



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

OFFICE OF
THE ADMINISTRATOR

EPA-SAB-DWC-92-002

November 27, 1991

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

Subject: Review of Issues Relating to the Drinking Water Health Criteria Document for Chlorinated Acids/Alcohols/Aldehydes/Ketones

Dear Mr. Reilly:

The Toxicology/Clinical Subcommittee of the Science Advisory Board's Drinking Water Committee met April 4-5, 1991 in Washington, D.C. to review issues relating to the Office of Drinking Water's Health Criteria Document on Chlorinated Acids/Alcohols/Aldehydes/Ketones. As potential disinfection by-products, these compounds must be considered in regulatory efforts. The Office of Drinking Water stressed that this is a very preliminary draft and that SAB advice was being sought to strengthen the draft as it progressed through further iterations.

The Science Advisory Board was asked to address a number of issues, including the identification of deficiencies due to significant gaps in data. These issues and our responses are summarized below:

- 1) Which studies should serve as the basis for non-carcinogenic risk assessment? With a few exceptions the studies selected for non-carcinogenic risk assessment were appropriate and justified.
- 2) Does the Committee agree with the line of investigation on addressing the question of a possible threshold for dichloro acetic acid (DCA) induced hepatocellular cancer in B6C3F1 mice? The approach being taken on evaluating the possibility of a threshold for the carcinogenicity of dichloroacetic acid in mice is correct but is limited and should be expanded to include both rat and mechanistic studies.

- 3) Does the Committee agree with EPA that chloral hydrate (trichloroacetaldehyde) has a tumor potency in mice similar to that of DCA? The tumor potency of chloral hydrate in mice may be similar to that of dichloroacetic acid but further studies are needed as well as an evaluation of any epidemiological studies that may have been done on this formerly widely used medication.
- 4) Should the MCLG for DCA be set on the basis of carcinogenicity or neurotoxicity? We cannot make a recommendation at the present time on this issue, but the Committee recognizes the importance of neurotoxicity and strongly urges EPA to continue research in this area.
- 5) What relative source contribution should be applied to the risk assessment of these chemicals? This question cannot be answered since insufficient information was provided upon which to make a judgment.

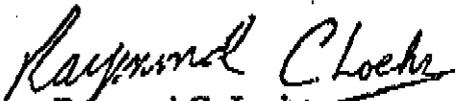
The Committee recommends that the health criteria document be separated into two or three individual documents. As currently structured, it is very difficult to follow. The compounds with the most information, dichloroacetic acid, trichloroacetic acid, and trichloroacetaldehyde, tend to become lost in minimal discussions of the ketones and alcohols. In addition, the Committee offers specific comments related to the document which are contained in the attached report.

In our opinion, the material presented on the occurrence of these compounds in drinking water can be presented in a more detailed and informative fashion. We also question why trichloroethanol is of concern as a pollutant when it does not appear to have been found in drinking water. Furthermore, on the basis of information supplied by EPA scientists at the meeting, we recommend an expansion of the discussion and evaluation of the developmental toxicity studies. We would also like to suggest that the studies on immunotoxicity be sharply focused since there are already existing data which indicate that there may be effects on the immune system. In addition, we strongly recommend that the Agency define the toxicity/carcinogenicity of the brominated analogs of these chlorinated compounds since they are likely to be formed with either chlorination or ozonation. Finally, we recommend that a more complete description be given in the document on possible mechanisms, particularly the possibility of peroxisomal proliferation and how this might affect the extrapolation of the murine liver tumor data to humans.

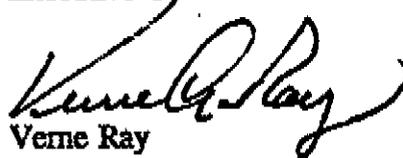
The preliminary draft criteria document was prepared for the Criteria and Standards Division, Office of Drinking Water, by ICAIR Life Systems Inc. of Cleveland Ohio. We recommend that the procedure by which the data were developed should be added to the Life Systems report.

We appreciate having been given the opportunity to conduct a review at such an early stage in the development of this document and look foreword to a continuing dialogue as the document progresses. We request that the Agency respond formally to the scientific advice provided herein, particularly in regard to the Committee's concerns about the document which go beyond the original questions posed by the Agency.

Sincerely,



Raymond C. Loehr
Chairman
Executive Committee



Verne Ray
Chairman
Drinking Water Committee
and
Chairman
Toxicology/Clinical
Subcommittee



AN SAB REPORT: REVIEW OF DRINKING WATER HEALTH CRITERIA DOCUMENT

**REVIEW OF THE OFFICE OF
DRINKING WATER'S HEALTH
CRITERIA DOCUMENT ON
CHLORINATED ACIDS/
ALCOHOLS/ALDEHYDES/KETONES
BY THE DRINKING WATER
COMMITTEE**

U. S. ENVIRONMENTAL PROTECTION AGENCY

NOTICE

This report has been written as a part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

U.S. Environmental Protection Agency

ABSTRACT

The Toxicology/Clinical Subcommittee of the Science Advisory Board's Drinking Water Committee met April 4-5, 1991 in Washington, DC to review issues relating to the Office of Drinking Water's preliminary draft Health Criteria Document on Chlorinated Acids/Alcohols/Aldehydes/Ketones. The Subcommittee answered specific questions posed by the Office of Drinking Water, and obtained informational briefings from the Office of Research and Development (ORD), in particular the Health Effects Research Laboratory (HERL), concerning specific ongoing or anticipated research efforts to provide answers for some of the questions regarding the toxicity of these disinfection by-products and to fill in data gaps.

In reviewing the preliminary draft document presented by the Agency, the Subcommittee concluded the following: 1) with a few exceptions the studies selected for non-carcinogenic risk assessment were appropriate and justified; 2) the approach being taken on evaluating the possibility of a threshold for the carcinogenicity of dichloroacetic acid in mice is correct but is limited and should be expanded to include both rat and mechanistic studies; 3) the tumor potency of chloral hydrate in mice may be similar to that of dichloroacetic acid but further studies are needed as well as an evaluation of any epidemiological studies that may have been done on this formerly widely used medication; 4) no recommendation can be made at the present time regarding whether the MCLG for DCA should be made on the basis of its carcinogenicity or neurotoxicity, but we recognize the importance of the latter and strongly urge EPA to continue research in this area; and 5) that there was insufficient information to make a judgment concerning what relative source contribution should be applied to the risk assessment of these chemicals.

The Committee recommends that the document be separated into two or three individual documents. As currently structured, it is very difficult to follow. The compounds with the most information, dichloroacetic acid, trichloroacetic acid, and trichloroacetaldehyde, tend to become lost in minimal discussions of the ketones and alcohols.

Key Words: chlorinated acids; trichloroacetate; dichloroacetic acid; chloral hydrate; MCLG

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1.0 EXECUTIVE SUMMARY

The Toxicology/Clinical Subcommittee of the Science Advisory Board's Drinking Water Committee reviewed issues related to the Office of Drinking Water's Health Criteria Document on Chlorinated Acids/Alcohols/Aldehydes/Ketones. These compounds are potential disinfection by-products and thus, are important to regulatory efforts.

In reviewing the preliminary draft document presented by the Agency¹, the Subcommittee concluded the following: 1) with a few exceptions the studies selected for non-carcinogenic risk assessment were appropriate and justified; 2) the approach used to evaluate the possibility of a threshold for the carcinogenicity of dichloroacetic acid in mice is correct but is limited and should be expanded to include both rat and mechanistic studies; 3) the tumor potency of chloral hydrate in mice may be similar to that of dichloroacetic acid (DCA) but further studies are needed as well as an evaluation of any epidemiological studies that may have been done on this formerly widely used medication; 4) no recommendation can be made at the present time regarding whether the MCLG for DCA should be made on the basis of its carcinogenicity or neurotoxicity, but we recognize the importance of the latter and strongly urge EPA to continue research in this area; and 5) that there was insufficient information to make a judgment concerning what relative source contribution should be applied to the risk assessment of these chemicals.

In our opinion, the material presented on the occurrence of these compounds in drinking water can be presented in a more detailed and informative fashion. We also questioned why trichloroethanol is of concern as a pollutant when it does not appear to have been found in drinking water. Furthermore, on the basis of information supplied by EPA scientists, we recommend an expansion of the discussion and evaluation of the developmental toxicity studies. We would also like to suggest that the studies on immunotoxicity be sharply focused since there are already existing data which indicate that there may be effects on the immune system. In addition, we strongly recommend that the Agency define the toxicity/carcinogenicity of the brominated analogs of these chlorinated compounds since they are likely to be formed with either chlorination or ozonation. Finally, we recommend that a more complete description be given in the document on possible mechanisms, particularly the possibility of peroxisomal proliferation and how this might affect the extrapolation of the murine liver tumor data to humans.

We recommend that the document be separated into two or three individual documents. As currently structured, it is very difficult to follow. The compounds with the most information, dichloroacetic acid, trichloroacetic acid, and trichloroacetaldehyde, tend to become lost in minimal discussions of the ketones and alcohols.

¹ The document was prepared by ICAIR Life Systems Inc. of Cleveland, Ohio. The author was Dr. Herbert Cornish and the editor was Dr. William Bradin.

2.0 INTRODUCTION

2.1 Background

The possible adverse effects of disinfectants and their by-products have been of long-term interest to the Drinking Water Committee. There have been numerous interactions between the Committee and the Office of Drinking Water. The Toxicology/Clinical Subcommittee of the Science Advisory Board's Drinking Water Committee met April 4-5, 1991 in Washington, DC to review issues relating to the Office of Drinking Water's Health Criteria Document on Chlorinated Acids/Alcohols/Aldehydes/Ketones. The purpose of this meeting was two-fold. First, to answer specific questions posed by the Office of Drinking Water as discussed in the charge. And second, to obtain information from the Office of Research and Development (ORD), in particular the Health Effects Research Laboratory (HERL), concerning specific ongoing or anticipated research efforts to provide answers for some of the questions regarding the toxicity of these disinfection by-products and to fill in data gaps.

We recognize that the criteria document is in a very formative stage. This gave us the unique and exciting opportunity to have input at the level where it might greatly influence the final document. In addition, it provided the chance to discuss and comment upon research strategies that the Agency could take to answer some of these important questions. We recognized not only the preliminary nature of the document, but also the fact that in some cases there were ample experimental data and in others there was simply a paucity of available information.

2.2 Charge to the Subcommittee

The Subcommittee went beyond only replying to the questions specifically asked by the Agency. We felt that it was appropriate to help identify at an early stage, those points with which the scientific community would clearly agree based on the experimental evidence, those which may be of some controversy because of differences of opinion or interpretation of results, and those which are in need of additional information. In the latter, case it is important to recognize that priorities need to be established based on either the importance of the toxic endpoint or the relationship to possible widespread human exposure.

The Subcommittee was asked to respond to the following questions:

- a. Which studies should serve as basis for non-carcinogenic risk assessment?
- b. Does the Science Advisory Board agree with the following line of investigation: Hepatocellular cancers were observed in B6C3F1 mice given high concentrations (1-5 g/L) of dichloroacetic acid (DCA) in less than a lifetime (52-61 weeks) of exposure (Herren-Freund et al., 1987; Bull et al., 1990). A more recent study (DeAngelo et al., 1991) employed lower concentrations

(0.05 - 0.5 g/L) over an exposure period of 75 weeks. In this study, increased prevalence of liver cancer was correlated with pathologic changes, tissue necrosis with nodular hyperplasia and increased peroxisome proliferation. DCA appeared to lack activity when tested in a series of genotoxicity assays. A recently completed study using 0.5 g/L over a lifetime exposure to B6C3F1 mice (Daniel and DeAngelo, personal communication) also measured an increased prevalence of hepatocellular cancer. Thus, the pathologic changes seen at the high doses do occur also with less severity at low doses. The complete analysis of these changes is ongoing. Additional studies are planned to address the issue of a threshold for DCA carcinogenicity.

- c. Does the Science Advisory Board agree with the following assessment: Chloral hydrate (trichloroacetaldehyde monohydrate) has a clear record of genotoxicity in microbial (Hayworth et al., 1983) and mammalian (Russo et al., 1984) systems with a propensity to induce aneuploidy in eukaryotic systems.
- d. Acute and long-term exposures to DCA by humans and animals indicate neuropathy as a toxic endpoint. In these studies, although doses are high, there is no NOAEL indicated. Should extra uncertainty be added to the risk assessment calculation to account for uncertainty regarding this endpoint? Should the basis for the MCLG be set on carcinogenicity or neurotoxicity?
- e. Which relative source contribution should be applied to the risk assessment of these chemicals? For its draft calculations, EPA used 80% for chloral hydrate since it is very unlikely to be found in food. For all others, 20%, the normal default value was used.

3.0 DISCUSSION OF ISSUES

3.1 Which Studies Should Serve as the Basis for Non-Carcinogenic Risk Assessment?

The study chosen for the 10-day health advisory for dichloroacetate is that of Stacpoole et al. (1987). The text and table are inconsistent in that the text refers to the 50 mg/kg dose as a NOAEL (No Observed Adverse Effect Level) and the table classifies it as a LOAEL (Lowest Observed Adverse Effect Level). Moreover, the newly completed 90-day dog study should be incorporated in the derivation of the 10-day longer term health advisories.

The drinking water equivalent level (DWEL) derivation for DCA uses two factors of 10 and justifies their use because of the class C carcinogenicity determination. The document needs to clarify the basis for these factors. However, the new carcinogenicity studies need to be included in the DWEL and longer term health advisory determinations.

Selection of the NOAEL of 7 mg/kg for the 1-day health advisory was based on a single large study of hospitalized patients. The Committee questions the clinical experience with this drug, which has been widely used for many years. We cannot help but believe that there must be a better and more extensive data base in humans for selection of this NOAEL. Factors to be considered should include in the selection of any clinical study for setting standards for environmental agents:

- a. the general health of the group under study compared to the universal population of the United States,
- b. administration clinically as a single large daily dose rather than subdivided, throughout the day. Obviously the latter would more appropriately mimic water intake.

Interaction between trichloroacetaldehyde and alcohol is not adequately handled in the report. This is an often cited interaction. At the same time, it is a reflection of high doses of the aldehyde as well as the ethanol. This material must be reworked to present a clear rationale as to why or why not, under the conditions associated with drinking water, an interaction might or might not be or potential concern.

3.2 Does the SAB Agree with the Line of Investigation on Addressing the Question of a Possible Threshold for DCA-Induced Hepatocellular Cancer in B6C3F1 Mice?

Evidence for a threshold for DCA carcinogenicity using B6C3F1 mice was presented to the Subcommittee. We support the continued efforts to determine the dose-response relationship for carcinogenicity as an end-point for TCA and chloral hydrate. Such studies are important not only in regard to DCA (and TCA) but also in determining the Agency's

approach to dealing with agents which cause mouse liver tumors. We would also recommend similar studies be performed with rats in order to support the classification of DCA as either C or B2. Whether it is a B or C should be based on knowing whether it causes tumors in rats, that is, on knowledge and not considering it only in one species, if others have not been examined. If there is a difference in susceptibility of mice and rats to DCA, we recommend that metabolic disposition and mechanistic studies should be carried out to account for any species differences and, therefore, extrapolation of the murine findings to humans.

3.3 Does the Science Advisory Board Agree with the Following Assessment: Chloral Hydrate (Trichloroacetaldehyde Monohydrate) has a Clear Record of Genotoxicity in Microbial (Hayworth et al., 1983) and Mammalian (Russo et al., 1984) Systems with a Propensity to Induce Aneuploidy in Eukaryotic Systems.

From the references cited, chloral hydrate would appear to be a weak mutagen in *Salmonella* TA-100. However, studies of genetic activity in mouse germ cells indicate that this chemical can produce effects on premeiotic and staminal gonial cells. Significant numbers of hyper-haploid cells were observed at both 82.7 and 165.4 mg/kg following i.p. treatment of chloral hydrate. Due to both the level administered and the route of administration, the relevance of these studies for risk assessment in drinking water can be questioned.

3.4 Does the SAB Agree with EPA that Chloral Hydrate has a Tumor Potency in Mice Similar to that of DCA?

It is appropriate to tentatively consider chloral hydrate as a hepatocarcinogen in mice with similar potency as that observed with TCA (it makes more sense to compare to TCA than to DCA for metabolic and weight of evidence reasons). However, final judgment about the potential carcinogenic risk to humans, and hence classification by EPA, should await a more thorough bioassay in both mice and rats. As noted above for DCA (Section 3.2), an understanding of the advisability of species extrapolation based on mechanism (either dose or species) is critical. In addition, we recommend searching for any epidemiological data on this drug, which in the past, had been widely used for prolonged periods.

3.5 Should the MCLG for DCA be Set on the Basis of Carcinogenicity or Neurotoxicity?

At the present time we cannot recommend whether the Agency should establish the MCLG for DCA based on its carcinogenicity or neurotoxicity. In the case of the former, it is important that Dr. DeAngelo's results from his current studies on lower doses than previously used be taken into consideration. In the case of the latter, there is a paucity of data presented, but preliminary studies in rats suggest that neurotoxicity is a concern in support of previous observations in both experimental animals and man. Additional information is necessary before the NOAEL can be firmly established. This is an important area for consideration by Dr. McPhail's neurotoxicity section.

3.6 What Relative Source Contribution Should be Applied to the Risk Assessment of these Chemicals?

This question relates to what relative source contribution should be applied to the risk assessment of these chemicals. We were unable to recommend any percentage for these. The exposure section was not present in the document. This absence is a continued concern of the Committee as these documents come to it for review. There appears to be no reason for not considering drinking water as the sole source of these compounds (with the obvious exception of trichloroacetaldehyde used in medicine), but in the absence of information no definitive recommendation can be given.

3.7 Additional Issues Addressed by the Subcommittee

We had additional comments, recommendations, and concerns beyond the original questions posed by the agency. These include the following:

- a. We were very concerned about the manner in which the levels of these chemicals identified in the Drinking Water surveys were presented. Averages give little information. We recommend a more thorough analysis of the data, possibly following the model of the American Water Works Association. This occurrence data should include ranges and some measures of the frequency distribution of concentrations (e.g. the 95% confidence interval). We further recommend that those chemicals which are disinfectant by-products have their occurrence data segregated according to type of disinfectant and, if possible be related to total organic carbon in the systems surveyed.
- b. From the data presented on occurrence, it was not clear why trichloroethanol was included since it has not been identified in these sources. While a metabolic intermediate in the metabolism of a number of chlorinated chemicals, it is doubtful that exposure to the compound itself will occur. We recommend that the Agency consider not including this chemical in the document.
- c. We recommend that the Agency greatly expand the discussion and evaluation of the developmental toxicity studies. The presentation by Dr. Robert Kovloch of Dr. Kate Smith's work was most informative. The data from his studies suggest that for some of these chemicals the endpoints need to be considered as possible basis for establishment of reference doses or at least as support for the data presented from other studies used to establish these RfD's.
- d. We were interested in seeing the approach taken by Dr. Leubke in the area of immunotoxicity, but would recommend that a more carefully focused approach be taken to follow up studies that have already reported positive findings. We recommend that studies specifically address the effects of these chemicals on the immune system.

- e. We strongly recommend that the Agency define the toxicology/carcinogenicity of brominated and mixed bromochloro analogs of the chlorinated acetic acids, aldehydes and ketones. These compounds will be produced by both chlorination and ozonation of waters containing bromide. It is very likely that they will possess many of the toxicological/carcinogenic properties of the chlorinated analogs. Since the relative proportions of brominated and chlorinated by-products varies with the disinfectant used (chlorinated analogs higher with chlorine, brominated compounds higher with ozone) their relative potency can have a substantive impact on the choice between disinfectants in a given water supply.
- f. In a number of cases, the descriptions of key studies were inadequate for full evaluation by the Subcommittee. For example, in the consideration of the effects of DCA in humans, there is a concern over hypoglycemia. However, without a knowledge of the magnitude of the effect and whether it occurs in normal glycemic individuals, we cannot judge the relative importance of the findings. We strongly recommend that for these key studies selected to be used in establishing health advisory's and the DWEL, a more thorough, quantitative description of the studies be presented.
- g. In the consideration of possible mechanisms for the carcinogenicity of DCA and TCA, we recommend a more thorough discussion of hepatic peroxisomal proliferation. This is critical not only for these compounds in and of themselves, but also in relationship to the Agency's other criteria documents such as that on perchloroethylene.
- h. We recommend that the Agency include in its Criteria Document a discussion of the Human Exposure Studies performed to date on chlorinated acids/alcohols/aldehydes/ketones. An assessment is needed on what currently is known about (1) the prevalence and geographical distribution of these chemicals throughout the U.S., (2) the studies performed, if any, regarding human body burden, and (3) the metabolism and pharmacokinetics for these chemicals. Identifying the gaps in our knowledge in these areas will be most beneficial in determining future research needs.

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