

**FINAL STATEMENT OF REASONS  
TITLE 27, CALIFORNIA CODE OF REGULATIONS**

**SECTION 25805, SPECIFIC REGULATORY LEVELS: CHEMICALS CAUSING  
REPRODUCTIVE TOXICITY**

**MAXIMUM ALLOWABLE DOSE LEVELS:  
HYDROGEN CYANIDE AND CYANIDE SALTS (ORAL EXPOSURE)**

This is the Final Statement of Reasons for the adoption of oral Maximum Allowable Dose Levels (MADLs) for hydrogen cyanide (HCN) and cyanide salts (CN salts). These chemicals are known to the State of California to cause reproductive toxicity (male reproductive endpoint) under Proposition 65<sup>1</sup>. On March 22, 2013, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt the proposed levels under Title 27, California Code of Regulations, section 25805(b)2. OEHHA proposed an oral MADL of 9.8 micrograms per day for cyanide salts that readily dissociate in solution (expressed as cyanide), and corresponding oral MADLs of 10 micrograms per day for HCN, 19 micrograms per day for sodium cyanide (NaCN) and 25 micrograms per day for potassium cyanide (KCN). The Initial Statement of Reasons set forth the scientific basis for the proposed amendments. A public comment period was provided from March 22 to May 6, 2013. The Notice stated that a public hearing would be held only on request. No request for a public hearing was received. One written public comment was received.

PEER REVIEW

On March 22, 2013, OEHHA provided the notice of proposed rulemaking and the Initial Statement of Reasons for the proposed MADLs for HCN and CN Salts to the members of the Developmental and Reproductive Toxicant Identification Committee for their review and comment as required by Section 25801(f). No comments were received from any committee members.

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<sup>1</sup> The Safe Drinking Water and Toxic Enforcement Act of 1986 (Health and Safety Code, section 25249.5 et seq.)

<sup>2</sup> All further references are to Title 27, California Code of Regulations, unless otherwise noted.

**SUMMARY AND RESPONSE TO COMMENTS**

On May 6, 2013, OEHHA received written comments from Andrew M. Jaques, on behalf of the Cyanide Council (hereinafter referred to as “CN Council”). The comments are summarized and responses are provided below.

**Comment 1**

The CN Council stated that it “continues to believe that it is inappropriate to consider HCN and CN Salts for the Prop 65 list as reproductive hazards and also to apply the Authoritative Bodies mechanism to this broad class of substances.”

**Response 1**

This comment relates to the listing of HCN and CN salts under Proposition 65 rather than to establishment of MADLs. This comment is not relevant to the regulatory action in question.

**Comment 2**

The CN Council stated that the proposed MADL “would set a safe harbor limit vastly lower than any existing standard for cyanide, seemingly in total disregard for the very steep dose response curve that is well understood for cyanide.” The CN Council commented that OEHHA’s identification of the lowest concentration from the National Toxicology Program’s (NTP) 90-day drinking water study as a Lowest Observable Effect Level (LOEL) (30 parts per million [ppm] in drinking water, equivalent to 1.4 milligrams per kilogram of body weight per day [mg/kg-day]) is inconsistent with the review conducted by the Agency for Toxic Substances and Disease Registry (ATSDR). In addition, the CN Council noted that the U.S. Environmental Protection Agency (U.S. EPA) used a benchmark dose level (BMDL) of 1.9 mg/kg-day in deriving oral reference dose (RfD) values for HCN and CN Salts, relying on the data from the NTP 90-day drinking water study. The CN Council stated that MADLs for HCN and CN Salts would be an order of magnitude higher than those proposed if OEHHA were to use the approaches by ATSDR or U.S. EPA.

## Response 2

In establishing MADLs for HCN and CN Salts, OEHHA used the same study, the NTP (1993) drinking water study in rats<sup>3</sup> that U.S. EPA used for deriving RfDs for this group of chemicals. In its review of the data observed in the NTP study, U.S. EPA concluded, “For the purpose of this review, a LOAEL [Lowest Observed Adverse Effect Level] of 1.4 mg/kg-day was identified, based on significantly decreased relative and absolute cauda epididymis weights in male rats.”<sup>4</sup> Therefore, OEHHA’s identification of 1.4 mg/kg-day as a LOEL is consistent with U.S. EPA’s conclusion.

The CN Council cited the findings from a 1998 ATSDR document titled, “Toxicological Profile for Cyanide.” This 1998 document is not available to OEHHA. However, OEHHA reviewed the 2006 ATSDR document under the same title<sup>5</sup>, which includes the statement, “This edition supersedes any previously released draft or final profile.”

The NTP (1993) study was included in the ATSDR review. With regard to the findings from the NTP (1993) study, ATSDR stated:

“The intermediate-duration oral MRL [Minimal Risk Level] was based on a NOAEL [No Observable Adverse Effect Level] of 4.5 mg CN<sup>-</sup>[cyanide ion]/kg/day and a LOAEL of 12.5 mg CN<sup>-</sup>/kg/day in rats exposed for 13 weeks (NTP 1993). In this study, groups of 10 male and 10 female F344/N rats were given sodium cyanide in drinking water at concentrations of 0, 3, 10, 30, 100, or 300 ppm. The reported average cyanide intakes were 0, 0.2, 0.5, 1.4 (males), 1.7 (females), 4.5 (males), 4.9 (females), or 12.5 mg/kg/day, respectively). Statistically significant decreases, compared to controls, were observed in the absolute weights of the left epididymis (7%), left cauda epididymis (13%), and left testis (7.6%) of rats treated at 12.5 mg/kg/day. In addition, 13.6% reductions compared to controls were observed in spermatid heads per testis and spermatid counts per mL suspension in rats treated at 12.5 mg/kg/day. The authors considered these to be evidence of a mild adverse effect of cyanide on the male reproductive system. The statistically

<sup>3</sup> NTP (National Toxicology Program). (1993). NTP technical report on toxicity studies of sodium cyanide (CAS No. 143-33-9) administered in drinking water to F344/N rats and B6C3F1 mice. NTP TR 37; NIH Publication 94-3386. Public Health Service, U.S. Department of Health and Human Services; NTP, Research Triangle Park, NC. Available online at [http://ntp.niehs.nih.gov/ntp/htdocs/ST\\_rpts/tox037.pdf](http://ntp.niehs.nih.gov/ntp/htdocs/ST_rpts/tox037.pdf).

<sup>4</sup> 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>. (Page 32).

<sup>5</sup> ATSDR (Agency for Toxic Substances and Disease Registry). 2006. Toxicological profile for cyanide. U.S. Department of Health and Human Services, Public Health Service, Atlanta, Georgia, USA. Available online at: <http://www.atsdr.cdc.gov/toxprofiles/tp8.pdf>

significant reductions (7.4–8.6% lower than controls) in left cauda epididymis weights observed at 1.4 and 4.5 mg/kg/day were not considered biologically significant in the absence of any other significant effect. The small (<4%), statistically significant, but not dose-related, reductions observed in spermatozoa motility in the 1.4, 4.5, and 12.5 mg/kg/day groups were within the range of normal values and were not considered biologically significant by the study investigators.”<sup>6</sup>

ATSDR therefore identified statistically significant adverse effects on the male reproductive system at the lowest dose evaluated,<sup>7</sup> but made a judgment that they were not biologically significant.

With regard to the interpretation of its findings from the 1993 study, NTP concluded:

“These data suggest that subchronic exposure to low doses of sodium cyanide may produce mild, but perhaps significant, adverse effects on the male reproductive system. The observed differences in sperm motility, while statistically significant, are not considered to be biologically significant, as they represent a relatively small percentage difference from the controls and are well within the range of normal values reported by various laboratories. However, the reductions in cauda epididymal weight, cauda sperm count, and testicular spermatid count are all consistent with a small but measurable adverse effect on male rat reproduction. Based on results of previous studies, these collective reproductive changes alone are probably insufficient to decrease fertility in rats (Chapin et al., 1985; Gray et al., 1992); however, the interactive effects of fertilization and development were not evaluated. In addition, the relative sensitivity of humans to such changes is considered to be greater than that of rats (Working, 1988). Therefore, a potential for adverse reproductive effects in humans following subchronic exposure to cyanide or cyanogenic compounds exists.”<sup>8</sup>

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<sup>6</sup> ATSDR (Agency for Toxic Substances and Disease Registry). 2006. Toxicological profile for cyanide. US Department of Health and Human Services, Public Health Service, Atlanta, Georgia, USA. Available online at: <http://www.atsdr.cdc.gov/toxprofiles/tp8.pdf>

<sup>7</sup> Endpoints for male reproductive effects, including weights of the testis, epididymis, and cauda epididymis, counts of testicular spermatids, and counts and motility of epididymal sperm, were evaluated only in rats exposed to 0 (control), 30, 100 or 300 ppm of NaCN in drinking water.

<sup>8</sup> NTP (National Toxicology Program). (1993). NTP technical report on toxicity studies of sodium cyanide (CAS No. 143-33-9) administered in drinking water to F344/N rats and B6C3F1 mice. NTP TR 37; NIH Publication 94-3386. Public Health Service, U.S. Department of Health and Human Services; NTP, Research Triangle Park, NC. (Pages 36-37) Available online at [http://ntp.niehs.nih.gov/ntp/htdocs/ST\\_rpts/tox037.pdf](http://ntp.niehs.nih.gov/ntp/htdocs/ST_rpts/tox037.pdf).

Thus, the conclusion by U.S. EPA that 1.4 mg/kg-day was a LOAEL, based on significantly decreased relative and absolute cauda epididymis weights in male rats, is consistent with NTP's conclusions. ATSDR's identification of 4.5 mg CN<sup>-</sup>/kg-day as a NOAEL is inconsistent with the conclusion by U.S. EPA; moreover, ATSDR's conclusion that statistically significant reductions in the cauda epididymal weight in rats following exposure to NaCN is not biologically significant is inconsistent with the conclusions by the study author (NTP). While U.S. EPA is identified as an authoritative body for reproductive toxicity for purposes of Proposition 65, ATSDR is not. OEHHA concurs with the identification of 1.4 mg/kg-day as a LOAEL by U.S. EPA.

Relying on the data from the NTP (1993) drinking water study, U.S. EPA conducted Benchmark Dose modeling and selected a Benchmark Response (BMR) level corresponding to a change in the mean response equal to 1 standard deviation (SD) from the control mean for cauda epididymal weight. U.S. EPA found that the BMD associated with a 1 SD decrease in cauda epididymal weight in rats is 3.5 mg/kg-day, and its 95% lower confidence limit (BMDL) is 1.9 mg/kg-day. By applying an uncertainty factor of 3,000 to this BMDL, the U.S. EPA established RfDs for HCN and CN Salts.

OEHHA notes that exposure to NaCN at an estimated dose of 1.4 mg CN<sup>-</sup>/kg-day via drinking water resulted in a statistically significant 7.4% reduction in cauda epididymal weight ( $p < 0.05$ ). The BMDL of 1.9 mg/kg-day, identified in the U.S. EPA BMD modeling, is 36% higher than the LOEL of 1.4 mg/kg-day. The MADL must comply with the Proposition 65 requirement that "the exposure will have no observable effect assuming exposure at one thousand (1000) times the level in question."<sup>9</sup> Therefore, since the BMDL calculated by U.S. EPA is above the empirical LOEL in the study, OEHHA has used the empirical LOEL as the basis for calculating MADLs for HCN and CN salts. Consistent with that approach and in the absence of data indicating that there is a scientifically more valid methodology, OEHHA has divided the LOEL by a factor of 10 consistent with the provision of the relevant regulation that says, "When data do not allow the determination of a NOEL, the lowest observable effect level (LOEL) shall be divided by 10 to establish a NOEL for purposes of assessment." (Section 25803(a)(7))

### **Comment 3**

The CN Council presented extensive discussions about the ubiquitous nature of cyanide compounds in the environment that are either naturally occurring in or released from materials or products that contain naturally occurring cyanide, including a range of food products such as tubers of the cassava (tapioca, manioc) plant, lima (moon) beans, sweet potato, corn, cabbage, linseed, millet, and bamboo, in pits of stone fruits, such as

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<sup>9</sup> Health and Safety Code, section 25249.10(c).

cherries, peaches, and apricots and in apple seeds. The CN Council also discussed a number of sources of cyanide in ambient air, including tobacco smoke, smoke from forest fires and automobile exhaust. The comments also argued that “naturally occurring sources of CN are likely to result in exposures greater than [the] MADL.” On this basis, the CN Council commented that there is no clear basis for declaring that this action has no significant adverse impact on business in California.

### **Response 3**

Regarding exposures to naturally occurring cyanide in foods, Proposition 65 regulations specify that:

“Human consumption of a food shall not constitute an “exposure” for purposes of Section 25249.6 of the Act to a listed chemical in the food to the extent that the person responsible for the exposure can show that the chemical is naturally occurring in the food.” (Section 25501(a))

“A person otherwise responsible for an exposure to a listed chemical in a consumer product, other than food, does not “expose” an individual within the meaning of Section 25249.6 of the Act to the extent that the person can show that the chemical was a naturally occurring chemical in food, and the food was used in the manufacture, production, or processing of the consumer product. Where a consumer product contains a listed chemical, and the source of the chemical is in part from a naturally occurring chemical in food and in part from other sources, “exposure” can only occur as to that portion of the chemical from other sources.” (Section 25501(b))

Thus, the Proposition 65 warning requirement and the oral MADLs for HCN and CN salts do not apply to exposures to naturally-occurring cyanide in foods.

With regard to exposures to cyanide from other sources such as tobacco smoke identified in the comments, the warning provision of Proposition 65 provides that “no person in the course of doing business shall knowingly and intentionally expose any individual to a chemical known to the state to cause cancer or reproductive toxicity without first giving clear and reasonable warning to such individual, except as provided in [Health and Safety Code] Section 25249.10”. One exemption provided in that section is that “the exposure will have no observable effect assuming exposure at one thousand (1000) times the level in question.”

MADLs are developed as an aid to businesses in determining if exposures they cause to a listed chemical are at least 1000 times below the no observed effect level, and therefore do not require a warning. In the absence of a MADL, a business has exactly the same requirement under Proposition 65, but must make its own determination of the level of exposure at which a warning is required. Thus, as noted in the Initial Statement of Reasons for the amendments<sup>10</sup>, given that the MADL is simply offered as compliance assistance for businesses subject to the Act, OEHHA does not anticipate that the regulation will have any significant statewide adverse economic impact directly affecting businesses. To the contrary, adopting the MADL could save businesses a significant amount of time and expense since they do not need to independently calculate a MADL.

### ALTERNATIVES DETERMINATION

In accordance with Government Code section 11346.9(a)(4), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more cost effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action. OEHHA has determined that no reasonable alternative considered by OEHHA or that has otherwise been identified or brought to the attention of OEHHA would either be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons, or would be more cost-effective to affected private persons and equally effective in implementing the statutory policy or other provision of law than the proposed regulation.

For chemicals known to the state to cause reproductive toxicity, an exemption from the warning requirement is provided by the Act when a person in the course of doing business is able to demonstrate that an exposure for which the person is responsible will have no observable reproductive effect, assuming exposure at 1,000 times the level in question (Health and Safety Code sections 25249.9, 25249.10 and 25249.11). The maximum dose level at which a chemical has no observable reproductive effect is referred to as the No Observable Effect Level (NOEL). The Act also provides an exemption from the prohibition against discharging a listed chemical into sources of drinking water if the amount discharged does not constitute a "significant amount," as defined, and the discharge is in conformity with all other laws and regulatory requirements (Health and Safety Code sections 25249.9 and 25249.11). Thus, these exemptions apply when the exposure or discharge in question is at a level that does not exceed the NOEL, divided by 1,000.

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<sup>10</sup> Available at [http://www.oehha.ca.gov/prop65/law/pdf\\_zip/032213CnISORMADL.pdf](http://www.oehha.ca.gov/prop65/law/pdf_zip/032213CnISORMADL.pdf)

Regulations previously adopted by OEHHA provide guidance for determining whether an exposure to, or a discharge of, a chemical known to cause reproductive toxicity meets the statutory exemption (Sections 25801-25821). These regulations provide three ways by which a person in the course of doing business may make such a determination: (1) by conducting a risk assessment in accordance with the principles described in Section 25803 to derive a NOEL, and dividing the NOEL by 1,000; or (2) by application of the specific regulatory level adopted for the chemical in Section 25805; or (3) in the absence of such a level, by using a risk assessment conducted by a state or federal agency, provided that such assessment substantially complies with Section 25803(a). The specific regulatory levels in Section 25805 represent one one-thousandth of the NOEL for their respective chemicals.

#### LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not impose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.