UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C 20460

EPA-SAB-DWC-90-015

OFFICE OF
THE ADMINISTRATOR

April 26, 1990

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

Subject: Science Advisory Board's review of the document "Reaction Kinetics and Reaction Products of Chlorine and Chloramines in the Digestive Tract"

Dear Mr. Reilly,

The Toxicology Subcommittee of the Science Advisory Board's Drinking Water Committee met in Washington, D.C. December 8, 1989 to review the document produced for the Office of Drinking Water "Reaction Kinetics and Reaction Products of Chlorine and Chloramines in the Digestive Tract".

The document reviewed focuses on the extrapolation of information about reactions between commonly used disinfectants and saliva and gastric juices at high dose levels to predict the reactions of the much lower doses commonly found in disinfected drinking water. The Subcommittee agrees that the mechanisms involved at low doses differ from those of high doses and thus a simple linear relationship should not be used for extrapolation. Using current methods the toxicity of the disinfectants may not be distinguishable from the toxicity of the by-products, and thus the toxicity of the by-products should be studied separately. Thus, studies are needed for the character and the toxicity of the by-products at low dose levels both for chlorine and for chloramines used as disinfectants. In addition several components of a major research program are recommended.

We appreciate the opportunity to conduct this particular scientific review. We ask that the Agency formally respond to the scientific advice provided herein.

Sincerely,

Raymond C. Loehr
Chairman
Executive Committee

William H. Glaze
Chairman
Drinking Water Committee

Verne A. Ray
Chairman
Toxicology Subcommittee

EPA U.S. Environmental Protection Agency Washington, DC
EPA-SAB-DWC-90-015

Report of the Drinking Water Committee

Review of the 1989 EPA Report: Reaction Kinetics and Reaction Products of Chlorine and Chloramines in the Digestive Tract

A SCIENCE ADVISORY BOARD REPORT APRIL 1990

1.0 EXECUTIVE SUMMARY

The Toxicology Subcommittee of the Science Advisory Board's Drinking Water Committee met in Washington, D.C., on December 8, 1989 to review the document produced for the Office of Drinking Water entitled "Reaction Kinetics and Reaction Products of Chlorine and Chloramines in the Digestive Tract", written by Dr. Frank E. Scully, Jr. (Old Dominion University) and Dr. William White (University of Vermont).

The document focuses on the extrapolation of information about reactions of saliva and gastric juices with disinfectants commonly found in disinfected drinking water at high dose levels to predict the reactions that may occur of much lower dose levels. The Subcommittee agrees that the mechanisms involved at low dose levels differ from those as high dose levels, and that a simple linear relationship therefore, should not be used for extrapolation. Further, the toxicity of the disinfectants may not be distinguishable from the toxicity of the by-products, and thus the toxicity of the by-products should be studied separately. Consequently, studies are needed for the characterization and the toxicity of the by-products at low dose levels both for chlorine and for chloramines used as disinfectants. Although chlorine reacts quickly, chloramine tends to be more stable in saliva and gastric juices. Due to the stability of chloramine in saliva there is some potential for adsorption in the mouth, esophagus, and stomach. Therefore, some toxicological effects of chloramine may be attributable to the parent compound.

The Subcommittee recommends that this problem area receive more research support. The particular research recommended here should include both in vivo and in vitro studies. Specific research efforts recommended include verifying the differences between rat and human saliva, performing studies on the by-products formed and determining the reaction chemical by-products that may be formed.

c. Do the findings only apply to oxidants or are other chemicals implicated?

d. Can the toxicology of disinfectants be distinguished from the toxicology of *in vivo* by-products at typical drinking water exposure levels?

e. Are further kinetic studies needed to quantify rates of decomposition that would be biologically significant? If so, what chemical by-products (*in vivo*) studies should be conducted to identify biologically significant products?

f. Could the Committee suggest *in vivo* toxicological studies that would help to specify and quantify the toxicology of biologically active species produced *in vivo*?

The study of reaction kinetics of ingested oxidants such as disinfectants is complex for several reasons. First, it is difficult to quantify the reactions since the mouth and stomach are leaky reaction vessels. Second, the mouth and stomach are dynamic systems and ingestion of food or even the smell of food generates acidic fluids that can change reaction kinetics dramatically. For these and other reasons discussed below, the existing knowledge in this area is not complete. Because of the importance of this information in regulating disinfectants and disinfection by-products, the Committee recommends that studies be conducted to provide the missing information.

3.0 DISCUSSION OF ISSUES CONCERNING THE REPORT

In the report that follows several issues raised by the Office of Drinking Water are addressed, followed by a general conclusion from the Committee in Section 3.6. It is important to recognize, however, that the issues tend to overlap and are not necessarily independent.

3.1 How do kinetic considerations of chlorine and chloramine reactions with endogenous compounds affect the interpretation of available data on the toxicity of the disinfectants themselves?

Available information suggests that free chlorine does not survive long enough in saliva to be available for absorption and to produce any direct systemic effects of toxicological

significance. It is possible that very high doses of chlorine (>> 100 ppm) might be high enough to provide some free chlorine, but there are no data to suggest that the resulting concentrations would be sufficient to produce significant toxicological effects. Thus the Subcommittee concurs that in the procedure of extrapolating the data obtained from animals administered high doses of chlorine, linear extrapolation may not be justified.

On the other hand, chloramine has sufficient stability in saliva so that there is the potential for some chloramine absorption via the buccal mucosa, esophagus, and stomach. Therefore, some of the toxicological effects produced by chloramine may be attributable to the parent compound.

The report reviewed here does raise concerns about the potential role of secondary products formed from these disinfectants. As discussed in the report, there is reason to believe that the nature of these products will vary, depending on of disinfectant concentration. Thus, the toxicological hazards of consuming the disinfectants will vary, depending on the amounts and nature of the products formed within discrete ranges disinfectant concentration. It is possible that products may be formed at low doses which are not observed at high doses and that these are more toxic or less toxic than those observed at high doses. Consequently, the Committee recommends avoiding the assumption of a simple linear relationship between production of these secondary products and disinfectant dose. Studies should be made of the actual dose-response relationships of the reaction products, to the extent possible.

3.2 Does consideration of chlorine and chloramine reactivity with endogenous compounds affect the characterization of risk associated with the use of these chemicals as disinfectants?

The formation of secondary products in the mouth, esophagus and stomach following the ingestion of chlorine or chloramine could contribute to the potential hazards associated with the use of these disinfectants. However, the impact on the risk characterization cannot be predicted on the basis of current information. The nature of by-products formed, the variability of their formation and destruction with varying concentrations of disinfectant, and their toxicology will have to be explicitly

considered. It is doubtful that these problems can be adequately dealt with using the currently available model studies that were discussed in the report. Specifically, the model discussed dissipation of residual disinfectant but was able to identify reaction products only in the most general of terms.

As mentioned above, there is some possibility that some portion of a chloramine dose could be systemically absorbed. In this case, the biologically available absorbed dose would have to be known and its systemic concentration correlated with the resulting toxicity caused by all components to determine whether the chloramine itself or by-products are of greater concern. Further, if the carcinogenic or non-carcinogenic toxic effect is observed only at very high levels of exposure, it is not always the case that it can be scaled down linearly to low doses. At high doses chloramine levels may overwhelm the ability of the endogenous compounds in saliva or gastric juice, and of exogenous compounds such as food, to react with the chloramine. At lower dose levels the small amounts of chloramine would not be absorbed to the same degree and the chloramine would be unlikely to have much toxicological significance. This plausible non-linear mechanism argues against using a simple linear extrapolation for the dose-response relationship in every case.

3.3 Can the toxicity of disinfectant be distinguished from the toxicity of <u>in vivo</u> by-products at typical drinking water exposure levels?

In general, the bioassay systems cannot distinguish differences between toxic effects produced by the parent disinfectant compound and those produced by secondary products generated either by chemical or biochemical processes. However, insight into <u>potentially</u> toxic products generated chemically or biochemically could allow for the more complete prediction of toxicity.

To pursue this avenue, we must increase our understanding of these by-products by studying them separately. However, in order to do this, the by-products must be synthesized in quantities sufficient for toxicological testing. Endpoints of toxicity in these by-product toxicity studies might correlate with those seen in toxicity studies with the disinfectant agent. In such a case, the toxicity could be attributed to the secondary by-product.

However, it should be remembered that high levels of primary disinfectant may be producing by-products, concentrations of by-products, and toxicity endpoints that are different from those that result at lower level doses. This could be due to differences in distribution, metabolic pathway kinetics and chemical characteristics of the primary disinfectant in reaction with body fluids or tissues. At typical drinking water levels, (i.e. low concentration of primary disinfectant) it is likely that such low levels of secondary products are formed that it may be impossible technically to find and prove the involvement of secondary products in toxicity.

3.4 What mass balance studies are needed to show which competitive kinetic rates are important in the formation and decomposition of biologically significant by-products?

Before comparative kinetic studies are undertaken, the reactions and by-products that are important must be identified. Because these disinfectants are both oxidants and chlorine substitution agents, the stoichiometry of the reactions must be studied. Disinfectants that both oxidize and form new products by substitution typically result in different products as a function of disinfectant dose and substrate concentration. Products and reactions important at low concentrations may become oxidized and thus unimportant at high doses. It is therefore recommended that reactions and by-products produced be identified as a function of halogen concentration.

After the important by-products and the reactions producing them have been identified, further kinetic studies are needed to quantify rates of formation and decomposition for those that are biologically significant. These studies will likely be different for chlorine and chloramine, as discussed below.

3.4.1 Chlorination

The report being reviewed here already has identified that, with the large concentration of reducing agents present in the digestive tract, chlorine at normal dose levels is reduced to chloride. The issue is the formation of biologically significant by-products and their subsequent decomposition. The first question is, are these by-products formed fast enough at low doses of chlorine to compete with the reduction reactions

removing free chlorine to chloride? Secondly, are the toxic by-products formed by either halogenation or oxidation reactions stable enough to be biologically active? The report did not identify the likely additional reducing agents present *in vivo*. These reducing agents include reduced sulfur functionality, nitrite, iodide and ammonia. The Committee recommends further studies on chlorination products only if studies show that stable toxic by-products are produced.

3.4.2 Chloramination

The reactions which need further study following chlorination of drinking water are the reactions of chloramines: NH_2Cl and organic-N-Cl. These compounds are much less likely to be reduced to chloride, as mentioned above. The overall effect of reducing agents in human saliva and gastric fluid on reducing NH_2Cl and organic-N-Cl can be easily studied by measuring oxidant demand. Products of reactions with cells and secretions lining the gastrointestinal tract are less easily modelled. The question which needs additional study is the extent of formation of toxic (perhaps non-oxidant) by-products from NH_2Cl and organic-N-Cl reactions and potential direct systemic toxicity of these compounds should they survive unreduced. The major gaps in the data are the reaction kinetics of these chloramines, especially under gastric fluid chloride and pH levels, and the reactions with the cells lining the gastrointestinal tract. Additional chloramine kinetic studies are recommended, on both oxidation and substitution reactions, to fill the existing data gaps. Also studies need to be made on interactions with nitrite, ammonia, iodide and reduced sulfur compounds found in the digestive tract but not are discussed in the report.

3.5 Are *in vivo* toxicological studies needed to help specify and quantify the toxicologically active species produced *in vivo*?

Performing *in vivo* studies may be difficult. On the other hand, it will be difficult to define the risk from water disinfection based on the risk from one or even a few such active by-products because of unknowns regarding relative concentrations under realistic conditions and possible interactions.

for reactions at low doses that could be different both qualitatively and quantitatively from those which occur at high doses. Chlorine may react so quickly that there are not significant toxicological effects at low doses linearly relatable to those at high doses. Chloramine is not absorbed at the same degree at low doses as it is at high doses. At high doses chloramine levels may overwhelm the ability of the endogenous compounds in saliva or gastric juice and of the exogenous compounds such as food to react with it. Further, it is possible that toxic compounds are created at low doses which become subsequently destroyed at high doses. Because of this possible difference in the reactions (with possible differences in toxicity), the Subcommittee does not recommend that high-to-low dose extrapolation be used for these compounds. To properly assess their toxic potential, it is necessary to conduct studies throughout the concentration range encountered in disinfected waters.

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