UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

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OFFICE OF
THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

EPA-SAB-DWC-LTR-92-002

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

Subject: Science Advisory Board Review of the Office of Drinking Water (ODW) Issue Paper on Cyanogen Chloride

Dear Mr. Reilly:

The Drinking Water Committee (DWC) of the Science Advisory Board met in Washington, D.C. April 4-5, 1991 to review, among other topics, the Office of Drinking Water issue paper on cyanogen chloride. The DWC was asked to comment on the appropriateness of using hydrogen cyanide (HCN) toxicity data as a surrogate for cyanogen chloride (ClCN) data in developing a reference dose (RfD). Cyanogen chloride is a by-product of chloramine disinfection that is being considered for regulation (June 1993) in drinking water under the disinfection by-product rule. Currently there are no definitive studies of ClCN for chronic or subchronic toxicity, mutagenicity, teratogenicity, reproductive or carcinogenic effects. Also, no environmental occurrence data on ClCN are available.

The Committee was charged with evaluating whether it is scientifically valid to use HCN toxicity data to quantify ClCN toxicity or is it necessary to conduct research on the toxicity of ingested ClCN to establish the basis for a risk assessment in the drinking water guidelines.

The Committee recommends that the option of conducting research on the toxicity of ingested ClCN be implemented. This recommendation is based primarily on the need to ascertain that there are no adverse toxicological effects from ClCN at levels below the effects exhibited by HCN before the Agency can confidently employ safe criteria based on HCN requirements. Since such direct experimental evidence has not been acquired, it is premature to adopt criteria based on HCN.

The following factors were addressed by the Committee in its discussion of the two options presented:

1. Due to the fact that there is a paucity of toxicological data on which to make an informed judgment, there is no a priori basis for concluding that any one chemical reaction of cyanogen chloride will have a greater or lesser influence on the compounds toxicity than any other. It depends on whether the compound has sufficient stability to reach critical macromolecular targets and whether binding to such sites will have adverse biological consequences. The basic difference between ClCN and HCN is the generation of a chloride radical. Therefore, experiments should be conducted to determine if reactions subsequent to formation of the radical have any toxicological significance. Such reactions occur as ClCN is converted to cyanide, therefore, this question cannot be addressed entirely by metabolic balance studies. It might be addressed by examining the mutagenic activity of the compounds (ClCN & HCN) in in vitro experiments. (e.g. do they form DNA adducts that lead to mutation). The extent to which ClCN produces localized irritation of the gastro-intestinal tract in relationship to equimolar neutralized solutions of potassium cyanide should be examined.

2. One of the first questions to be addressed in dealing with whether HCN data should be a surrogate for ClCN data is to examine whether or not the body really encounters ClCN as such. Pharmacokinetic studies following oral administration are needed. These should address uptake, distribution, metabolism and excretion. ClCN administered orally may undergo different reactions then those seen with inhalation studies. The Committee recommends that appropriate disposition studies be performed using dose-related experiments following both Cl and CN radiolabelled compounds taking care to document the extent to which labelled chlorine exchanges with the body's chloride pool. This would help answer this question. Since ClCN is stable at low pH's (e.g. at the stomach's pH) it's reaction rate with glutathione (GSH) may be partially inhibited by HCl, thus allowing for other nucleophilic reactions to predominate.

3. Fourteen day oral administration studies as done by EPA for other chemicals would be appropriate as well as longer-term studies if, indeed, there is a substantial amount of ClCN actually absorbed.

4. Although it may not be so important from the regulatory standpoint, from the scientific standpoint it is important to really know if serum does detoxify, and if this is related to albumin binding. This study could be incorporated into the pharmacokinetic studies.

5. Normally, it would be predicted from the literature related to CN reactivity with rhodanese, that the major disposition of CN is through conversion of CN to SCN^- ($CN^- + S_2O_4^{=} \rightarrow SCN^- + SO_4^{=}$). The limitation appears to be $S_2O_4^{=}$ availability in a species. At low levels of ClCN, studies should be performed to determine whether other reactions such as GSH interaction takes precedence over the rhodanese reaction.

6. The Committee recommends that ClCN be administrated in life-time animal experiments at several doses that are sublethal with respect to HCN (by-product to GSH reaction) to allow any non HCN toxicological effects to be expressed.

We appreciate having been given the opportunity to conduct this particular review. We request that the Agency provide us with a formal response to this Advisory effort.

Sincerely,

Raymond C. Loehr

Raymond C. Loehr, Chairman
Executive Committee

Verne A. Ray

Verne A. Ray, Chairman,
Drinking Water Committee

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