DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

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From Senior Toxicologist, Chemical Hazard Assessment Team, Office of Food Safety (HFS-301)

Subject Review of Draft EPA IRIS Documents on Health Hazard Assessment for Cyanide

To: Suzanne Fitzpatrick, Ph.D. (HF-32)
Senior Science Policy Analyst, Office of the Commissioner

Through: Supervisor, Chemical Hazard Assessment Team, OFS (HFS-301) M. A. 7/15/10

This is written in response to your request to review and to provide feedback on the Environmental Protection Agency (EPA) draft Integrated Risk Information System (IRIS) document titled Toxicological Review of Hydrogen Cyanide and Cyanide Salts.

The main focus of this evaluation was on the sections that described the results of studies that employed oral dosing of cyanide compounds and that were examined in the development of the Oral Reference Dose (RfD) derivation. Comments based on the review and evaluation of this document follow.

1) In Section 5.1, Oral Reference Dose, under Subsection 5.1.1, Choice of Principal Study and Critical Effect, the first two sentences would be more accurate if they described or qualified the "data" and "studies" being referred to as "dose-response" ones. There are studies that examined the health effects of subchronic and chronic exposure to cyanide (CN) via diet (e.g., cyanogenic plants, cassava intake) in humans. They are just not dose-response studies. This point also applies to the introductory sentence of Section 4.1.2, Subchronic and Chronic Oral Studies.

2) In the Section 5.1, Oral Reference Dose, under Subsection 5.1.1, the dosages noted in many instances in the EPA document as administered in a particular study do not correspond to the actual dosages indicated as administered in the original publication (e.g., Manzano et al., 2007). It appears that the dosages of the cyanide salts (e.g., KCN, NaCN) presented by the investigators in their papers were converted by EPA and instead expressed as comparable doses of the cyanide ion (CN^-). However, the dosages of a study discussed in the text of the EPA document are often not presented as such. They are still labeled as a KCN or NaCN dose even after apparently being converted (in some cases inaccurately converted), or with no indication of what cyanide compound is being referred to at all. Correction and clarification of the dosage information for each study is crucial for accuracy in the identification of the lower dose limits of adverse reactivity (e.g., LOAEL) to CN compounds. These issues also exist in Subsection 4.2.1, Oral Studies, where studies are examined at length in addition to applying in places in Table 4.6.

3) In a number of instances in Section 5.1, Subsection 5.1.1, when a series of dosages administered in a study are presented the notation that a subject group in the study also received 0 (i.e., zero) of a CN compound was not included in the study description. This information should be included because it indicates to the reader that there was a control group that served as a comparison for the experimental effects resulting in a group administered CN compounds.

4) In the presentation of the Jackson (1988) study on pp 65 (paragraph 3), EPA interprets the study findings as indicating the no observable adverse effect level (NOAEL) was 0.7 mg CN^-/kg/day and the lowest observable adverse effect level (LOAEL) for decreased thyroid T_3 and T_4 levels and changes in behavior was 1.4 mg CN^-/kg/day. This contrast a previous interpretation of the findings of this study by ATSDR in their 1997 Toxicological Profiles for Cyanide document which suggested that the LOAEL for decreased thyroid T_3 and T_4 levels and behavioral changes was at the 0.4 mg CN^-/kg body weight. This apparent contradiction in the interpretation of the results of this study needs as to be reexamined and addressed.

5) Throughout Subsection 5.1.1, Choice of Principal Study and Critical Effect, the nature and findings of a range of studies are described. Also included for each study are statements why it was not selected as the "principal" study. It doesn't seem necessary to state "why" for each study especially because some of the claimed reasons seem manufactured or in some cases questionable or inaccurate. For example, it is indicated that the Manzano et al. (2007) study "is limited by poor reporting of study design and observed histologic effects. Due to these limitations....this study was not selected as the principal study." Examination of the paper describing this study does not appear to support these statements concerning the study. Another example is the use of a "bolus" delivery of a CN compound is cited for the reason a number of studies weren't considered but closer examination of some of these studies indicated that the dose of CN was delivered in half the dose twice (not once) a day. In another place, data from bolus administration of a CN compound is stated as not representative of subchronic to chronic exposure to CN so it is not relevant. There are issues with bolus exposure to an agent but it is not related to "duration of exposure" effects. In another instance, the use of gavage administration of the CN compound was suggested a reason for not considering the findings of the study when in fact the compound was administered orally via tap water. The primary studies that need explanation of why they aren't the principal one are those that demonstrated adverse effects at doses at or lower than the principal critical study selected to derive the RfD.

6) Several studies that were described and examined in Subsection 5.1.1 as a possible candidate(s) for the principal critical study or studies that characterized the lower dose limits of adverse effects assessed the histopathologic effects of subchronic to chronic exposure to CN on various body tissues and nervous system sites. Many studies described aberrant histological changes of a similar nature in at number common sites such as the thyroid, liver, kidney and/or nervous system. The position taken in this EPA IRIS document in the interpretation of the findings of these studies is that because these abnormal changes weren't quantified and depicted with the changes or lesions

characterized in a dose-related fashion then the study findings are not valid for identification of NOAEL or LOAEL values and for consideration as well as a principal study. However, this interpretation is problematic. Histopathological evaluation by its nature is such that it can not always be quantified with respect to agent-induced toxic changes in a valid and/or numerical way. Often abnormal pathology changes also may involve a "ceiling effect" where higher dose levels aren't necessarily associated with a systematic increase in tissue site damage. Thus, the nature of the histopathological studies described in this document should not preclude identification of NOAEL or LOAEL values for the study as suggested by EPA. The lowest dose in a particular study associated with abnormal histopathology should be considered the LOAEL for adverse effects of this nature and the corresponding next lowest dose, if available, would be the NOAEL. Also with respect to these studies, EPA also sometimes indicated that in these studies the adverse effect occurred at unspecified doses so no LOAEL could be identified when the effects actually emerged in all dose treatment groups (and not the control group) in the study. And, in fact a dose-response nature to the histopathological changes is also noted by authors in some references as is the incidence of the adverse effect (being changes are seen in all dosed animals).

7) The discussion of the study Kamalu and Agharanya (1991) on pp 34 and pp 66 indicated that thyroid T_3 decreased by 55% with CN exposure. However, the study reported it decreased by 36%. Also by the manner in which the data from Kamalu (1993) and Kamalu and Agharanya (1991) was presented and discussed on pp 66, it seems that the LOAEL value is based on and derived from both these studies which is not the case. Only Kamalu (1993) had exact dose of exposure information available; thus, clarification of the presentation of information here is needed.

8) The presentation of the results of the study (NTP, 1993) identified by EPA as their "principal study" and its identified "critical effects" along with the analyses performed on the data from this study needs improvement in its accuracy, consistency, clarity and conciseness. This would strengthen the argument and support for the selection of this study by EPA. For example, sometimes changes seen across dose levels in this study are described as dose-related (e.g., spermatid count) when no significant changes is seen across a number of doses (only at the highest dose), so at best, there may be a trend toward the decrease being dose-related. Whereas, a dose-related trend of increased epididymal spermatid concentration that is suggested by the data is always referred to as a measure that not affected by CN exposure. In another example, the significant decrease in epididymal sperm motility versus the control group observed at all dose levels of CN was not considered of biological significance because it was not dose-related. But, at other times, this same significant decrease is cited as support for other CN-induced changes.

EPA selected decreased cauda epididymal weight in rats as the most sensitive endpoint and the critical effects of male reproductive toxicity and the focus of the Bench Mark Dose (BMD) analyses. However, data on cauda epididymal weight of mice is also considered in the BMD modeling results along with the principal rat data. The reason for

this is not clearly addressed. If it is to serve as a point of reference, comparison or support, this point is never subsequently addressed after the analyses were performed.

9) In Subsection 5.1.4, RfD Comparison Information, in addition to the other "unselected" studies evaluated and discussed, the existence of studies that demonstrated CN-induced adverse neurological histopathology changes at LOAEL doses lower than that of the selected principal study should be noted, even though EPA has presented their reasons for not selecting these latter studies. CN-related adverse effects on the brain and spinal cord have been demonstrated as an effect that occurs in humans exposed to this compound. It might also be appropriate to note that some neurological-based evaluations of toxic effects that do not result in numerical measures per se are not applicable to the BMD approach. So the decision to use the BMD analyses may bias against using some types of toxicity findings such as these that assessed the effects on the central nervous system.

10) Feedback from the review and evaluation by CFSAN of the EPA IRIS document, Toxicological Review of Hydrogen Cyanide and Cyanide Salts, is described above. Many of these points also apply to the presentation of the same findings of the CN studies considered relevant by EPA found in the oral exposure part of the separate draft IRIS document that summarizes the health hazard assessment and derivation of the RfDs for CN.

Sue Anne Assimon

Sue Anne Assimon, M.S., Ph.D.

cc:
HFS-300 (Beru)