Proposition 65 Maximum Allowable Daily Level (MADL) for Reproductive Toxicity for Cadmium (Oral Route)

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Office of Environmental Health Hazard Assessment (OEHHA)
Reproductive and Cancer Hazard Assessment Section

Summary

The maximum allowable daily level (MADL) for cadmium exposure by the oral route is **4.1 µg/day**. This value was derived as described below, based on a developmental toxicity study in mice conducted by Ali et al. (1986).

Background

This report describes the derivation of a maximum allowable daily level (MADL) for cadmium (CAS # 71-43-28), a chemical listed under Proposition 65 as known to the State to cause reproductive toxicity, effective May 1, 1997. Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. Procedures for the development of Proposition 65 MADLs are provided in regulation (Title 22, California Code of Regulations [22 CCR], Sections 12801 and 12803).

The Proposition 65 listing of cadmium was based on a finding by the Developmental and Reproductive Toxicant (DART) Identification Committee, the Proposition 65 state's qualified experts for reproductive toxicity, that the chemical had been clearly shown by scientifically valid testing according to generally accepted principles to cause developmental and male reproductive toxicity. As part of its deliberations, the Committee reviewed the document "Evidence on Developmental and Reproductive Toxicity of Cadmium" (OEHHA, 1996), a comprehensive review of the scientific literature on the adverse reproductive effects of cadmium. This review serves as the primary reference for MADL development.

As defined in regulations, MADLs are derived from No Observable Effect Levels (NOELs) or Lowest Observable Effect Levels (LOELs) (22 CCR Sections 12801 and 12803). The values discussed below are the highest exposure level at which no effect was observed, or the lowest exposure level at which an adverse effect was observed, under the specific conditions of the study in question. Where multiple reproductive effects provide the basis for the determination that a chemical is known to the state to cause reproductive toxicity, the reproductive effect for which studies produce the lowest NOEL is utilized for the determination of the NOEL (22 CCR Section 12803(a)(1)). Accordingly, only a single MADL is being developed, based on the effect producing the lowest NOEL.

Study Selection

Relevant studies were reviewed in the document "Evidence on Developmental and Reproductive Toxicity of Cadmium" (OEHHA 1996). An update of the literature search conducted for that document identified additional human and animal studies of interest that were also reviewed and considered for the establishment of the MADL. These studies are identified in the Appendix.

The NOEL is based on the most sensitive study deemed to be of sufficient quality (22 CCR Section 12803(a)(4)). For oral cadmium exposures, the study by Ali et al. (1986) has been identified as providing the most suitable effect level for calculating an oral MADL.

Developmental effects were observed at all concentrations used in the Ali et al. (1986) study. Hence, the study provides a LOEL, but not a NOEL, for developmental toxicity. The study protocol involved exposure of pregnant females to cadmium, in the form of cadmium acetate, in the drinking water throughout the gestation period. Decreased pup birthweight was observed at 8.4 ppm. Dams were allowed to deliver and suckle their litters without further cadmium exposure. The study reported a LOEL of 4.2 ppm for adverse effects manifested postnatally, such as reduced weight gain and altered locomotor activity; no NOEL was identified for these effects.

For endpoints of male reproductive toxicity, the most sensitive appropriate study was that of Laskey et al. (1980). The study involved exposure of both male and female rats to cadmium chloride in drinking water, from the beginning of gestation though postnatal growth and maturation, and on through one round of mating. Cadmium concentrations in the drinking were 0, 0.1, 1.0, and 5.0 ppm. The LOEL of 5 ppm was based on reduced epididymal sperm counts. The NOEL for this endpoint was 1 ppm.

Since developmental toxicity was observed at slightly lower levels of exposure than those at which male reproductive toxicity was observed, the MADL is based on the developmental effect (22 CCR Section 12803(a)(1)).

MADL Calculation

The NOEL is the highest dose level which results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day (22 CCR Section 12803(a)(1)). The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (22 CCR Section 12803(b)).

Because the study by Ali et al. (1986) did not contain a NOEL, the LOEL was converted to a NOEL for purposes of assessment by dividing by 10 (22 CCR Section 12803(a)(7)). According to information provided in the paper, the average daily cadmium intake for animals in the LOEL group was 0.706 mg/kg/day. Accordingly, the LOEL of 0.706 was divided by 10 to establish a NOEL of 0.07 mg/kg/day. The NOEL is converted to a

milligram per day dose level by multiplying by the assumed human body weight. For developmental toxicity, the assumed body weight of the pregnant woman is 58 kg:

$NOEL_{oral}$ = 0.07 mg/kg-day × 58 kg = 4.1 mg/day

The MADL is derived by dividing the NOEL by one thousand (1,000) to arrive at the maximum allowable dose level (22 CCR Section 12801(b)(1)). Thus, the adjusted NOEL was divided by 1,000 to obtain the MADL:

$MADL_{oral}$ = 4.1 mg/day ÷ 1000 = 4.1 μg/day

This level applies to the oral route. Review of the literature to develop a MADL for inhalation exposures is underway.

References

Ali MM, Murthy RC, Chandra SV (1986). Developmental and long term neurobehavioral toxicity of low level, *in utero*, cadmium exposure in rats. *Neurobehav Toxicol Teratol* **8**:463-468.

Laskey JW, Rehnberg MJ, Cahill DF, Pieirzak-Flis Z (1980). Chronic ingestion of cadmium and/or tritium. II. Effects on growth, development and reproductive function. *Environ Res* **22**:466-475.

Office of Environmental Health Hazard Assessment (OEHHA, 1996). Evidence on the Developmental and Reproductive Toxicity of Cadmium. Reproductive and Cancer Hazard Assessment Section, OEHHA, California Environmental Protection Agency, Sacramento, CA 95812, October. [http://www.oehha.ca.gov/prop65/CRNR_notices/hid.html]

Appendix

Additional references reviewed since publication of "Evidence on Developmental and Reproductive Toxicity of Cadmium" (OEHHA 1996)

The following studies were identified in a literature search conducted to identify relevant literature published subsequent to the development of the OEHHA (1996) review. They were reviewed along with the studies in OEHHA (1996) to evaluate the most appropriate basis for derivation of a MADL.

Antonio M, Benito M, Leret M, Corpas I. (1998). Gestational administration of cadmium alters the neurotransmitter levels in newborn rat brains. *J Appl Toxicol* **18**:83-88

Antonio M, Corpas I, Leret M. (1999). Neurochemical changes in newborn rat's brain after gestational cadmium and lead exposure. *Toxicol Letters* **104**:1-9

Blottner S, Frolich K, Roelants H, Streich J, Tataruch F. (1999). Influence of environmental cadmium on testicular proliferation in roe deer. *Reprod Toxicol* **13**:261-267

Corpas I, Antonio M. (1998). Study of alterations produced by cadmium and cadmium/lead administration during gestational and early lactation periods in the reproductive organs of the rat. *Ecotoxicol Environ Safety* **41**:180-188

Desi I, Nagymajtenyi L, Schulz H. (1998). Behavioral and neurotoxicological changes caused by cadmium treatment of rats during development. *J App Toxicol* **18**:63-70

Foote R. (1999). Cadmium affects testes and semen of rabbits exposed before and after puberty. *Reprod Toxicol* **13**:269-277

Galicia-Garcia V, Rojas-Lopez M, Rojas R, Olaiz G, Rios C. (1997). Cadmium levels in maternal, cord and newborn blood in Mexico city. *Toxicol Letters* **91**:57-61

Lafuente A, Alvarez-Demanual E, Marquez N, Esquifino A. (1999). Pubertal dependent effects of cadmium on episodic prolactin secretion in male rats. *Arch Toxicol* **73**:60-63

Nagymajtenyi L, Schulz H, Desi I. (1997). Behavioural and functional neurotoxicological changes caused by cadmium in a three-generational study in rats. *Hum Experim Toxicol* **16**:691-699

Odland J, Nieboer E, Romanova N, Thomassen Y, Lund E (1999) Blood lead and cadmium and birth weight among sub-arctic populations of Norway and Russia. *Acta Obstet Gynecol Scand* **78**:852-860

Omu A, Dashti H, Mohamed A, Mattappallil A (1995) Significance of trace elements in seminal plasma of infertile men. *Supplement to Nutrition* **11**:502-505

Piasek M, Schonwald N, Blanusa M, Kostial K, Laskey J (1996) Biomarkers of heavy metal reproductive effects and interaction with essential elements in experimental studies on female rats. *Arh hig rada toksikol* **47**:245-259

Richter M, Schmidt B, Gutte G (1997) Reproductive toxicological fundamental investigations on adult male rats of the WIST/Lppt stock on the determination of swelling after administration of cadmium chloride. DTW *Dtsch Tierarztl Wochenschr* **104**:176-178

Saadi E, Sikorski R (1998) Levels of cadmium in pubic hair of women with threatened abortion and in full-term pregnancy. *Ginekol Pol* **69**:878-883