Response to Comments Pertaining to the Notice of Intent to List Hydrogen Cyanide and Cyanide Salts as Causing Reproductive Toxicity Under Proposition 65

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

July 2013

On March 22, 2013, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Intent to List Hydrogen Cyanide (HCN) and Cyanide (CN) Salts under Proposition 65[1] as a chemical known to the State to cause reproductive toxicity (male reproductive toxicity endpoint). The action was based on the authoritative bodies provision[2] of the Proposition 65 implementing regulations and findings by the U.S. Environmental Protection Agency (U.S. EPA) in the U.S. EPA Integrated Risk Information System (IRIS) file on Hydrogen Cyanide and Cyanide Salts[3] and the U.S. EPA Toxicological Review of Hydrogen Cyanide and Cyanide Salts[4]. OEHHA found that HCN and CN Salts meet the criteria for listing provided in Title 27, Cal. Code of Regs., section 25306[5]. This document responds to comments on the Notice of Intent to List HCN and CN Salts under Proposition 65.

The conclusions in the U.S. EPA reports[6,7] regarding HCN and CN salts and male reproductive toxicity observed in animals exposed to cyanide satisfy the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations. The U.S. EPA IRIS file for HCN and CN salts establishes an oral chronic Reference Dose

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 *et seq*.) hereinafter referred to as Proposition 65 or the Act.
[2] Title 27, Cal. Code of Regulations, section 25306.
[3] U.S. EPA (U.S. Environmental Protection Agency) (2010). Hydrogen Cyanide and Cyanide Salts (CASRN Various). Integrated Risk Information System. Available online at: http://www.epa.gov/iris/subst/0060.htm
[4] U.S. EPA (U.S. Environmental Protection Agency) (2010). Toxicological Review of Hydrogen Cyanide and Cyanide Salts (CASRN Various); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/016F. U.S. EPA, Washington DC, September. Available online at: http://www.epa.gov/iris/toxreviews/0060tr.pdf.
[5] All further references are to Title 27, California Code of Regulations unless indicated otherwise.
[6] U.S. EPA (U.S. Environmental Protection Agency) (2010). Hydrogen Cyanide and Cyanide Salts (CASRN Various). Integrated Risk Information System. Available online at: http://www.epa.gov/iris/subst/0060.htm
[7] U.S. EPA (U.S. Environmental Protection Agency) (2010). Toxicological Review of Hydrogen Cyanide and Cyanide Salts (CASRN Various); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/016F. U.S. EPA, Washington DC, September. Available online at: http://www.epa.gov/iris/toxreviews/0060tr.pdf.

(RfD) for HCN and CN salts based on the male reproductive endpoint of decreased cauda epididymis weight in male F344/N rats:

> "In consideration of the available studies reporting low-dose effects of chronic and subchronic oral exposure to cyanide in animals, the NTP (1993) study was chosen as the principal study.... This study identified statistically significant male reproductive effects in rats and mice that increased in severity in a dose-dependent manner. The observed effects included decreased cauda and whole epididymis weights, decreased testes weight, and altered sperm parameters."
>
> "EPA has selected decreased cauda epididymis weight as the critical effect because it was determined that this effect represents the most sensitive endpoint indicative of male reproductive toxicity. The cauda epididymis is one of the three primary subsections of the epididymis (along with the caput and corpus) and functions as the site of sperm storage and maturation."[8,9]

The U.S. EPA Toxicological Review of HCN and CN Salts concludes that:

> "Reproductive effects, including decreased epididymis, cauda epididymis, and testis weights and decreased sperm parameters (epididymal sperm motility and testicular spermatid counts), have been observed in rats in a subchronic dietary study by NTP (1993). Decreases in the cauda epididymis and epididymis weights were also seen in mice (NTP, 1993).... Additionally, reproductive effects, specifically, alterations in testicular histology, have also been observed in a 14-week study in dogs (Kamalu, 1993)."[10]

One set of comments was submitted from the Cyanide (CN) Council on April 22, 2013. The comments are grouped and numbered by topic, and responses follow below.

1. Formal Identification Criteria

<u>Comment:</u>
The CN Council commented that cyanide sources are both natural and anthropogenic. Cyanide is ubiquitous in the environment and may occur in a wide array of different chemical forms. The proposed listing of CN salts as a category is not defined and thus "creates an unmanageable universe of potential chemicals, businesses and scenarios that could be subject to Prop 65 regulation and enforcement."

---

[8] U.S. EPA (U.S. Environmental Protection Agency) (2010). Hydrogen Cyanide and Cyanide Salts (CASRN Various). Integrated Risk Information System. Available online at: http://www.epa.gov/iris/subst/0060.htm

[9] U.S. EPA (U.S. Environmental Protection Agency) (2010). Toxicological Review of Hydrogen Cyanide and Cyanide Salts (CASRN Various); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/016F. U.S. EPA, Washington DC, September, page 68. Available online at: http://www.epa.gov/iris/toxreviews/0060tr.pdf.

[10] *Ibid,* page 93.

"OEHHA must clearly state exactly which chemical(s) it is proposing to include on the Prop 65 list in order to create a regulation that can actually be implemented by California businesses."

Response:

Formal identification of chemicals by an authoritative body requires in part that the document on which the listing is based specifically and accurately identifies the chemical (Section 25306(d)(2)). The U.S EPA documents that form the basis for listing in this case specify that HCN and CN salts are the subject of the documents[11,12]. In the documents, U.S. EPA concludes that HCN and CN salts cause male reproductive toxicity in rats and it uses that endpoint to set RfDs for HCN and CN salts (based upon the amount of CN^- released when the salts are dissolved). The Proposition 65 listing therefore is for HCN and CN salts. Salts are ionic compounds that, when dissolved in water or another solvent, dissociate into their respective anions and cations. This commonly understood definition of salts is readily available to any party by consulting standard scientific textbooks[13] or other sources[14]. Cyanide salts covered by the Proposition 65 listing are ionic compounds that release the CN anion and a (salt-specific) cation.

Comment:

"EPA's derivation of an RfD for CN^- based on the NTP (1993) study is not a formal identification by EPA that HCN and all CN Salts are male reproductive toxicants. The RfD is a numerical risk threshold, not a basis for a formal classification by an AB. …for the derivation of the RfC (inhalation risk concentration), the EPA used an HCN study (El Ghawabi) of human workers exposed for 5-15 years in the electroplating industry. The critical effect from this study was "thyroid enlargement and altered iodide uptake," not reproductive effects. At no point in the IRIS review of the HCN database does EPA identify any studies or endpoints related to reproductive toxicity."

---

[11] U.S. EPA (U.S. Environmental Protection Agency) (2010). Hydrogen Cyanide and Cyanide Salts (CASRN Various). Integrated Risk Information System. Available online at: http://www.epa.gov/iris/subst/0060.htm

[12] U.S. EPA (U.S. Environmental Protection Agency) (2010). Toxicological Review of Hydrogen Cyanide and Cyanide Salts (CASRN Various); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/016F. U.S. EPA, Washington DC, September. Available online at: http://www.epa.gov/iris/toxreviews/0060tr.pdf.

[13] "The chemical reaction between an acid and a base is called a neutralization reaction. The ionic compound that is formed along with the water in a neutralization reaction is called a salt." General Chemistry, Second Edition (pp 73). D.M McQuarrie and P.A. Rock.

[14] "Any of a large class of chemical compounds formed when a positively charged ion (a cation) bonds with a negatively charged ion (an anion), as when a halogen bonds with a metal. Salts are water soluble; when dissolved, the ions are freed from each other, and the electrical conductivity of the water is increased." Available at http://science.yourdictionary.com/salt

Response:
Reduced cauda epididymis weight, a manifestation of male reproductive toxicity, is expressly identified by U.S EPA as the basis for the oral RfD for HCN and CN salts[15,16]. This meets the criterion for formal identification of the chemicals as causing reproductive toxicity, in that the chemicals have "otherwise been identified as causing …reproductive toxicity by the authoritative body in a document that indicates that such identification is a final action" (Section 25306(d)(1)). Identification of a different toxicological endpoint as the basis for the RfC has no bearing on the formal identification of HCN and CN salts as causing reproductive toxicity.

Comment:
The CN Council suggested that "OEHHA should only consider those chemicals that have been 'formally identified' as causing reproductive toxicity." Citing its review of the U.S. EPA IRIS assessment, including U.S. EPA's derivation of an RfD for CN^-, the CN Council concluded that "The AB (U.S. EPA) has simply not formally identified HCN and most CN salts, aside from NaCN [sodium cyanide], as reproductive toxicants."

Response:
The U.S. EPA has formally identified HCN and CN salts as causing male reproductive toxicity[17,18]. In discussing the solubility and behavior of HCN and CN salts in solution, the U.S. EPA Toxicological Review of Hydrogen Cyanide and Cyanide Salts states that:

> "HCN is a weak acid with a pKa [acid dissociation constant] of 9.2; therefore, HCN and CN^- can interconvert based on pH and temperature. In solution under physiological conditions, the majority of HCN is present in the undissociated form. The simple cyanide salts, KCN [potassium cyanide] and NaCN, are very soluble in water and mildly soluble in ethanol. These compounds readily dissociate in water, and therefore, exposure to any of these compounds in

[15] U.S. EPA (U.S. Environmental Protection Agency) (2010). Hydrogen Cyanide and Cyanide Salts (CASRN Various). Integrated Risk Information System. Available online at: http://www.epa.gov/iris/subst/0060.htm
[16] U.S. EPA (U.S. Environmental Protection Agency) (2010). Toxicological Review of Hydrogen Cyanide and Cyanide Salts (CASRN Various); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/016F. U.S. EPA, Washington DC, September. Available online at: http://www.epa.gov/iris/toxreviews/0060tr.pdf.
[17] U.S. EPA (U.S. Environmental Protection Agency) (2010). Hydrogen Cyanide and Cyanide Salts (CASRN Various). Integrated Risk Information System. Available online at: http://www.epa.gov/iris/subst/0060.htm
[18] U.S. EPA (U.S. Environmental Protection Agency) (2010). Toxicological Review of Hydrogen Cyanide and Cyanide Salts (CASRN Various); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/016F. U.S. EPA, Washington DC, September. Available online at: http://www.epa.gov/iris/toxreviews/0060tr.pdf.

aqueous media results in exposure to CN^-. For the sake of comparability, doses in this review are given as CN^- unless stated otherwise."[19]

It is clear from the U.S. EPA reports[20,21] that it is the cyanide ion (CN^-) dissociated from hydrogen cyanide or a cyanide salt that is of toxicological concern. This is further supported by U.S EPA's guidance in the Toxicological Review document on the derivation and application of RfDs based on reproductive toxicity:

> "The RfDs for simple cyanide salts like NaCN and KCN, which freely dissociate into cyanide, are calculated from the RfD for CN^- by adjusting for molecular weight (i.e., the RfD is multiplied by the ratio of the total molecular weight of the compound to the molecular weight of the CN^-):
>
> RfD for aqueous HCN [HCN(aq)] = $6.3 \times 10^{-4} \times 27/26 = 7 \times 10^{-4}$ mg/kg-day
> RfD for NaCN = $6.3 \times 10^{-4} \times 49/26 = 1 \times 10^{-3}$ mg/kg-day
> RfD for KCN = $6.3 \times 10^{-4} \times 65/26 = 2 \times 10^{-3}$ mg/kg-day
> RfD for calcium cyanide [$Ca(CN)_2$] = $6.3 \times 10^{-4} \times 92/(2 \times 26) = 1 \times 10^{-3}$ mg/kg-day
> RfD for potassium silver cyanide [$KAg(CN)_2$] = $6.3 \times 10^{-4} \times 199/26 = 5 \times 10^{-3}$ mg/kg-day
> RfD for cyanogen $(CN)_2$ = $6.3 \times 10^{-4} \times 52/26 = 1 \times 10^{-3}$ mg/kg-day
>
> Use of the RfD for free cyanide to calculate RfDs of other cyanide compounds may be merited, but the ability of the individual cyanogenic species to dissociate and release free cyanide in aqueous solution (and at physiological pHs) should be taken into consideration."[22]

Thus, although the specific study identified by U.S. EPA as the basis for the RfD for CN^- used NaCN, it is clear from the above guidance on calculating RfDs for CN salts that U.S. EPA has not limited its identification of CN salts causing reproductive toxicity to just NaCN. Rather, U.S. EPA has identified HCN and other CN salts as causing male

---

[19] U.S. EPA (U.S. Environmental Protection Agency) (2010). Toxicological Review of Hydrogen Cyanide and Cyanide Salts (CASRN Various); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/016F. U.S. EPA, Washington DC, September, page 3. Available online at: http://www.epa.gov/iris/toxreviews/0060tr.pdf.

[20] U.S. EPA (U.S. Environmental Protection Agency) (2010). Hydrogen Cyanide and Cyanide Salts (CASRN Various). Integrated Risk Information System. Available online at: http://www.epa.gov/iris/subst/0060.htm

[21] U.S. EPA (U.S. Environmental Protection Agency) (2010). Toxicological Review of Hydrogen Cyanide and Cyanide Salts (CASRN Various); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/016F. U.S. EPA, Washington DC, September. Available online at: http://www.epa.gov/iris/toxreviews/0060tr.pdf.

[22] U.S. EPA (U.S. Environmental Protection Agency) (2010). Toxicological Review of Hydrogen Cyanide and Cyanide Salts (CASRN Various); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/016F. U.S. EPA, Washington DC, September, page 74. Available online at: http://www.epa.gov/iris/toxreviews/0060tr.pdf.

reproductive toxicity on the basis of dissociation of the CN ion, since it is the CN ion that is of toxicological concern**.**

2. Mechanism of Action

Comment:
The CN Council cited uncertainties regarding the exact mechanism(s) underlying the male reproductive toxicity of several CN salts observed in laboratory animals as reasons to limit the listing to NaCN only.

Response:
U.S. EPA did not express any uncertainty about the empirical demonstration of male reproductive toxicity by CN salts. In the presence of clear evidence of male reproductive toxicity of cyanide salts, lack of a complete understanding of the possible mode(s) of action is not a basis for discounting formal identification by the authoritative body of HCN and CN salts as causing reproductive toxicity.

3. Potential Data from Planned Future Studies

Comment:
The CN Council stated that it "is currently planning additional research on the male reproductive toxicity of sodium cyanide in order to address the significant deficiencies in the NTP drinking water studies in regards to their interpretability on the male reproductive endpoint." It requested OEHHA "to refer this case to the Developmental and Reproductive Toxicant (DART) Identification Committee for future review," once results from the additional research is available.

Response:

The regulations provide that if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria for "as causing reproductive toxicity" (Section 25306(h)), the chemical will not be listed under the authoritative bodies mechanism. However, data that do not currently exist cannot be applied to this criterion. Should information become available after the chemicals are listed that demonstrate that there is no substantial evidence that the criteria for "as causing reproductive toxicity" have been satisfied, OEHHA will refer the chemicals to the Developmental and Reproductive Toxicant Identification Committee for a recommendation concerning whether the chemicals should continue to be included on the Proposition 65 list of chemicals (as known to the state to cause reproductive toxicity) (Section 25306(j)).