UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

EPA-SAB-DWC-LTR-92-012

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

Subject: Review of the Drinking Water Criteria Document for Chlorine Dioxide

Dear Mr. Reilly:

The Drinking Water Committee (DWC) of the Science Advisory Board (SAB) met on February 11-12, 1992 and reviewed the Drinking Water Criteria Document for Chlorine Dioxide, among other issues. The Committee was asked to respond to four specific issues which formed the charge to the Committee. The Committee also addressed several additional concerns.

Responses to Specific Issues Raised in Charge to the Committee:

1. Has EPA selected the appropriate studies as the basis of the risk assessments for chlorine dioxide and chlorite.

We consider the selected studies to be appropriate. For chlorine dioxide, the NOAEL (no observed adverse effect level) of 3 mg/kg/day which gives a reference dose (RfD) of 0.03 mg/kg/day is conservative but appears to be well founded based on one of the more sensitive animal studies (Orme et al., 1985). Moreover, this number is supported by additional animal studies and could be supported by human studies (Lubbers et al., 1981) where a NOAEL of 0.036 mg/kg/day was identified. An uncertainty factor (UF) of 10 is not needed for extrapolation of animals to humans. If a UF of one is used it would yield a similar RfD.

For chlorite, there are several studies of extended duration (30 days to 2 years) in which the NOAEL is near 1 mg/kg/day. Nevertheless, this is also fairly

conservative since the study chosen for the derivation of the RfD (Hefferman et al., 1979) had a LOAEL (lowest observed adverse effect level) of 5 mg/kg/day which was based on depression of erythrocyte Glutathione (GSH) level which some might argue is not necessarily an adverse health affect.

2. Is it appropriate to use an uncertainty factor of 100 for chlorine dioxide and chlorite, instead of the usual 1,000 given the acute nature of the toxic response for these compounds?

The Committee agrees with the use of the uncertainty factor of 100. The document presents in a convincing manner data that these chemicals will not bioaccumulate, but more likely will be fairly evenly distributed throughout the body water with some binding to erythrocytes. Furthermore, the biological half--lives are fairly short. The effects seen are acute in nature. Although the oxidant reactions, which should be considered more chemical in nature than biological, are not completely understood, the variability among normal individual humans for these chemical reactions is not likely to be as great as that normally observed for normal human biological variability. The susceptibility of sensitive individuals to oxidant chemicals is self-limiting. Therefore, there is less concern with regard to within-species variability.

3. Does the SAB agree with the Agency on the proposed decision not to establish a MCLG (Maximum Contaminant Level Goal) for chlorate due to data limitations?

We are uncomfortable for both scientific and regulatory reasons to leave a blank in this area and offer no guidance to the water industry. However, the Committee understands the dilemma of having limited human data showing certain levels are toxic and animal data that would suggest that these levels should not be toxic if the usual extrapolations from the animal studies are carried out. The Drinking Water Committee recommends that until such time that there are more data available upon which to establish an MCLG that a Health Advisory (HA) be given. This would certainly give some sense of the possible toxicity of this compound to both the regulated industry and public health officials.

Not surprisingly, since an MCLG can not be determined, an HA cannot be set with precision. However, the data of Lubbers et al. (1981) could serve as a basis. If one were to calculate an RfD based on these studies, it would be:

$$RfD = \frac{0.036 \text{ mg/kg/day}}{1} = 0.036 \text{ mg/kg/day}$$

$$DWEL = \frac{0.036 \text{ mg/kg/day} \times 70 \text{ kg}}{2\text{L/day}} = 1.26 \text{ mg/L}$$

A safety factor of 1 is used since it is a NOAEL based on human data from a repeated dose study on an acute effect. It should also be noted that three of these 63 subjects were glucose-6-phosphate dehydrogenase deficient and therefore represented a sensitive population. This value is close to the drinking water equivalent level (DWEL) of 1 mg/L calculated in the criteria document using the study of Orme et al. (1985) on effects in rats.

The argument can be made though that a more sensitive population for a Health Advisory would be children. In this case:

$$\frac{0.036 \text{ mg/kg/day} \times 10 \text{ kg}}{1\text{L/day}} = 0.36 = 0.4 \text{ mg/L}$$

It should also be considered that this RfD is based on what appears to be a well conducted study. However, the number for the NOAEL is dictated by the study design, and this was the only dose used in this study. At that dose it was well tolerated. Based on the animal data demonstrating low toxicity and the limited epidemiological data indicating that much larger doses are needed to cause toxicity in humans, plus Michael's (1981) study showing up to 1.13 mg/L was without significant risk, it is likely that a higher dose could have been tolerated without adverse effects.

The Drinking Water Committee recommends this HA approach only as an interim measure. EPA should inform the public and the regulated community that it does intend to issue an MCLG when it has more relevant data. Obviously EPA must then determine what data are needed to do so and establish a strategy to obtain it as quickly as possible. In view of the possible discrepancies between humans and laboratory animals, serious consideration needs to be given to gathering human data including epidemiology studies, in vivo experiments and studies in vitro on erythrocyte sensitivity.

4. Considering that the studies with chlorine dioxide actually involved an exposure to a mixture of chlorine dioxide, chlorite and chlorate, would it be scientifically defensible to establish one MCLG for total residual oxidants when chlorine dioxide has been used as the disinfectant?

The Drinking Water Committee recommends that a combined MCLG not be derived. This is so for several reasons. An argument against the combined MCLG is that it is not clear what active forms are in the human body or if indeed all three chemicals are acting in the same manner, either directly or indirectly. Also, other disinfectants may produce the chlorite and chlorate, and individual MCLGs could be applied more consistently. Furthermore, we do not really know the variability in the relative proportions of these chemicals in the water at the tap. Also, it is unclear what would drive the combined MCLG. If the lowest MCLG were for chlorite, this would obviously drive the combined number. This would not be scientifically defensible if the other compounds are less toxic and thus should be allowable at greater levels. Certainly the combined MCLG number could not be derived by simply adding the three MCLGs. One could derive a formula for adding them based on not exceeding any individual MCLG, but this seems unworkable and unnecessary if the three MCLGs are established anyway.

Additional Issues Raised by the Committee:

In addition to answering the specific questions posed by the Water Office, the Drinking Water Committee in its review and discussion of the document had a number of concerns and suggestions which need to be addressed in future revisions of the document. These include the following:

1. The introduction needs to be considerably strengthened in discussing the disinfection by-product issue. It currently is rather vague. The Committee recommends it be more specific.

2. Relevant to the above, the Committee recommends that the Agency consider and discuss the strategy for dealing with the problem of disinfectant by-products resulting from treatment trains. For example, the combination of ozonation for primary disinfection and chlorine dioxide for maintaining a residual in the system may yield a variety of by-products since ozonation is likely to yield small, electron rich compounds with which the ClO_2 would react.

3. The database for the studies should be updated. For example, the study by Penn et al. (1990) which failed in its attempt to replicate the Revis (1986) studies, needs to be added. The Committee recommends that the Water Office continue to work with the Pesticides Office to obtain information on chlorates.

4. The occurrence data must be expanded and presented in more detail as to what is currently found in systems representing a variety of water qualities disinfecting with chlorine dioxide. This would include chlorite and chlorate occurrence data. It would also be informative to have comparative chlorate data for other processes such as the use of liquid sodium hypochlorite and free chlorine which produce OCl^- that degrades to chlorate in the distribution system. The Agency should consider the fact that the generation of these chemicals is also dependent upon the quality of the water being disinfected.

5. Concerning the use of the Haag (1949) data on survival, the question is not that the data are old and based on outmoded methodology, since death is death, but the inadequacy of the study itself. The criteria document is inconsistent in stating there is a decreased survival with ClO_2, but the number of animals per group (seven) was too low for determining the effect with chlorite even though the same number of rats was used in studies on both chemicals. Furthermore a formal analysis of the data (Kaplan-Meier curves) should be used.

We appreciate the opportunity to review this draft document. We look forward to your written response to the advice contained in this letter.

Sincerely,

Raymond C. Loehr

Dr. Raymond C. Loehr, Chair
Executive Committee

Verne C. Ray

Dr. Verne Ray, Chair
Drinking Water Committee

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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

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