

# **Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Sodium Dimethyldithiocarbamate for Oral Exposures**

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

### **Summary**

The maximum allowable dose level (MADL) for sodium dimethyldithiocarbamate exposure is **23 micrograms/day ( $\mu\text{g}/\text{day}$ )** for the oral route of exposure. Risk assessments for sodium dimethyldithiocarbamate use as a pesticide are usually based on the 40% pesticide formulation without correction for percent sodium dimethyldithiocarbamate. Thus for the 40% sodium dimethyldithiocarbamate pesticide formulation, the MADL is **58  $\mu\text{g}/\text{day}$** . The MADL values were derived as described below, based on a developmental toxicology study in rabbits (Wier, 1987b).

### **Background**

This report describes the derivation of MADL for sodium dimethyldithiocarbamate (CAS No. 128-04-01).

Sodium dimethyldithiocarbamate is a thiocarbamate herbicide with a reported average use in California in 2001 of 173 pounds, mostly on citrus crops (CDPR, 2002). It is also used commercially as a fungicide, microbiocide and slimicide in water treatment, and in rubber manufacture. Nationally, it is considered a high volume chemical by U.S. EPA with a production exceeding 1 million pounds annually.

Sodium dimethyldithiocarbamate is listed under Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act of 1986) as known to the State to cause reproductive toxicity (developmental toxicity), effective March 30, 1999. The Proposition 65 listing of sodium dimethyldithiocarbamate was based on a formal identification by the U.S. Environmental Protection Agency (U.S. EPA) of sodium dimethyldithiocarbamate as causing developmental toxicity (U.S. EPA 1994a,b). U.S. EPA is an authoritative body under Proposition 65 for identification of chemicals as causing reproductive toxicity (Title 22, California Code of Regulations, § 12306(1)).

Procedures for the development of Proposition 65 MADLs are provided in regulation (Title 22 Cal. Code of Regs. § 12801 and 12803). 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 (Title 22 Cal. Code of Regs. § 12803(a)(4)).

## Study Selection

Relevant studies on the reproductive toxicity of sodium dimethyldithiocarbamate have been identified through literature searches. These studies have been reviewed and considered for the establishment of the MADL.

No human studies relevant to sodium dimethyldithiocarbamate reproductive toxicity were identified. No relevant animal studies were identified in the open literature. A microbiocide containing 40% sodium dimethyldithiocarbamate as the active ingredient has been tested for developmental toxicity (rat and rabbit studies) in connection with pesticide registration of the agent (Table 1). The 40% sodium dimethyldithiocarbamate formulation is produced by solution phase synthesis and is stable under the resulting alkaline conditions (pH 11-14). These studies were conducted under federal guidelines, met the requirements of Good Laboratory Practices, and were intended to provide information for health risk assessment. It is generally assumed in developmental toxicity risk assessment that “an agent that produces an adverse developmental effect in experimental animal studies will potentially pose a hazard to humans following sufficient exposure during development [and]...the types of developmental effects seen in animal studies are not necessarily the same as those that may be produced in humans.” (U.S. EPA, 1991).

In the rat developmental toxicity study (Wier 1987a), the formulated sodium dimethyldithiocarbamate microbiocide was administered at doses of 0, 1.6, 23 or 240 mg sodium dimethyldithiocarbamate/kg-day by gavage to Sprague Dawley rats from gestation day 6 through 15. Maternal toxicity was induced at the two higher doses. A prominent fetal effect reported was enhanced ossification (lower incidence of incomplete ossification) in the two higher dose groups. This effect was seen in the appendicular and axial skeleton and also the skull. In the absence of other information, and taking into account the mineral chelating properties of the carbamates, the enhanced ossification was not considered an adverse effect. In addition, there was a statistically significant higher incidence of distended renal pelvis/ureter in the low and mid-dose groups. The developmental toxicity LOEL for this study was 1.6 mg/kg-day based on this effect; no NOEL was available since 1.6 mg sodium dimethyldithiocarbamate/kg-day was the lowest dose used.

The NOEL is based on the most sensitive study deemed to be of sufficient quality (Title 22 Cal. Code of Regs. § 12803(a)(4)). The study that meets this criterion is Wier (1987b). In this study, the sodium dimethyldithiocarbamate microbiocide was administered at doses of 0, 0.4, 4 and 40 mg sodium dimethyldithiocarbamate/kg-day by gavage to New Zealand white rabbits from gestation day 6 through 18. Effects on food intake during dosing were seen at the highest dose. At the mid dose (4 mg sodium dimethyldithiocarbamate/kg-day), statistically significant fetal effects were a lower

number of resorptions/implantation, and a higher incidence of extra ribs. The lower resorption rate at the mid dose was associated with a greater number of dams with fewer than 9 corpora lutea (0/17 in the control group, 5/18 in the mid dose group). An increased incidence of extra ribs was also found in a rabbit teratology study using potassium dimethyldithiocarbamate (Rodwell 1988), although at a higher level of exposure (NOEL 12.8 mg/kg/day) than in the study of sodium dimethyldithiocarbamate (Weir, 1987b, see Table 1). U.S. EPA (1994a) has noted that SDDC is an analog of PDDC for the purposes of identifying toxic effects. As was the case for sodium dimethyldithiocarbamate, this effect occurred in the lower dose range, but not at the highest dose. The NOEL for the rabbit sodium dimethyldithiocarbamate study, 0.4 mg sodium dimethyldithiocarbamate/kg-day, served as the basis for calculation of the MADL based on the finding of an increased incidence of 13<sup>th</sup> thoracic ribs, rudimentary or short. Extra ribs can reflect a homeotic shift, a failure of the genetic program for body patterning, which is broadly relevant to normal development in all species and so is directly relevant to potential effects in humans.

**Table 1. Studies on the developmental toxicity of sodium dimethyldithiocarbamate<sup>1</sup>**

Study	Animals	Treatment	Maternal toxicity	Developmental toxicity
Weir, 1987a	Rats, S-D 22/group	Gavage, 0, 1.6, 23, 240 mg/kg-day <sup>2</sup> gd 6-15	Clinical observations, Weight gain NOEL, 1.6 mg/kg-day	LOEL, 1.6 mg/kg-day
Weir, 1987b	Rabbits, NZW 18/group.	Gavage, 0, 0.4, 4, 40 mg/kg-day gd 6-18	NOEL, 40 mg/kg-day	Skeletal variations NOEL, 0.4 mg/kg-day

<sup>1</sup> abbreviations: S-D=Sprague-Dawley, NZW=New Zealand White, gd=gestation day

<sup>2</sup> doses are the amount of **sodium dimethyldithiocarbamate** administered and are calculated from the doses stated in the study for the pesticide product corrected for the percent sodium dimethyldithiocarbamate (40%)

## 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 (Title 22 Cal. Code of Regs. §12803(a)(1)). The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Title 22 Cal. Code of Regs. §12803(b)).

For the oral route of exposure, the following calculations were performed to derive the MADL for sodium dimethyldithiocarbamate, based on a NOEL of 0.4 mg/kg found in the rabbit study by Wier (1987b):

The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Title 22 Cal. Code of Regs. § 12803(b)). When the

applicable reproductive effect is upon the female or conceptus, human body weight of 58 kilograms is assumed.

$$0.4 \text{ mg/kg-day} \times 58 \text{ kg} = 23.2 \text{ mg/day}$$

The MADL is derived by dividing the NOEL by one thousand (1,000) to arrive at the maximum allowable dose level (Title 22, Cal. Code of Regs., § 12801(b)(1)). Thus, the adjusted NOEL is divided by 1,000 to obtain the MADL.

$$\text{MADL}_{\text{oral}} = 23.2 \text{ mg/day} \div 1000 = 23.2 \text{ } \mu\text{g/day} = \mathbf{23 \text{ } \mu\text{g/day}}$$
 after rounding.

[For a pesticide formulation of 40% sodium dimethyldithiocarbamate, the **MADL** =  $23.2 \text{ } \mu\text{g/day} \times 100 \div 40 = \mathbf{58 \text{ } \mu\text{g/day}}$ .]

The MADL of 23  $\mu\text{g/day}$  is applicable to exposure via oral, inhalation or dermal routes of exposure. If exposures occur by multiple (e.g. inhalation or dermal) routes, the total exposure to the chemical from a single source or product must be considered. If the total exposure resulting from any one or multiple routes is less than or equal to 23  $\mu\text{g/day}$ , the MADL has not been exceeded.

## References

California Department of Pesticide Regulation (CDPR 2002) Summary of Pesticide Use Report Data 2001 by Commodity. Available at <http://cdpr.ca.gov/docs/pur>

Rodwell DE (1988) Teratology study in rabbits with Busan85. SLS Study No 3138.19. Springborn Life Sciences, Inc., Wareham, MA .

U.S. Environmental Protection Agency (U.S. EPA, 1991) Guidelines for Developmental Toxicity Risk Assessment. Federal Register (56 FR 63798-826).

U.S. Environmental Protection Agency (U.S. EPA, 1994a) Proposed Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. Federal Register (59(229) FR 61432).

U.S. Environmental Protection Agency (U.S. EPA, 1994b) Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. Federal Register (59(8) FR 17788).

Wier PJ (1987a) Teratogenicity study in rats of MRD-86-933 (Aquatreat SDM: Approximately 40% sodium dimethyldithiocarbamate). Laboratory Project ID 293334, amended 1990. Exxon Biomedical Sciences, Inc., East Millstone, NJ.

Wier PJ (1987b) Teratogenicity study in rabbits of MRD-86-933 (Aquatreat SDM: Approximately 40% sodium dimethyldithiocarbamate). Laboratory Project ID 293334RB, amended 1990. Exxon Biomedical Sciences, Inc., East Millstone, NJ.

