

Addendum Information to July 13, 2009 Memo Addressing EPA Cyanide IRIS Document

Re: Comment 2

As indicated in Comment 2 of the CFSAN/FDA memo, there were many instances of the information about study dosages being incorrect or unclear in the sections of the document that was the focus of the review by CFSAN, those that addressed oral dose response data and its related issues. Some additional examples of oral studies that the dosages information was inaccurate that can be located at this time follow.

Manzano et al., 2007

The dosages of administration described in the actual published study were 0, 2.0, 4.0 or 6.0 mg KCN/kg body weight (bw)/day. The EPA IRIS Cyanide (CN) document instead indicated the dosages of KCN administered in this study was 1.4, 2.8 or 4.3 mg/kg bw/day. CFSAN thought possibly the dosages had been converted to CN⁻ and mislabeled instead as being KCN dose values. However, the original KCN dose values would not correspond to the CN⁻ values presented in the EPA IRIS document. So the conversion of KCN doses to CN⁻ doses appears to be performed incorrectly. Thus, accordingly, the LOAEL and NOAEL values noted for the effect of increased thyroid weight in this study are also inaccurate and would be lower values than now presented in the document. Some of the locations in the IRIS document these dosage errors are found in the discussion and presentation of the results of this study are pp 35, pp 65, and Table 4.6.

Other problems with the interpretation of the findings of this recent study exist because not all CN-induced abnormal changes found in this work and their associated NOAEL and LOAEL values were considered nor is the fact they were assessed in a quantitative way (e.g., thyroid weight, metabolic measures such as thiocyanate, urea) and thus amenable to the BMD approach. The study results were discounted by EPA because of EPA's focus instead on histological evaluation of the thyroid not being quantitative in nature (see discussion in Comment 6 in the 7/13/10 CFSAN/FDA memo for problems with this interpretation). This is now even more problematic because the correction of the CN⁻ dose value in turn makes the NOAEL/LOAELs lower in value, and close to or lower than the doses in the critical study (NTP, 1993) selected and from which the associated BMDL values were calculated. Hence, EPA now appears also to need to address and clarify these apparent discrepancies in the interpretation of low-dose data between studies that has now emerged with this dose correction.

Sato-Blanco et al., 2002b

The conversion of the 1.2 mg KCN/kg bw/day dosage administered in this study was noted as reflecting a dose of 0.58 mg CN⁻/kg bw/day. The correct conversion value for 1.2 mg KCN/kg bw/day would be 0.48 mg CN⁻/kg bw/day which would be the LOAEL value for neuropathology effects of CN exposure (NOAEL= 0.24 mg CN⁻/kg bw/day). Some of the locations in the IRIS document these dosage errors are found in the discussion and presentation of the results of this study are pp 35, pp 39, and Table 4.6.

Philbrick et al., 1979

There is a discrepancy in the estimated value of the dose of CN⁻ per kg bw that reflects the 1500 ppm KCN containing diet found in the study between the IRIS document and earlier ATSDR CN documents (1997 and 2006). The former derived the estimate to be 44 mg CN⁻/kg bw/day,

whereas, the latter estimated it to be 30 mg CN⁻/kg bw/ day. The basis of these differing converted values from the same exposure is not clear and suggests it needs to be checked as a potential inaccuracy.

Table 4-4, pp 31 and Table 4-5, pp 33

The titles of these tables refer to the experimental administration of NaCN. However, the “Dose” labels in the tables are noted only as “mg/kg-day”. The values of the doses presented appear to represent to CN⁻ values and not NaCN values. The tables needed to be properly labeled to clarify any confusion about compound type and its associated dose being referenced.

Other examples

Numerous additional instances of the lack (e.g., Soto-Blanco et al., 2002a; pp 66) of or mistaken identification (e.g., Jackson, 1988; pp 65) of the agent administered in studies, which often include the NOAEL and LOAEL dose values, were found in the IRIS document. The dose values were not properly qualified as to the type of CN compound (e.g., KCN, NaCN) or ion equivalent (e.g., CN⁻) being referred to in the discussion. This is information that is critical to the reader of the document. For example, this problem is frequently seen in the description of studies on pp 30 - 38, pp 60 - 61, and pp 65 - 67.

Finally, the feedback provided above is not an exhaustive list. They are additional examples. CFSAN is certainly not in the position to re-evaluate the nature of each reference presented throughout the document. Also we only focused on the sections that addressed the oral effects of CN exposure and did not review the sections addressing inhalation exposure to CN. Because in reviewing this document it appeared to be a pattern (vs. a single error or two) of these problems of accuracy and clarity in the presentation of dosage information, CFSAN made a general suggestion in Comment 2 that the dosage information for each of the studies appeared to potentially need reexamination by EPA to improve the document.

Re: Comment 5

Some examples of inaccuracies in the description of studies along with the justifications for not considering them as critical ones in Subsection 5.1.1 follow.

pp 66, 1st full paragraph

Two studies by Soto-Blanco et al. (2002a and b) are described. One study (2002a) noted once daily CN administration via gavage. The second study (2002b) noted administering CN through a “5-month drinking water study,” when the information in the published reference indicated that experimental animals were administered CN via milk for 3 months and then water for 2 months after weaning. One of the justification given at the end of this paragraph on pp 66 describing these studies was that the data could not be considered for the “principal” study because of “use of bolus dosing” (i.e., gavage). This was not a valid reason that pertains to at least one of two of these studies. In addition, the issue with the use of gavage data is not an absolute one as suggested here; it depends on the availability of other work.

pp 67, 1st full paragraph

Two studies by Soto-Blanco and Gorniak (2003 and 2004) are described in the IRIS document here. One study (2004) noted daily gavage administration of CN (with it actually being administered 2 times a day). The second study (2003) just indicated that experimental animals were treated with CN during lactation. Whereas in this second published reference, dams were noted as exposed to CN twice a day (~1.5 hours each) via drinking water and their offspring, or “kids,” were exposed via lactation. However, again, the justifications made for these 2 studies for their not being applicable for use as principal studies included “use of bolus” doses (i.e., gavage; also bolus usually is considered 1 large dose). One study did involve gavage administration but it wasn’t in one large bolus dose, and the other study involved oral exposure, twice a day over a fairly extended time. Thus, the rationale for not examining the low-dose data of one, or possibly both, of these studies does not hold for the “bolus”-related reason given, along with other possible ones (e.g., see Comment 6).

Table 4-6

In Table 4-6, the information listed for the Soto-Blanco and Gorniak (2003) study indicates that the route of administration was “gavage in water,” whereas, it was drinking water in dams and milk or lactation for their kids. The “species” description for this study in Table 4-6 should also include that the subjects were both dams and their offspring of kids.

These are some examples of problems associated with the information on the routes and types of exposure to CN described for some studies in the IRIS document. However, again, it may not be an exhaustive list of them. The existence of these discrepancies, among others, in study information reviewed in the IRIS document suggests that the checking of the accuracy of the descriptions and interpretations of the other studies presented by the authors of this document is warranted.