The California Environmental Protection Agency’s Office of Environmental Health Hazard Assessment (OEHHA) is requesting information as to whether hydrogen cyanide and cyanide salts meet the criteria for listing as a reproductive toxicant under the Safe Drinking Water and Toxic Enforcement Act of 1986.\(^1\) This action is being proposed under the authoritative bodies listing mechanism.\(^2\)

**Background on listing via the authoritative bodies mechanism:** A chemical must be listed under the Proposition 65 regulations when two conditions are met:

1) An authoritative body formally identifies the chemical as causing reproductive toxicity (Section 25306(d)\(^3\)).

2) The evidence considered by the authoritative body meets the sufficiency criteria contained in the regulations (Section 25306(g)).

However, the chemical is not listed if scientifically valid data which were not considered by the authoritative body clearly establish that the sufficiency of evidence criteria were not met (Section 25306 (h)). The U.S. Environmental Protection Agency (U.S. EPA) is one of several institutions designated as authoritative for the identification of chemicals as causing reproductive toxicity (Section 25306(l)). OEHHA is the lead agency for implementation of Proposition 65. After an authoritative body has made a determination about a chemical, OEHHA evaluates whether listing under Proposition 65 is required using the criteria contained in the regulations.

**OEHHA’s determination:** Hydrogen cyanide and cyanide salts appear to meet the criteria for listing as known to the State to cause reproductive toxicity under Proposition 65, based on findings of U.S. EPA in their documents, as indicated in the table below.

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\(^1\) Commonly known as Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986 is codified in Health and Safety Code section 25249.5 et seq.

\(^2\) See Health and Safety Code section 25249.8(b) and Title 27, Cal. Code of Regs. section 25306.

\(^3\) All referenced sections are from Title 27 of the Cal. Code of Regulations.
Chemical | CAS No. | Endpoint | Reference | Chemical Use
---|---|---|---|---

Formal identification and sufficiency of evidence:

In 2010, U.S. EPA updated their online Integrated Risk Information System (IRIS) entry for hydrogen cyanide and cyanide salts (U.S. EPA, 2010a). The new oral chronic RfD of 0.0006 mg/kg-day was based on the male reproductive endpoint of decreased cauda epididymis weight in male F344/N rats. This effect on the male reproductive system was observed in a 13-week drinking water study (NTP, 1993), with a BMDL1SD (lower 95% confidence limit on a benchmark dose associated with a 1 standard deviation (SD) change from the control mean) of 1.9 mg/kg-day.

In support of the IRIS entry, a comprehensive review and summary of the available toxicological data and the Agency’s evaluation were published as a Toxicological Review (U.S. EPA, 2010b). The U.S. EPA documents (2010a and 2010b) appear to satisfy the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.

U.S. EPA (2010a; 2010b, pp. 68-69) concludes that:

"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."
U.S. EPA (2010b) 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)."

U.S. EPA (2010b) reviews direct evidence of cyanide-induced male reproductive toxicity in rats, mice and dogs, as well as mechanistic support for this effect. Numerous studies cited by U.S. EPA's Toxicological Review document (2010b) demonstrate the adverse effects of cyanide on function of the thyroid gland. Additional studies provide evidence for hypothyroidism as a cause of male reproductive damage both during development and in adult animals. On this basis, U.S. EPA (2010b) notes "...that the observed reproductive effects following exposure to cyanide may be mediated through decreases in thyroid hormones mediated through the cyanide metabolite thiocyanate."

Based on either the U.S. EPA (2010a) IRIS entry or the Toxicological Review document (U.S. EPA 2010b), and the references cited in those documents, the evidence appears to be sufficient for listing hydrogen cyanide and cyanide salts as known to cause reproductive toxicity by the authoritative bodies mechanism.

**Request for relevant information:** OEHHA is committed to public participation in its implementation of Proposition 65. OEHHA wants to ensure that its regulatory decisions are based on a thorough consideration of all relevant information. If you wish to comment on whether these chemicals meet the criteria for listing provided in Section 25306, please submit your comments to OEHHA by 5:00 p.m. on Tuesday, July 12, 2011. We encourage you to submit comments in electronic form, rather than in paper form. Comments transmitted by e-mail should be addressed to coshita@oehha.ca.gov. Comments submitted in paper form may be mailed, faxed, or delivered in person to the addresses below:

**Mailing Address:**
Ms. Cynthia Oshita  
Office of Environmental Health Hazard Assessment  
P.O. Box 4010, MS-19B  
Sacramento, California 95812-4010  
Fax: (916) 323-8803

**Street Address:**
1001 I Street  
Sacramento, California 95814
Optional public forum: Upon request, OEHHA will schedule a public forum to provide individuals an opportunity to present oral comments on the possible listing of these chemicals. At the forum, the public may discuss the scientific data and other relevant information related to whether these chemicals meet the criteria for listing in the regulations.

Requests for a public forum must be submitted in writing no later than Friday, June 10, 2011. The written request must be sent to OEHHA at the mailing address above. If a public forum is requested, a notice will be posted on the OEHHA web site at least ten days before the forum date. The notice will provide the date, time, location and subject matter to be heard. Notices will also be sent to those individuals requesting such notification.

If you have any questions, please contact Ms. Oshita at coshita@oehha.ca.gov or at (916) 445-6900.

References


