Proposition 65 Oral Maximum Allowable Dose Level (MADL) for Developmental and Reproductive Toxicity for Chromium (Hexavalent Compounds)

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Office of Environmental Health Hazard Assessment
Reproductive and Cancer Hazard Assessment Branch

Summary

The maximum allowable dose level (MADL) for chromium (hexavalent compounds) is **8.2 µg/day** by the oral route of exposure. This value is based on the female reproductive effects of hexavalent chromium observed in the drinking water study in female rats by Murthy et al. (1996). The MADL is calculated based on a human female body weight of 58 kg (Title 27, California Code of Regulations, section 25803(b))[1].

Background

This report describes the derivation of an oral MADL for chromium (hexavalent compounds). The substance is also referred to as "hexavalent chromium." .

Chromium is used in the manufacture of stainless steel, as well as in production of other alloys. Other uses of chromium include the making of pigments and applications in leather tanning, as well as for welding. The general public can be exposed to hexavalent chromium via air or drinking water through sources including manufacturing emissions, its use as an anticorrosive agent in cooling systems, chrome plating, and via combustion releases (OEHHA, 2009).

Chromium (hexavalent compounds) was considered by the Developmental and Reproductive Toxicant Identification Committee (DARTIC) of the Office of Environmental Health Hazard Assessment's (OEHHA) Science Advisory Board at a public meeting held on November 20, 2008. At this meeting, the DARTIC determined that chromium (hexavalent compounds) was clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity (developmental toxicity, male reproductive toxicity and female reproductive toxicity). To facilitate its review, the DARTIC was provided with OEHHA's "Hazard Identification Materials for Hexavalent Chromium" (OEHHA, 2009). This document summarizes and discusses the available human, animal and other relevant data on the reproductive toxicity of chromium (hexavalent compounds).

[1] All further references to regulations are to Title 27 of the California Code of Regulations, unless otherwise noted.

Procedures for the development of Proposition 65 MADLs are provided in regulations (Sections 25801 and 25803). Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. As defined in regulations, a MADL is derived from a No Observable Effect Level (NOEL) based on the most sensitive study deemed to be of sufficient quality (Section 25803).

Study Selection

Relevant studies on the developmental, male reproductive, and female reproductive toxicity of chromium (hexavalent compounds) have been identified through comprehensive literature searches. As noted above, available studies have been summarized and discussed in OEHHA's "Hazard Identification Materials for Hexavalent Chromium" (OEHHA, 2009). Additional searches were conducted in order to identify whether any additional, relevant studies had been published subsequent to release of that document.

Section 25803 states that "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 shall be utilized for the determination of the NOEL."

Human Studies

While human data on chromium (hexavalent compounds) exposures provide evidence on the reproductive toxicity of hexavalent chromium for multiple endpoints (OEHHA, 2009), these studies provide only a limited basis for establishing quantitative dose-response relationships.

Animal Studies

Five developmental toxicity studies, conducted by the drinking water route in pregnant mice or rats, all found adverse effects on the offspring of treated animals (OEHHA, 2009). Commonly observed effects were reductions in fetal weights and litter size, and increases in resorption frequency. The Lowest Observable Effect Level (LOEL) reported was a dose of 5 mg/kg body weight-day in rats (resulting from consumption of a concentration of 50 ppm in drinking water), reported by Elsaieed and Nada (2002). The only non-zero NOEL reported was a concentration of 10 ppm in the drinking water of Swiss albino mice (De Flora et al., 2006), which is estimated by OEHHA to represent a dose of approximately 2.84 mg/kg-day. No data on mouse body weight or water consumption were provided for Swiss albino mice by De Flora et al. (2006). The dose was estimated based on body weight and water consumption data from Junaid et al. (1996), which was conducted using mice of the same strain. Mean water consumption for control mice was 8.52 ml/day, and the mean starting body weight was 30 g.

Data on the male reproductive toxicity of chromium (hexavalent compounds), summarized by OEHHA (2009), include studies conducted in mice, rats, rabbits, and monkeys. Adverse effects included significant reductions in sperm counts, as well as in testes weights. The lowest LOEL reported was 1 mg/kg-day, which was given to rats by intraperitoneal (i.p.) injection (Ernst, 1990). No NOEL was reported for that study. In another study, also conducted in rats by the i.p. route, the 1 mg/kg-day level was reported to be a NOEL (Saxena et al., 1990).

OEHHA (2009) summarizes data on the female reproductive toxicity of chromium (hexavalent compounds) from studies in mice and rats performed by the drinking water route. All of the available studies in both species provided evidence for adverse effects on the female reproductive system at concentrations in drinking water ranging from 5 ppm (ovarian alterations at the ultra-structural level) to 1,000 ppm (complete pregnancy failure in all exposed dams). Exposure to intermediate concentrations (500-750 ppm) was associated with effects including: lengthened estrous cycles; decreased mating and fertility indices; decreased numbers of corpora lutea, implantation sites, and live fetuses/litter; and increased frequencies of pre- and post-implantation loss, as well as resorption sites.

The most sensitive study of sufficient quality for use in determining the MADL for chromium (hexavalent compounds) was determined to be that of Murthy et al. (1996). In this study of female reproductive toxicity, two sets of adult female Swiss albino mice were exposed to potassium dichromate as a source of hexavalent chromium in drinking water. Set I consisted of four groups of 30 mice each that were given potassium dichromate at concentrations to provide 0, 250, 500, or 750 ppm hexavalent chromium in drinking water for 20 days (a complete cycle of folliculogenesis). Set II female mice were divided into four groups of 10 each. These animals were given 0, 0.05, 0.5, or 5 ppm hexavalent chromium. After 90 days of treatment, their ovaries were studied by electron microscopy.

Set I mice given 750 ppm hexavalent chromium showed significant reductions in the numbers of small, medium, and large follicles. Ovaries from animals of this group showed large numbers of atretic follicles, and in some cases were completely hemolytic. Less severe effects were seen at lower chromium concentrations. A subgroup of animals subjected to hormonally-induced super-ovulation showed significantly reduced numbers of ova with exposure to 500 or 750 ppm hexavalent chromium.

For Set II animals, exposed to much lower concentrations of hexavalent chromium over a longer period of time, ultrastructure evaluation revealed adverse effects at a concentration of 5 ppm. These effects included: follicular cell membranes in various states of disintegration "with the cytoplasmic material oozing out," as well as a reduction in the number of large follicles. The methods used were adequate for demonstrating a toxic effect of hexavalent chromium on ovarian follicles, and the results are consistent with observations of female reproductive toxicity from other studies. The NOEL was determined to correspond to a water concentration of 0.5 ppm. This concentration was

estimated to result in a dose of 0.142 mg/kg-day, based on the water consumption and body weight data from Junaid et al. (1996) provided above.

MADL Calculations

The NOEL is the highest dose level resulting in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day (Section 25803(a)(1)). The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Section 25803(b)). When the applicable reproductive effect is upon the female, a human body weight of 58 kilograms shall be assumed.

For the oral route of exposure, the following calculations were performed to derive the $MADL_{oral}$ for chromium (hexavalent compounds), based upon the Murthy et al. (1996) study in mice that provided a NOEL of 0.142 mg/kg-day for female reproductive toxicity.

Calculation of the NOEL for 58 kg woman:

0.142 mg/kg-day X 58 kg = 8.236 mg/day

Section 12803(a)(1) requires that "the reproductive effect for which studies produce the lowest NOEL shall be utilized for the determination of the NOEL," when multiple reproductive effects provide the basis for listing. Thus the NOEL for a 58 kg woman (8.236 mg/day) is used to calculate a MADL.

The MADL is derived by dividing the NOEL by one thousand (Section 25801(b)(1)). Thus, the adjusted NOEL was divided by 1,000 to obtain the MADL.

$MADL_{oral}$ = 8.236 mg/day ÷ 1,000 = 0. 008236 mg/day or **8.2 µg/day** after rounding.

This MADL applies to exposure to chromium (hexavalent compounds) by the oral route.

There are no empirical data available to establish MADLs for chromium (hexavalent compounds) by other routes of exposure. Most studies of absorption of chromium (hexavalent compounds) after oral administration to rodents found that only 1-2% of the administered dose is bioavailable, with marginally higher numbers for humans (OEHHA, 2009). Chromium has been shown to be absorbed by humans during occupational inhalation exposures (OEHHA, 2009).

For the purpose of Proposition 65, exposure by the oral or inhalation routes or via multiple routes that leads to an absorbed dose equal to that resulting from oral exposures to **8.2 µg/day** should be considered the MADL.

References

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