OMB Staff Working Comments on EPA's Toxicological Review of Hydrogen Cyanide and Cyanide Salts and draft IRIS Summary (dated June 2010)

July 12, 2010

General Science Comments:

OMB staff focused this review on EPA's responsiveness to the external peer review. Where EPA agrees with the comments, we suggest that appropriate conforming changes be made in the main text of the toxicological review and the IRIS summary.

Scientific comments on Appendix A:

- Page A-6, in responding to reviewers comments regarding the uncertainty factors for the RfD, EPA accurately notes that 3 of the reviewers suggested that the UF for interspecies extrapolation could be reduced.
    - Each of the reviewers provides a scientific rationale for why they feel a full 10x default is not needed, including consideration of what is known regarding pharmacokinetic similarities among species, the use of the most sensitive species to develop the point of departure, and mode of action considerations.
    - However, EPA states that because a PBPK model is not available, the 10 fold factor is needed.
    - It seems that EPA is invoking a default before considering what is known about kinetics and mode of action. As per the 2005 EPA cancer guidelines, although they don't apply to non-cancer endpoints, the majority of peer reviewers seem to suggest that it would be appropriate to include consideration what is known about the science before invoking a default. Instead, EPA appears to be waiting for a PBPK model before they are willing to consider removing a full 10x default, rather than looking at the weight of evidence regarding the science and then deciding if a full 10x default is needed.
    - EPA may want to reconsider the majority opinion of the peer reviewers (3 of the 5) and evaluate the existing science regarding mode of action and pharmacokinetics across species to reevaluate whether the full 10x factor is needed. The majority of reviewers suggest that only 3x is needed.

- Page A-6, we note that one of the peer reviewers comments on the subchronic to chronic uncertainty factor for the RfD and notes what is known about the mode of action of thyroid disruption by cyanide to suggest that a full 10x factor is not needed.
    - EPA's response notes that the 91 day study "falls well short of lifetime duration" as part of their justification for maintaining the full factor. We note, as we did in previous interagency comments, that IRIS defines chronic exposure as: "Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species)." As the study chosen was clearly chronic by definition, why is a 10x factor applied? In addition, we know from studies presented in the tox review that HCN is not expected to

accumulate, so why would exposure duration require a 10x factor in this case? If the study was not chronic in duration, these data would provide evidence that a full factor of 10x is not needed. As the study chosen was clearly chronic by definition, it is unclear why a full 10x factor is applied.
    - Again, EPA appears to be applying the default, rather than first considering what data do exist (in this case data on mode of action) to inform what a more scientifically supported uncertainty factor could be.

- Page A-9, in discussing the two reviewer recommendations to decrease the LOAEL to NOAEL uncertainty factor, EPA seems to not address the point made by reviewers that, while EPA is not relying on Leeser for the RfC, the reviewers suggest that it still provides useful supporting information to inform the determination of the LOAEL to NOAEL uncertainty factor. One reviewer also notes that this UF could be decreased because EPA is selecting the LOAEL from the lowest value from among all the monitored factories.
    - EPA may want to consider these comments and reevaluate the need for the full uncertainty factor.

- Page A-10, two reviewers also commented that the subchronic to chronic UF was not needed. One discusses the mode of action regarding thyroid enlargement and the other mentions that the study was 15 yrs long and showed no correlation between exposure and severity.
    - EPA does not appear to respond to Dr. Fishers comments regarding mode of action.
    - Regarding the lack of correlation seen in the study, EPA cites the Philbrick study which provides some support for increased duration of exposure not leading to an increase in effects. However, instead of relying on the findings of the ElGhawabi study, EPA points to a possible low sample size and/or failure to consider iodine status. If EPA believes this study to be of medium confidence, and is relying on it for the point of departure, it seems a bit inconsistent that EPA would choose to not rely on it to provide information that could decrease the application of uncertainty factors.
    - It seems that EPA is applying the uncertainty factors first and then looking for very robust information to move away from them, rather than considering the weight of evidence provided by the existing scientific literature before applying an uncertainty factor. EPA states “in the absence of any chronic inhalation studies…..a UF of 3 was retained”. Is there clear EPA guidance which states that there must be a chronic inhalation study to remove an UF relating to subchronic to chronic extrapolation? If so, EPA should transparently share these guidelines with the public. If there is no such guidance, it is unclear why EPA cannot consider what is known regarding mode of action (and much can be learned from the NAS report on perchlorate which looked at mode of action relating to iodine uptake) in conjunction with existing literature to conduct a weight of evidence evaluation to inform the UF application. It seems two reviewers took this approach.

Scientific Editorial Comments:

- Page A-9, EPA may want to note that the peer reviewer who suggests that the intraspecies variability could exceed an order of magnitude also notes that "this may be compensated for if any of the other UF's are overestimated."

- On page A-12, a public commenter notes that the RfVs are below background exposures. It is not clear that EPA has responded to this comment. Is it correct?

- It is not clear that EPA has responded to comments on page 5 of the peer review report regarding the organization of the document, or concerns about the limited discussion of public health significance.

- Page 25 of the peer review report, Dr. Fisher recommends that EPA consult with a clinical thyroid endocrinologist to help inform the subchronic to chronic UF application. This comment is not mentioned in Appendix A and EPA does not appear to respond to this comment. Has such an expert been consulted? EPA may want to address this comment in Appendix A.

Comments on the IRIS summary and UF application:

- Considering that the maximum uncertainty factors (a total of 3000) have been applied to both the RfD and RfC, it is unclear how the overall confidence of both values could be anything but low. EPA's justification for an RfD and RfC confidence of "low to medium" appears unsupported by the science as presented in the documents. In both cases, EPA's confidence in the study is "medium". While perhaps the study itself may be fine, it is not clear that EPA has taken into account the intended use of the study: for the setting of the RfD/RfC. If the study was truly of medium confidence for RfD/RfC setting, then the maximum uncertainty factors would not need to be applied.
    - EPA may want to reconsider their confidence rankings for the study, the database, and the overall RfD/RfC taking into account the fact that the study and database still lead to the EPA requirement for the application of uncertainty factors totaling 3000 (the EPA maximum value).

    - It is interesting to note that even though it has been over 20 yrs since the previous assessment, EPA is more uncertain regarding HCN toxicity than they were previously. Has the science not advanced at all? This provides an interesting reality check regarding the state of the science vs the state of EPAs science policy default to use more uncertainty factors. Can we say anything about how the science has evolved to inform us over the last 20 years. Are we more certain that the proposed numbers are more accurate? Does the UF of 3000 tell us that we are less certain?

    - We also note that in the earlier and proposed revised RfC assessments EPA relies upon the same 1975 study for the RfC determination. Has the

database become less robust thus warranting a change in RfC UFs from 1000 to 3000 when the exact same study and exact same point of departure is used? In the existing RfC assessment a 3x database uncertainty factor was applied. It is unclear what has changed scientifically causing EPA to now apply a 10x database uncertainty factor. Don't we have more information regarding mode of action and kinetics compared to what we knew in the 1990's when the assessment was first conducted?

- Similarly the UFs applied to the RfD have changed from 100 to 3000. What is the message the public should be inferring from these changes? Are we now relying on more uncertain data than we have been?