UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

August 18, 1992

OFFICE OF
THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

EPA-SAB-DWC-LTR-92-014

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Subject: Review of the Criteria Document on Ozone and Ozonation By-Products

Dear Mr. Reilly:

The Drinking Water Committee (DWC) of the Science Advisory Board (SAB) reviewed progress in developing maximum contaminant levels (MCL's) for ozone and ozonation by-products in drinking water at its February 11-12, 1992 meeting in Washington, DC. The Committee reviewed the June 24, 1991 draft document: *Revised Final Draft for the Drinking Water Criteria Document on Ozone and Ozonation By-Products.*

The Committee was asked to address three specific questions in its review of the Criteria: 1) Are the risk assessments of ozonation by-products carried out satisfactorily?; 2) Are there other ozonation by-products which should be included in this document?; and 3) Should EPA examine the mechanism of toxicity of bromate in rats in terms of whether renal tumor formation is due to direct action of bromate or indirectly through formation of DNA adducts in kidney?

Ozone is one of only a few methods that are generally considered appropriate for producing drinking water with minimal risks of spreading waterborne infectious disease. The Committee recognizes that this review is only meaningful in the context of the overall drinking water disinfectant issue. Therefore, it is necessary to consider MCL's for ozone by-products as they relate to limitations that come about by establishing MCL's previously considered by the Committee (chlorination by-products) or concurrently (chlorine dioxide and its by-products). MCL's in each of these areas must be considered in the context of the clear benefits disinfection has in protecting the public health. In addition to the specific issues identified by the Office of Water's Science and Technology and Drinking Water Programs,

the Committee feels compelled to provide some perspective as to how proposed regulations for ozone by-product impact options for alternate disinfectants to chlorine. The Committee suggests that these issues be considered for inclusion in the criteria document as a means of providing essential background for understanding these kinds of persistent problems.

Critical Issues of Concern:

1) Ozone, used alone or, more likely, in combination with postdisinfectant treatments, is the major viable option to chlorination when concentrations of chlorination by-products become limiting in the use of chlorine and/or chloramines.

2) The use of ozone in source waters containing bromide may produce bromate in concentration ranges that result in additional cancer risks in excess of the 10^{-4} per lifetime risk (e.g., 5 μg/L) and could easily exceed 10^{-3} as calculated by the linearized multistage model. This chemical has already been classified as a probable human carcinogen by the International Agency for Research on Cancer (IARC).

3) Brominated organic by-products (e.g. bromoform and dibromoacetic acid) will be produced in waters containing bromide at concentrations exceeding those anticipated from chlorination of the same water and maybe as hazardous as their chlorinated analogs.

4) It is not anticipated that granular activated carbon (GAC) or other absorbent technologies are likely to significantly reduce the production of bromate. The impact of GAC on the formation of brominated byproducts in these systems is likely to be minimal because organic carbon concentrations may not be limiting in bromate formation (i.e. the availability of bromide is likely to be limiting in many if not all such situations).

5) Based on draft MCL's, there are likely to be severe limitations on the use of chlorine dioxide as an effective alternative to either chlorine or ozone.

6) Virtually no data exist to define and quantitate formation of by-products that will result from possible treatment combinations of ozone/chlorine or ozone/chloramine. Such combinations are thought necessary to prevent the outgrowth of microorganisms in the distribution system. On theoretical grounds, at least, these combinations could exacerbate by-product formation.

7) Aside from bromate, formaldehyde and acetaldehyde formation, little is known about the formation of toxic and carcinogenic byproducts with ozonation. Some of these by-products appear at appreciable concentrations and have properties of potential concern, but may have yet to be tested adequately (glyoxal and methylglyoxal).

8) Data to predict by-product formation of important by-products under varying conditions (e.g. pH, temperature, bromide concentration and total organic carbon concentrations) are not available for disinfectants other than chlorine. Consequently, there are no bases for systematically determining whether regulation of a single disinfectant by-product will increase or decrease the carcinogenic risks to the general population.

9) There are no systematic data bases that clearly associate the occurrence and quantity of disinfectant by-products with the use of particular disinfectants. The Agency has mandated the collection of such data in water supplies, but has not made provision for collecting and analyzing these data in any meaningful way. Therefore, even an empirical analysis of the impact of alteration of disinfectant use cannot be made.

With the above in mind, we have serious concerns about the rational development of regulations in the drinking water disinfectant area. There is little doubt that scientifically defensible regulations for individual by-products can be developed using current guidelines. However, as long as they are considered individually it appears quite likely that the sum total of such regulations could be irrational. This could present a dilemma to the regulated communities. Some of these alternatives may actually increase the calculated risks from cancer and/or seriously compromise the ability to prevent the spread of waterborne infectious disease.

Research Information Needed:

In our opinion the solution to this dilemma is to be found in developing the research information that is needed to allow decisions to be made. Due to disruptions in the health research budget in drinking water over the past 5-7 years, it is unlikely that this information can be developed to the point of supporting rational regulations in less than 5-10 years. The most basic types of research information are needed in the following areas:

1) Determining effective disinfection/filtration control strategies for specific resistant organisms (e.g., *Giardia, Cryptosporidium*).

2) Conducting research to determine the nature of major byproducts of alternate disinfectants and combinations (e.g., ozone, ozone/chlorine, ozone/ chloramine),

3) Developing the most basic of toxicological information with major identified by-products (e.g. chlorate, glyoxal, methylglyoxal, MX, etc.)

4) Developing models for utilizing water characteristics to predict the rate and extent of formation for critical disinfectant by-products (e.g bromate, brominated organics, chlorate) for all viable alternatives.

5) Determining whether current EPA methods for cancer risk assessment are appropriate for several by-products (e.g. bromate, trichloroacetic acid, dichloroacetic acid, chloral hydrate).

6) Determining the extent to which various options for removing DBP precursors are feasible for reducing chronic toxicity and cancer risk from disinfectant by-products (e.g. bromide removal, removal of total organic carbon).

REVIEW OF DRAFT CRITERIA FOR OZONE BY-PRODUCTS

In general, the draft poorly documents the health effects of ozone by-products, does not bring the reader to any understanding of the critical issues with the ozonation of drinking water, and frequently leaves the real regulatory issues unresolved. In some instances the document's presentation of the results of the studies are actually in error (e.g., indicating that ozone byproducts were tested as promoters when they were actually tested as initiators). The document would be more useful if the available data were interpreted and a rationale for selecting particular levels of concern were developed. It is essential that the document analyze conflicting bits of information to come to particular judgements. For example, it is not useful to find that the Agency has not decided whether it will treat orally consumed formaldehyde as a carcinogen or not. It is the role of the Committee to comment on the Agency's judgment in this area, not to develop it for the Agency. Furthermore, this is an issue in other regulatory programs in addition to drinking water.

Issue 1 - Are the risk assessments of ozonation by-products carried out satisfactorily?

Formaldehyde: The 1-day, 10-day and longer term health advisories should not be based on the Johannsen et al. (1986) study. As the document states, this group did not observe the stomach lesions at a dose of 50 mg/kg per day. However, neither

did they see these lesions at 100 mg/kg, a dose approximating those in which definite lesions were observed in three other studies by two independent groups. The only positive effect observed in the Johannsen et al. (1986) study at 100 mg/kg was decreased weight gain that was associated with decreased water and food consumption. Since the body weight effects are probably associated with the depressed food and water consumption, it cannot be specifically attributed to formaldehyde. The Committee suggests that the NOAEL derived from the Til et al. (1988) study be utilized as a more credible study. It has the advantage that the response is consistent with the results obtained from longer term studies (Til et al., 1989; Tobe et al., 1989).

The lifetime health advisory was handled in a satisfactory way.

The Agency must come to a clear-cut decision about the potential carcinogenicity of formaldehyde in drinking water. It is the view of the Committee that the weight of evidence argues against a carcinogenic risk associated with formaldehyde in drinking water. However, an argument could be made to consider formaldehyde a carcinogen based on the inhalation data, supported by the data on formaldehyde genotoxicity. The document has chosen to make neither case, making it impossible for the Committee to critique the Agency proposal.

Acetaldehyde: There is an inconsistency in the number derived for the 10-day health advisory in the document (50 μg/L) and that provided in the summary (10 mg/L). The figure for the 1-day health advisory, which was said to be derived from the 10-day health advisory, is also 10 mg/L.

This discrepancy arises from the failure to address and resolve contradictions in the available data base in a systematic manner. Are the elevations in serum enzymes associated with liver damage in the Farbiszewski et al. (1987) study at 4.5 mg/L consistent with the absence of such effects in other studies utilizing much higher doses? For example, Til et al. (1988) used 675 mg/kg per day. Other studies (Siegers et al., 1974; Strubelt et al., 1987) utilizing single oral doses of greater magnitude also failed to demonstrate such effects at higher doses.

Glyoxal/Methylglyoxal: The appropriateness of developing longer-term health advisories for glyoxal based on decreased aspartate aminotransferase and total serum protein is questionable. Increases in AST might be interpreted as indicating hepatic damage, but decreases were observed. Decreases in total serum protein coupled with decreased total serum protein might be of significance considering the in vitro data

indicating that these compounds inhibit protein synthesis. However, the document did not supply any information as to the magnitude of the effect in vivo or if there was any attempt to determine what caused these changes. The figure derived from these data is also carried over to the development of a reference dose and a drinking water equivalent level.

It is clear from the review that testing of glyoxal and methylglyoxal as potential carcinogens should be a high priority for the Agency. Both compounds are clastogenic under a variety of experimental conditions and induce both unscheduled DNA synthesis and indications of promoting activity in in vivo assays. These are much stronger indications of carcinogenic activity than the bacterial and in vitro mutagenesis studies. Although the occurrence of these chemicals in ozonated drinking water is poorly documented in the present document, the limited data available indicate levels > 10 μg/L which suggests that these compounds may be among the most prevalent by-products of ozone identified to date. It must also be kept in mind that there is some probability that these chemicals may arise spontaneously in vivo. This fact doesn't make them safer than exogenous compounds. However, it does add further emphasis to previous recommendations of this Committee concerning the need to understand the mechanisms by which drinking water contaminants may or could produce cancer.

In the calculation of the RfD (Criteria Document, p. D-VIII-10) an uncertainty factor of 1000 is used plus another factor of 10. This extra factor does not seem justified in view of the reasons given on page D-VIII-2 of the Criteria Document where 1000 is used for a subchronic study identifying a LOAEL.

Hexanal/hexanoic acid: The submicrogram/L concentrations of hexanal/hexanoic acid that are produced by ozonation and the lack of adequate toxicological data makes derivation of criteria for these compounds of limited value.

Heptanal/heptanoic acid: Limited formation (highest noted was 2.9 μg/L) with ozonation and apparent non-toxic nature of these compounds suggests that to develop data on these compounds may be of low priority.

Hydrogen peroxide: There is some difficulty in rectifying the apparent observation that typical concentrations of hydrogen peroxide in surface waters range from 51 to 231 mg/L (Karch and Associates, 1988) with the levels found after formation of 34 μg/L of hydrogen peroxide in water disinfected with ozone (Langlais

et al., 1991). Since the Karch and Associates (1988) reference is not generally available, can the basis of these figures be made clearer?

The study of Ito et al. (1982) referred to on page G-V-2 of the Criteria Document indicates that there are two doses (150 and 600 mg/kg) and a LOAEL for gastric and duodenal lesions was identified at 600 mg/kg, but no NOAEL was identified. What happened to the 150 mg/kg dose? Furthermore, it is stated (page G-VIII-9 of the Criteria Document) that no RfD could be calculated since only a LOAEL and not a NOAEL was found, but for other chemicals RfD's are calculated from LOAELs.

Bromate: The Committee agrees with the decisions made about bromate. It is clear from the traditional linearized multistage analysis that bromate is among the most important and potentially troublesome disinfectant by-product identified to date. Clearly, there remain substantial gaps in the data on this chemical as is illustrated by the lack of reliable information on which to develop estimates of safe levels for non-carcinogenic effects. The chemistry of this anion suggests that it acts by inducing oxidative stress, and the data from human poisonings suggest the possibility of hemolytic anemia. There are also reasons to pursue the dose-response for assessing the role of these oxidative mechanisms in the induction of cancer. It is not clear which of the data sets of Kurokawa were used to make the cancer risk estimates.

Issue 2 - **Are there other ozonation by-products which should be included in this document?**

There are undoubtedly other ozonation by-products that should be included in these documents. However, for most by-products the toxicological information will be inadequate to develop standards. In the Committee's view, it is important to identify the deficiencies in the analytical data for ozonation by-products. Therefore, the discussion of studies of mixtures of unidentified ozonation by-products should be supplemented by a more thorough discussion of ozone chemistry and a better effort made to indicate what ozonation by-products have been identified to date.

Issue 3 - **Should EPA examine the mechanism of toxicity of bromate in rats in terms of whether renal tumor formation is due to direct action of bromate or indirectly through formation of DNA adduct in kidney?**

The question is not too clear. There are at least two potential causes for the tumors induced by bromate. One would be the induction of an oxidative stress specifically in the target tissue. This hypothesis is consistent with observations of

lipid peroxidation and the formation of oxidatively modified purine bases in renal DNA following acute treatments with bromate. The second mechanism would be indirectly, or at least less direct induction of toxicity to the renal tubule cells. Such activity would be presumably secondary to hemolysis, an effect suggested by a number of the human cases of acute poisoning with bromate, but not specifically noted in any of the publications with experimental animals.

It is clearly important to know how renal tumors are induced by bromate. Good dose-response information on these two phenomena could provide a much better basis for estimating the carcinogenic risks due to bromate at concentrations that occur in ozonated drinking water. Obviously, pharmacodynamic modeling could contribute to interspecies differences as well. The Committee notes that good dose response information is lacking for non-carcinogenic effects of bromate as well.

We appreciate the opportunity to review this draft criteria document and look forward to your response to our recommendations.

Sincerely,

Raymond C. Loehr

Dr. Raymond C. Loehr, Chair
Science Advisory Board

Verne R. Ray

Dr. Verne Ray, Chair
Drinking Water Committee

References Cited

Farbiszewski, R., Gabryel, H., Boron-Kaczmarska, A. Holownia A., and A. Sokol. 1987. Blood plasma peptides of rats after administration of ethanol or acetaldehyde. Alcohol and Alcoholism 22:41-46.

Ito, A., Naito, M., Naito, Y., and H. Watanabe. 1982. Induction and characterization of gastro-duodenal lesions in mice given continuous oral administration of hydrogen peroxide. Gann 73(2):315-322.

Johannsen, F.R., Levinskas, G.J., and A.S. Tegeris. 1986. Effects of formaldehyde in the rat and dog following oral exposure. Toxicol. Lett. 30(1):1-6.

Karch and Associates, Inc. 1988. Cancer risk assessment for hydrogen peroxide in drinking water. Prepared for the Metropolitan Water District of Southern California, Los Angeles.

Langais, B., Reckhow, D.A., and D.R. Brink (eds.). 1991. Ozone in Water Treatment. Application and Engineering. Lewis Publishers. Chelsea, MI. pp. 238-242.

Siegers, C.P., Strubelt, O., and H. Breining. 1974. The acute hepatotoxic activity of alcoholic beverages and some of their congeners in guinea pigs. Pharmacology 12:296-302.

Strubelt, O., Younes, M., Urch, T., Breining, H. and R. Pentz. 1987. Hepatoxicity of acetaldehyde in rats. Mutat. Res. 113:357-391.

Til H.P., Woutersen, R.A., Feron, V.J., and J.J. Clary. 1988. Evaluation of the oral toxicity of acetaldehyde and formaldehyde in a 4-week drinking water study in rats. Fd. Chem. Toxic. 26(5):447-452.

Til, H.P., Woutersen, R.A., Feron, V.J., Hollanders, V.H., Falke, H.E., and J.J. Clary. 1989. Two-year drinking water study of formaldehyde in rats. Fd. Chem. Toxic. 27(2):77-87.

Tobe, M., Naito, K. amd Y. Kurokawa. 1989. Chronic toxicity study on formaldehyde administered orally to rats. Toxicology. 56:79-86.

ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD
DRINKING WATER COMMITTEE

CHAIRMAN

Dr. Verne A. Ray, Medical Research Laboratory, Pfizer Inc., Groton, Connecticut

VICE CHAIRMAN

Dr. Vern L. Snoeyink, Department of Civil Engineering, University of Illinois, Urbana, Illinois

MEMBERS/CONSULTANTS

Dr. Richard J. Bull, College of Pharmacy, Washington State University, Pullman, Washington

Dr. Gary P. Carlson, Department of Pharmacology and Toxicology, School of Pharmacy, Purdue University, West Lafayette, Indiana

Dr. Keith E. Carns, East Bay Municipal Utility District, Oakland, California

Dr. Lenore S. Clesceri, Rensselaer Polytechnic Institute, Materials Research Center, Troy, New York

Dr. David G. Kaufman, Department of Pathology, University of North Carolina, Chapel Hill, North Carolina

Dr. Ramon G. Lee, American Water Works Service Company, Voorhees, New Jersey

Dr. Edo D. Pellizzari, Research Triangle Institute, Research Triangle Park, North Carolina

Dr. Mark D. Sobsey, Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina, Chapel Hill, North Carolina

Dr. James M. Symons, Department of Civil and Environmental Engineering, University of Houston, Houston, Texas

SCIENCE ADVISORY BOARD STAFF

Mr. A. Robert Flaak, Assistant Staff Director and Acting Designated Federal Official, Science Advisory Board (A-101F), U.S. EPA, 401 M Street, SW, Washington, DC 20460

Mrs. Frances Dolby, Staff Secretary, Drinking Water Committee, Science Advisory Board (A-101F), U.S. EPA, 401 M Street, SW, Washington, DC 20460

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.

Distribution List

Administrator
Deputy Administrator
Assistant Administrators
Deputy Assistant Administrator for Research and Development
Deputy Assistant Administrator for Water
EPA Regional Administrators
EPA Laboratory Directors
EPA Headquarters Library
EPA Regional Libraries
EPA Laboratory Libraries