COMMENTS

on the EPA Memorandum titled: *Revised and Partially Updated Draft - Toxicological Interactions of Cadmium, Lead and Zinc: A Case Study for Mixtures/Human Health Risk Assessment*, dated September 27, 1995.

Prepared by Dale Bruns, Ph.D. - Ecological Toxicologist

The following memo has been prepared in response to PCCE Task Schedule #14, Item #2, dated February 9, 1996, which requests a preliminary review of the EPA Memorandum titled: *Revised and Partially Updated Draft - Toxicological Interactions of Cadmium, Lead and Zinc: A Case Study for Mixtures/Human Health Risk Assessment*, dated September 27, 1995. The correspondence attached indicates that this EPA Memorandum was transmitted to U.S. EPA Region III Toxicolgist Dr. Roy Smith, Ph.D., on October 23, 1995

As per the February 9, 1996 PCCE Task Schedule #14 and our recent conversation, I have read through the technical report entitled "Draft Toxicological Interactions of Cadmium, Lead and Zinc: A Case Study for Mixtures/Human Health Risk Assessment" by Colman et al. 1995. The following is my feedback based on a general reading of the document to be familiar with it and this letter should not be considered as a thorough written review of the report. I would be happy to provide that at a later date if this task is needed.

1. I agree with the overall conclusion of the study which focused on review, analysis, and evaluation of information on binary (i.e. combinations of two metals) and ternary (i.e. combinations of three metals) interactions among Pb, Cd, and Zn to determine if zinc acts to mitigate the critical effects of cadmium and lead on human health relative to chronic doses.

2. The overall conclusion is that the information on these interactions does not provide a comprehensive set of data relevant to human exposure to these metals at or near a contaminated site. Thus, the data and information from this review are insufficient to predict the magnitude of the interactions for various proportions of the mixture components. This means that an "overall toxicity" of the mixture and combinations thereof cannot be estimated. As the report indicates (p. 61), for some endpoints the interaction data are not sufficient to determine if the interaction will be additive or less-than- or greater-than-additive. In this case, Superfund guidance uses a default approach for risk assessment and assumes dose additivity for the individual components of the mixture (also stated on p. 61). I would expect from this report that EPA will take this approach for risk assessment at Palmerton and not make adjustments to interactions based on bioavailability of these metals; the present document does not make this statement directly but this would be the logical outcome of the report's findings in my opinion.

3. In general, a number of problems were identified in the studies that were reviewed: there were either deficiencies in study design (relative to the questions addressed in the above report), the data were on endpoints not relevant to critical effects or sensitive for toxicity to humans, or conflicting results were evident. The literature review procedure seemed adequate and based on standard EPA and ATSDR databases and reports. Also, the report was updated for primary papers identified from computer searches (1990-1995); some citations in secondary sources were not used due to budgetary and time constraints but I would not expect that these would change any crucial findings in the report.

4. I can review the results and findings regarding the binary interactions at a later date if requested for more detail. At the present time, I will just highlight some of the problems identified with the studies on ternary interactions - since these are most directly relevant to the conditions at Palmerton. First, there were only three studies on ternary interactions that were found; this is a rather limited database but I do not think any critical papers have been missed in the review - it is expensive and difficult to conduct such studies and there are just few of them. Also, one of the three papers was not published in a peer-reviewed journal (where studies undergo more rigorous review by colleagues in the field) but I have not been able to confirm this.

   Second, all three studies used doses of metals that were notably high and thus have limited applicability to human exposure studies.

   Third, the critical effects of Cd (tubule damage in kidneys) and Zn (decreased erythrocyte enzyme activity indicative of altered copper status) were not included in any of these three studies.

   And fourth, the study by Saxena et al. (1989) did show evidence of a synergistic interaction between Cd and Pb and that this combined toxicity was inhibited by Zn. However, they only examined this in regard to testicular damage which is considered insensitive or even of questionable relevance to environmental exposure of humans to Cd or Pb.

5. I also believe that it is useful to note the findings of metal uptake by wildlife (mice, rabbits, deer) in a study conducted at the Palmerton site (Storm et al. 1994, pp. 19-20 in report). All three metals had elevated concentrations in litter and soil compared to "background" levels. In the current report the investigators' conclusion is stated: "Thus very high levels of Zn in soil did not prevent the accumulation of higher concentrations of Cd in kidney (a sensitive target organ for Cd) or Pb in bone (a storage tissue for Pb) than seen in animals from a relatively uncontaminated area".

6. Finally, I would like to conclude by pointing out comments made by Weiss and LaVelle (1991, p. 57 in report) regarding bioavailability studies. They suggest that studies of Pb bioavailability (and other metal bioavailability) in rodents and rabbits be viewed with caution because of differences from humans. These animals have continuous feeding behavior, they reingest feces, they have high biliary excretion of lead, and they have differences in their digestive tracts - all of which tend to decrease bioavailability relative to that in humans.