and observed in both sexes. It was noted that bromodichloromethane also produces tumors in the rat kidney, a site which is probably independent of vehicle effects with chloroform whereas hepatic tumors are likely to be seen primarily, if not exclusively, with THMs administered in the presence of a vehicle such as corn oil. Thus, quantitation of carcinogenic risks using hepatic tumors appear not to be applicable to drinking water exposure. Appropriate research has been proposed for studying the pharmacokinetics and metabolism of bromodichloromethane. However, research on defining the mechanism by which the compound induces tumors in non-hepatic target organs appears to be critical.

h. Based on its definitions and criteria for the classifications of chemicals as carcinogens or non-carcinogens EPA has classified dibromochloromethane in group C: possible human carcinogen based on liver tumors in mice. Does the SAB agree with the conclusions in light of the flaws of the studies conducted?

The Committee recommends that the EPA classify dibromochloromethane in group C. The gavage error alluded to in the EPA briefing document occurred in a low-dose group only. There was no indication of the intestinal or other tumor types in the high-dose group and no evidence or carcinogenicity in rats.

i. Is the weight-of-evidence classification for bromoform of B2 correct?

The Committee noted that the EPA classified bromoform in group B2 based on the incidence of neoplastic lesions of the large intestine in female rats.

Classification of a compound as a probable human carcinogen based on the induction of a tumor at a single site at low incidence in a single species is not scientifically defensible. However, the Committee noted that the intestinal tract is not a common tumor site and that bromoform is the one THM that is the most clearly mutagenic. Thus, the Drinking Water Committee supports the classification of bromoform in the B2 category.

j. Is there information other than that presented in the Criteria Document concerning exposure?

The Committee recommends that a section on human exposure and body burden to chloroform be incorporated into the Criteria Document because it would provide direct evidence as to the magnitude (i.e., concentrations) and occurrence of chloroform in people. In addition, the pharmacokinetic properties of THMs should be discussed because it is important to know the dose to target organs and tissues, and its rate of elimination from the body at the environmental exposure levels encountered by people. Pharmacokinetic data in animals and humans have been reported for chloroform; these data should be discussed in this section of the Criteria Document. Exposure, body burden and pharmacokinetic information on chloroform would significantly better place into perspective the potential toxicological implications. Much of the information on exposure could be obtained from the records from utilities routinely applied to state agencies.

2. INTRODUCTION

The Science Advisory Board's Drinking Water Committee met on October 25-26, 1990 to review the Office of Drinking Water's document *Revised External Draft for the Drinking Water Criteria document on Trihalomethanes (THMs).* During the meeting the Committee received oral presentations from EPA staff. The Committee appreciates the opportunity to review the document prior to the final preparation of the criteria document.

The Committee addressed the following issues:

a. Does the SAB agree with the selection of the key study serving as the basis for carcinogenic and non-carcinogenic risk assessments?

b. Studies with chloroform indicate that the vehicle of administration may influence the toxicity exhibited by chloroform. Based on the available data, can the same inference be made with the brominated THMs?

c. The mutagenicity data for the THMs are largely negative or equivocal. Could the THMs collectively or individually be considered as epigenetic carcinogens?

d. The THM standard applies to the sum of the four predominant THMs. Based on the health effects of the individual THMs, is it reasonable to continue to consider this group as a mixture or would separate assessments be more appropriate for regulation?

e. Are there any restrictions to using mouse liver tumor data as the basis of quantitative risk assessments?

f. Is there reason to suspect chloroform acts on the rat kidney through the alpha-2u-globulin mechanism?

g. Are hepatocellular adenomas and carcinomas the appropriate basis for quantification of carcinogenicity for bromodichloromethane? Would the occurrence of these tumor types be expected if the compound were administered in drinking water? Is the current quantitation applicable to drinking water exposure? Should further research be initiated testing this compound in drinking water?

h. Based on its definitions and criteria for the classifications of chemicals as carcinogens or non-carcinogens EPA has classified dibromochloromethane in group C: possible human carcinogen based on liver tumors in mice. Does the SAB agree with the conclusions in light of the flaws of the studies conducted?

i. Is the weight-of-evidence classification for bromoform of B2 correct?

j. Is there information other than that presented in the Criteria Document concerning exposure? (Question raised by the Committee.)

3. SPECIFIC ISSUES

3.1 Does the SAB agree with the selection of the key studies serving as the basis for carcinogenic and non-carcinogenic risk assessments?

3.1.1 Carcinogenic Risk Studies

The Committee has evaluated the studies selected by the agency and concludes that the studies utilized for estimating carcinogenic risks with THMs are the best currently available for deciding whether these chemicals are human carcinogens and for estimating the potency of these chemicals as carcinogens. The Drinking Water Committee has to point out, however, that because of the very high levels of exposure employed is the studies on animals, it is far from proven that these studies provide a basis for declaring that these chemicals are carcinogens at the concentrations they are encountered in drinking water. While more specific comments are made below about studies involving individual THMs, a number of points apply to all these chemicals.

a. The induction of renal and hepatic tumors occurs at doses which also produce cytotoxic effects and subsequent reparative hyperplasia. While the Agency makes the argument that these effects do not uniformly result in tumor induction (a true statement), there are strong indications that these phenomena play a role along with species and/or strain dependent reactions. There is every indication that liver damage is responsible for liver tumor induction in B6C3Fl mice and cannot be excluded as playing a role in renal induction in rats.

b. Although the mechanism is not clear, there is strong evidence that a corn oil vehicle/chloroform interaction is responsible for the induction of liver tumors in mice since they were observed when corn oil was used as the vehicle[1] but not when water served as a vehicle[2]. Although the Agency recognized this when assessing risks from chloroform, the possibility of such interactions in the induction of liver tumors by bromodichloromethane (BDCM) and dibromochloromethane (DBCM) has apparently not been considered. In the case of bromodichloromethane, tumors were induced at organ sites that are apparently not sensitive to vehicle effects. Thus, it would seem prudent to concentrate on these other organ sites in assessing risk for this compound. In case of dibromochloromethane, induction of liver tumors in mice is the only evidence of carcinogenicity. Therefore, the C classification for dibromochloromethane taken by the Agency would appear to be appropriate.

c. It is notable that the order of potency of the THMs for induction of hepatic tumors in mice parallels their potency as hepatotoxins (BDCM > $CHCl_3$ - DBCM > Hrr3).[3] Therefore, the Committee recommends

that the Agency consider a non-hepatic target organ for bromodichloromethane. The proposed selection of target organs with regard to the carcinogenicity of the other THMs appears justified.

3.1.2 Non-Carcinogenic Risk Studies

Concerning the question as to whether or not the selection of the studies for the non-carcinogenic endpoints of the trihalomethanes is correct, the Committee generally finds these studies to be appropriate. In many cases, the results of other studies reinforce the one selected.

For chloroform, the study by Jones et al.[4] for the one-day Health Advisory (HA) is appropriate for use in classifying the non-carcinogenic effects, although the time between the dosing and histological observation (72 hours) may have been too long to observe any transient effects of the lower doses.

The 10-day HA is based on the study of Thompson et al.[5] which used pregnant rabbits. General toxicity was not the intended purpose of this study so that its use may be questionable. However, since it addresses a sensitive population and also gives a Lowest Observed Adverse Effect Level (LOAEL) similar to that of the study of Chu et al.[3] which examined the more conventional endpoints in a better designed 28-day study, it would not be unreasonable to use the Thompson study.

The use of the Drinking Water Equivalent Level (DWEL) value in calculating the long-term HA to avoid having the long-term HA higher than the short-term HA is appropriate. The use of the studies of Heywood et al.[6] for both the DWEL and long-term HA is warranted. These were chronic studies (7.5 years) in dogs and appear to have been adequately conducted. The resulting HA values are more conservative than those which would have been calculated from the results of the studies of Palmer et al.[7] or Jorgenson et al.[2]

For bromodichloromethane, setting the one-day HA on the same study as the ten-day HA is warranted in view of the lack of any other good information. The 14-day study of Condie et al.[8] is quite appropriate since it was intended for this purpose. Furthermore, the value is very close to that which would be derived from the National Toxicology Program (NTP) 14-day study[9] where mortality, clinical signs and gross pathology were examined. For the long-term HA, the NTP data from a 90-day study in mice are applicable even though corn oil gavage was used. It should be noted that the study by Chu et al.[10] using water as the vehicle would yield similar numbers. Similarly a DWEL based on the NTP chronic study is reasonable even though it requires the use of an additional uncertainly factor.

For dibromochloromethane, the use of the same study (Condie) for the one-day HA and the ten-day HA in lieu of an appropriate single dose study is merited. The 90 day NTP study[11] is appropriate for the longer term Has especially since there are supporting studies which would give similar values. The use of the 90-

day NTP study to establish the DWEL from a No Observed Adverse Effect Level (NOAEL) with an added uncertainly factor is not unreasonable.

For bromoform, a problem with the study of Burton-Fanning[12] can be cited: the endpoint is limited to central nervous system effects and the possible involvement of other systems is unknown. There is a reluctance by EPA to use the data of Condie et al. for the ten-day HA because the calculated value of 14.5 mg/liter would be higher than the one-day HA. EPA therefore proposes to use the NTP 90-day study data.[13] The Committee recommends that since the Condie study was intended for short-term exposures, was adequately conducted using the correct endpoints, and used mice which are an appropriate model, the data in the investigation should be used. Because of the reasonable concern in establishing a 10-day HA which would be higher than a one-day HA, it would seem appropriate to use 5 mg/liter for the 10-day HA also. It should be noted that the concern over the high one-day HA may be tempered by the findings of Condie et al. The NTP data are suitable for the long term HA. The Committee concurs with the suggestion that the EPA examine the use of the chronic NTP study data for determining the DWEL. This could change the DWEL in either direction. If similar exposure levels are used in both studies, it could increase the DWEL by eliminating the additional uncertainty factor of 10 used because a 90 day study was the basis. However, the DWEL would be decreased if a significantly lower NOAEL or LOAEL had to be used in the calculations.

The Committee recommends that EPA use references given in draft criteria document for the non-carcinogenic risk assessments with the exceptions noted. Namely, the Condie study should be used for the 10-day HA for bromoform just as it was for bromodichloromethane and dibromochloromethane, and strong consideration should be given to the chronic NTP study on bromoform for determination of the DWEL for this compound.

3.2 Studies with chloroform indicate that the vehicle of administration may influence the toxicity exhibited by chloroform. Based on the available data, can the same influence be made with the brominated THMs?

There is strong evidence that the interaction between corn oil and chloroform is responsible for the induction of liver tumors in mice. The possibility of such interactions in liver tumor induction by bromodichloromethane and dibromochloromethane must be seriously considered. The quantity and quality of corn oil administered are of concern. The possible effect of corn oil contamination and the effect of corn oil dosage might be factors which could perturb the normal physiology of the organism.

Thus the Committee recommends that the hepatic carcinogenicity produced by THMs administered in an oil vehicle be disregarded for making quantitative estimates of risk. There is no evidence to suggest that this vehicle affected tumorigenicity at other target sites.

3.3 The mutagenicity data for the THMs are largely negative or equivocal. Could the THMs collectively or individually be considered epigenetic carcinogens?

The Committee addressed the question of whether the mutagenicity data on the THMs collectively or individually support a label of epigenetic carcinogens. A review of the data, as indicated below, does not support a contention that these compounds can be considered collectively as epigenetic carcinogens. Even if there existed a broad consensus on the meaning of the term epigenetic carcinogen, the four compounds -- tribromomethane, chlorodibromomethane bromodichloromethane and trichloromethane would not qualify because tribromomethane and bromodichloromethane have demonstrated sufficient activity in several assays to be considered genotoxic and the evidence for chlorodibromomethane and trichloromethane is inconclusive for genotoxicity.

Literature from the draft THM criteria document provided to the Committee as well as additional references are also included in this review. Also telephone communications with Dr. Errol Zeiger of the NTP program and Dr. Angela Auletta of the Gene-Tox program of EPA's Office of Toxic Substances were conducted to acquire perspective and other test data. The majority of the data from the NTP program have been published recently.[14]

The major difficulty encountered with the Ames Salmonella results on the THMs is the method of testing. Some investigators have used a closed container (desiccator) to incubate the agar plates and others have not. When a closed environment was used, these types of compounds have tended to produce positive results. Another example of this is the closely related compound dichloromethane.

There are a number of conflicting results in the literature on the genotoxicity of the THMs. Part of this condition is due to differences in methodology, part due to interpretation of results and part due to the physical nature of the compounds. This condition makes analysis difficult and places additional emphasis on distinguishing between levels of human exposure and levels used in the in vitro assays. This distinction is identified in the paper of Morimoto and Koizumi,[15] who comment that the THM concentrations that caused significant increases in SCE frequencies in their experiments were 10^3 -10^4 times higher than those found in drinking water.

The Committee recommends, therefore, that these THMs not be considered by the Agency as epigenetic carcinogens.

3.4 The THM standard applies to the sum of the four predominant THMs. Based

on the health effects of the individual THMs, is it reasonable to continue to consider this group as a mixture or would separate assessments be more appropriate for regulation?

The Committee recommends that separate MCL values be calculated for each of the THMs because their carcinogenic properties differ significantly in both quantitative terms.

3.5 Are there any restrictions to using mouse liver tumor data as the basis of quantitative risk assessments?

Based on the implied differential toxicity of chloroform in corn oil vs. water, EPA quantified the cancer risk for chloroform based on kidney tumors in rats given chloroform in drinking water. The evidence of mouse liver tumors was considered qualitatively in the total weight of evidence for carcinogenicity. It is doubtful that the Agency should consider the mouse liver in quantitative assessments.

The use of the mouse liver tumors induced by chloroform with corn oil in the qualitative classification of chloroform as a carcinogen is prudent. Its use for quantitative risk assessment is suspect for the following reasons:

a. Liver tumors could not be produced in mice in the absence of corn oil.

b. Liver tumors are not induced in other species by administering chloroform alone.

c. Initiation of the rat liver by dimethylnitrosamine allowed promotion of liver tumors by chloroform in corn oil.[16]

d. Chloroform given without vehicle or in aqueous media to mice initiated with dimethylnitrosamine inhibited development or liver tumors.

e. Recent data has clearly demonstrated that the liver of C3H mice, the parental strain of the B6C3F1 hybrid from which the high spontaneous rate is inherited, has a high population of immortal cells that are promotable,[17] relative to the C57BL, the parenteral strain with a low spontaneous incidence of liver tumors.

f. Chloroform administered in corn oil is clearly hepatotoxic at doses used in the bioassays. Chloroform in an aqueous vehicle was without observable effect, adding to the argument that these tumors are secondary to cell necrosis and reparative hyperplasia.

g. Recent research indicates that the capacity for metabolizing THMs by

reductive dehalogenation is a prominent pathway in mice, but not in rats.[18] This substantial difference in the hepatic metabolism of the THMs could be responsible for species differences in tumorigenic responses.

The Committee recommends that mouse liver tumor induction should be utilized in making the weight-of-evidence judgment that chloroform is a carcinogen. However, these data should not be used for making quantitative assessments of risk because these tumors have been observed only when corn oil and not water is used as the vehicle and because of the uncertainty nature of these mouse tumors.

3.6 Is there reason to suspect chloroform acts on the rat kidney through the alpha-2u-globulin mechanism?

It would appear that alpha-2u-globulin has no apparent role in the etiology of chloroform - induced renal tumors in rats as proposed for other chemicals (unleaded gasoline, d-limonene, perchloroethylene.

3.7 Are hepatocellular adenomas and carcinomas the appropriate basis for quantification of carcinogenicity for bromodichloromethane? Would the occurrence of these tumor types be expected if the compound was administered in drinking water? Is the current quantitation applicable to drinking water exposure? Should further research be initiated testing this compound in drinking water?

Based on the experiments with chloroform and corn oil, it seems inappropriate to consider the induction of hepatic tumors in B6C3F1 mice for quantitating risks. Bromodichloromethane induces tumors at other sites, at least one of which (the rat kidney) appears to be independent of the vehicle effects observed with chloroform. A cursory examination of the data suggests that the induction of intestinal tumors might actually be more appropriate for estimating risk because it involves a site where tumors are not commonly seen in the rat and the resulting incidence is quite high in males and observed in both sexes. The only drawback is that there have been no studies of the mechanism by which bromodichloromethane produces tumors at this site.

If these other sites are considered the actual impact on the risk assessment is minimal, but it is important to adhere to the principle that the most appropriate data should be utilized rather than falling back to the most sensitive site default.

It is clear from bioassay results bromodichloromethane is the critical THM produced in drinking water disinfection. It fits both EPA and International Agency for Research on Cancer (IARC) criteria for weight of evidence in that it produces tumors in multiple species at multiple sites, including sites at which tumors are relatively rare in the test species. Therefore, this compound is critical

to the assessment of whether THMs produced in the disinfection of drinking water present a carcinogenic risk to humans. Appropriate research has been proposed for studying the pharmacokinetics and metabolism of this THM in some detail. However, research on defining the mechanism by which the compound induces tumors in non-hepatic target organs is at least as critical. The Committee recommend, therefore that EPA undertake such studies.

Therefore, the Committee recommends that EPA utilize renal or intestinal tumors to estimate the carcinogenic risks to man. There can be little confidence that the hepatic tumors induced in mice by bromodichloromethane are not dependent upon the corn oil vehicle utilized in the NTP bioassay.

3.8 EPA has classified dibromochloromethane in group C: possible human carcinogen based on liver tumors in mice. Does the SAB agree with the conclusions in light of the flaws of the studies conducted?

The classification of dibromochloromethane in group C appears appropriate. The gavage error alluded to in the EPA briefing document occurred in the low dose group. There was no indication of the intestinal or other tumor types in the high dose group and no evidence of carcinogenicity in rats.

Although this reduced the statistical power of the study somewhat, it is hard to imagine that additional studies would uncover any other significant tumors sites. Therefore, the Committee recommends that EPA classify dibromochloromethane in group C. This is consistent with the action taken by the IARC.

3.9 Is the B2 weight of evidence classification for bromoform correct?

EPA has classified bromoform in group B2 based on the incidence of neoplastic lesions of the large intestine in female rats. The IARC concluded that the incidence of this tumor type was not sufficient to consider bromoform as a probable human carcinogen.

Classification of a compound as a probable human carcinogen based on the induction of a tumor at a single tumor site at low incidence in a single species is not scientifically defensible. Since the positive results were observed in the same study that failed to indicate a carcinogenic response in a second species, the only strict interpretation possible is that the response is species specific for the rat and not extrapolatable to other species. On the other hand, the Committee notes that the intestinal tract is not a common tumor site and that bromoform is the one THM that is more clearly mutagenic. (These points were also debated by the IARC working group and the issue of classification was a close call for the working group.) Although the Committee feels that it is far from established that chlorinated drinking water represents a carcinogenic hazard, it is notable that intestinal tumors are one site that has been associated with chlorination in

epidemiological studies. The Committee recognized that the data supporting

classification of bromoform in the B2 vs. C category is not clear cut.

Therefore, the Committee concurs with EPA's classification of bromoform as a B2 carcinogen.

3.10 Is there information other than that presented in the Criteria Document concerning exposure?

It is recommended that a section on human exposure and body burden to chloroform be incorporated into the criteria document because it provides direct evidence as to the magnitude (i.e., concentrations) and widespread occurrence of chloroform in people. In addition, the pharmacokinetic properties of chloroform should be discussed because it is important to know the dose to target organs and tissues, and its rate of elimination from the body at the environmental exposure levels encountered by people.

Pharmacokinetic data in animals and humans have been reported for chloroform; these data should be discussed in this section of the Criteria Document. Exposure, body burden and pharmacokinetic information on chloroform would significantly better place into perspective the potential toxicological implications.

Even though national surveys on prevalence/occurrence of chloroform and other volatile organic chemicals in drinking water have been performed they do not provide insight to human exposure and body burden. This information is vital to the understanding of the prevalence and extent to which people have been exposed to chloroform from drinking water and its relative importance to other routes and sources of exposure (e.g., ingestion from food, inhalation, dermal). Temporal variations in human exposure may also occur as new control technologies or alternate disinfection processes are employed in the future, and the trends in long-term temporal variations (by seasons and over several years) will be important information regarding the effectiveness of changing technologies.

A national survey of human exposure to chloroform, other THMs and volatile organics in drinking water has not been performed. There are, however, a number of pertinent geographical probability-based studies which have been conducted over the past 10 years to assess human exposure and body burden.[20-32] Populations in locations such as Bayonne and Elizabeth, NJ; Devils Lake, ND; Greensboro, NC; Antioch, Carson, El Legundo, Lomita, Hermosa Beach, Manhattan Beach, Pittsburgh, Redondo Beach, Torrance, and West Carson, CA; Niagara Falls and Buffalo, NY; Baton Rouge, LA; Beaumont and Houston, TX; and Chapel Hill, NC have been surveyed.[20-24]

In most of these populations a 3-stage probability sample was selected so that inferences could be drawn to the target population of interest. Briefly, first-stage sampling units (FSU) defined by Census blocks were selected. Then clusters of housing units were selected at the second stage within the FSU's and these

homes were screened to identify individuals with characteristics believed to be positively correlated with exposure to the chemicals (including chloroform) of interest. The third stage was a stratified sample of screened eligible individuals. These studies also provide for a comparison of the routes of exposure (e.g., drinking water vs. air) and short-term temporal variations.

The literature contains other small-scale non-probability based investigations on human blood levels of chloroform for the Gulf Coast and other areas.[33-37] These data should be critically evaluated, however, since subsequent methodological investigations in the early 1980s have demonstrated shortcomings in the heated purge and trap procedure used for measuring chloroform. Pfaffenburger et al.[38] reported information of chloroform from trichloroacetic acid (TCA) at elevated pH. TCA is a metabolite from 1,1,1-trichloroethane, which is ubiquitous in human blood originating from inhalation exposure.

Recently, the Centers for Disease Control has completed the development and validation of an isotopic dilution method for about two dozen VOCs in blood.[39] Blood chloroform measurements are planned for the future and it is recommended that the Office of Drinking Water utilize this information for developing future criteria documents.

Preliminary reports also indicate that chloroform in drinking water may lead to significant inhalation (from showers, washing clothes) and dermal (bathing swimming) exposure.[40] Such information is relevant in developing strategies for Health Advisory documents.

Finally, it is recommended that ODW coordinate with Agency for Toxic Substances Diseases Research (ATSDR) when compiling information on human exposure to VOCs. including chloroform and other THMs, since ATSDR also develops criteria documents for hazardous waste sites containing much of the same information (metabolism, pharmacokinetics, exposure).

In summary, the drinking water criteria document on chloroform is severely deficient on human exposure and pharmacokinetic issues. It is recommended that the Office of Drinking Water compile relevant information on human exposure, body burden, and pharmacokinetics and toxicological implications. In many cases routine monitoring data are being obtained by water utilities and reported to state agencies but are not being systematically collected by EPA. The Committee recommends that the Agency avail itself of this information on THMs, and induced other water contaminants, for use in assessing exposures.

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