Proposition 65 Proposed Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Avermectin B1

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

SUMMARY

The proposed maximum allowable dose level (MADL) for avermectin B1 is **4.4 micrograms/day (µg/day).** This value is based on developmental effects of avermectin B1 as observed in the reproduction study in CD-1 mice (U.S. EPA, 2005). 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

Avermectin B1 *(abamectin)* (CAS No. 71751-41-2) was listed in December 2010 as a chemical known to the State of California to cause developmental toxicity. The listing is based on its formal identification by an authoritative body,[2] the U.S. Environmental Protection Agency (U.S. EPA), as a chemical causing developmental toxicity. The criteria used by OEHHA for the listing of chemicals under the "authoritative bodies" mechanism can be found in Section 25306.

Procedures for the development of Proposition 65 MADLs are provided in 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 regulation, a MADL is derived from a No Observable Effect Level (NOEL) based on the most sensitive study deemed to be of sufficient quality. 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.

[1] All references are to sections of Title 27, Cal. Code of Regs. unless otherwise indicated
[2] Health and Safety Code section 25249.8(b) and Title 27, Cal. Code of Regs., section 25306.

STUDY SELECTION

The U.S. EPA 2005 and 1993 documents include discussions of studies providing the basis for listing avermectin B1 as causing reproductive (developmental) toxicity under Proposition 65 (OEHHA 2008). OEHHA reviewed these studies for use in determining a MADL. Also, OEHHA searched the scientific literature for studies or reports that provide information on the developmental toxicity of avermectin B1 that were published after the U.S. EPA review. OEHHA identified only one study of developmental toxicity, the endpoint relevant for use in MADL determination, published after the U.S. EPA review (Gledhill, 2005). This study was not considered to be of sufficient quality for use in MADL determination because it was a pilot study with only three animals per dose group and no control group.

U.S. EPA (2005) identifies an oral developmental toxicity study (Merck Sharpe & Dohme Research Laboratories, 1996) in which CD-1 mice (20-22 animals per dose group) were exposed to the delta-8,9 isomer of avermectin B1 via oral gavage daily on gestation days 6-15 at 0, 0.75, 1.5 and 3.0 mg/kg/day (Guideline No. . 870.3700; U.S. EPA, 2005). This study provided a developmental Lowest Observable Effect Level (LOEL) of 0.75 mg/kg-day (cleft palate and hindlimb extension). For purposes of Proposition 65, this is the most sensitive study deemed to be of sufficient quality (Section 25803(a)(4)). Since adverse developmental effects were seen at the lowest dose used in this study, the LOEL is divided by 10 to establish a NOEL for purposes of assessment (Section 25803(a)(7)).

MADL CALCULATION

The study in CD-1 mice provided a NOEL of 0.075 mg/kg-day (the LOEL of 0.75 mg/kg-day divided by 10). Pursuant to the regulation, the NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL. Since the applicable reproductive effect is upon the female or conceptus, human body weight of 58 kilograms is assumed.

Calculation of the NOEL for a 58 kg woman:

$$0.075 \text{ mg/kg-day} \times 58 \text{ kg} = 4.35 \text{ mg/day}.$$

The proposed MADL is derived by dividing the NOEL by 1,000 (as required by Section 25801(b)(1) and Health and Safety Code Section 25249.10(c)). Thus, the NOEL was divided by 1,000 to obtain the MADL.

Proposed MADL = 4.35 mg/day ÷ 1,000 = **4.4 µg/day** (after rounding)

REFERENCES

Gledhill, A (2005). Comparative Maternal and Pup Exposure Following Dietary and Gavage Dosing in the Rat. Central Toxicology Laboratory, Cheshire, UK. CTL Number UR0795. Submitted by Syngenta Crop Protection Inc., Greensboro, NC 27419.

Merck Sharpe & Dohme Research Laboratories (1996). Oral Developmental Toxicity Study in CD-1 mice L653,2820. Study ID 151200.

Office of Environmental Health Hazard Assessment (OEHHA 2008). Chemical Meeting the Criteria for Listing under Proposition 65 as Known to Cause Reproductive Toxicity via the Authoritative Bodies Mechanism: Avermectin B, California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Sacramento CA. Available at http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/pdf_zip/AvermectinNOIL062708.pdf

U.S. Environmental Protection Agency (U.S. EPA, 1993). Support Document for the Addition of Chemicals from Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) Active Ingredients to EPCRA Section 313. U.S. EPA Office of Pesticide Programs, Washington, DC.

U.S. Environmental Protection Agency (U.S. EPA, 2005). Avermectin B1 and its delta-8,9-isomer; Pesticide Tolerance. Final Rule. *Federal Register* **70**(31):7876-7886. Available at: http://www.federalregister.gov/articles/2005/02/16/05-2985/avermectin-b1