

Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for N-Methylpyrrolidone for Dermal and Inhalation Exposures

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

Summary

The maximum allowable dose level (MADL) for N-methylpyrrolidone is **3,200 micrograms/day ($\mu\text{g}/\text{d}$) for the inhalation route** and **17,000/ μg day for the dermal route**. The MADLs were derived separately from animal toxicology studies with developmental endpoints that used inhalation (Staples 1990) and dermal (BASF 1993b) exposures.

Background

This report describes the derivation of a MADL for N-methylpyrrolidone (CAS No. 872-50-4). N-methylpyrrolidone is a solvent used in occupational settings and consumer products such as paint strippers.

N-methylpyrrolidone 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 June 15, 2001. The Proposition 65 listing of N-methylpyrrolidone was based on the formal identification by the U.S. Environmental Protection Agency (U.S. EPA 1994a, 1994b) of N-methylpyrrolidone as causing developmental toxicity. U.S. EPA is an authoritative body under Proposition 65 for identification of chemicals as causing reproductive toxicity (Title 22, California Code of Regulations, Section 12306 (22 CCR 12306)).

Procedures for the development of Proposition 65 MADLs are provided in regulations (22 CCR 12801 and 12803). Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. As specified 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 (22 CCR 12803).

Study Selection

No relevant human studies were identified from literature searches. A table of relevant available animal studies using the inhalation and dermal routes of exposure is provided below (Table 1). Full, original reports of most of these studies were obtained for review. The controlling regulations specify that “the NOEL shall be based on the most sensitive study deemed to be of sufficient quality” (22 CCR 12803(a)(7)). The studies providing

the appropriate NOELs for inhalation and dermal MADLs were Staples (1990), and BASF (1993b), respectively. The basis for selection of these studies is discussed below.

Nine inhalation studies were available, one in Himalayan rabbits and eight in rats. The inhalation exposures were to vapor, aerosol or vapor/aerosol mixtures. Several of the rat studies reported effects at about 150 ppm, the maximum concentration for NMP in the vapor phase at room temperature. Higher air concentrations used in other studies resulted in aerosol or combination vapor/aerosol exposures at room temperature. Aerosol could also be directly generated at lower air concentrations. Of the inhalation studies in Table 1, only that of Lee et al. (1987) applied the chemical as an aerosol.

Table 1. Inhalation and dermal toxicity studies relevant for development of a MADL for N-methylpyrrolidone (NMP) by the inhalation and dermal routes¹.

			Endpoints affected at LOEL
inhalation studies			
Staples 1990 (fetal evaluation study)	Rat (SD) M&F 12 wk prior to mating; F gd 0-20	<u>116</u> ppm ¹ , 6 h/d <u>130</u> mg/kg/d ²	↓ fetal weight no maternal toxicity
Staples 1990 (postnatal evaluation study)	Rat (SD) P0: M&F 12 wk prior to mating; F gd 0-20, pnd 4-21 F1: no direct exposure	10, 50 , <u>116</u> ppm, 6 h/d 11, 56 , <u>130</u> mg/kg/d ²	↓ pup weight, pnd 1- 21 no parental toxicity
Lee et al 1987	Rat (CD) gd 6-15	25- 90 ppm aerosol 6 h/d	no fetal or maternal effects

Table 1. (continued)

			Endpoints affected at LOEL
inhalation studies			
Hass et al. 1994	Rat (Mol:WIST) gd 7-20	<u>150</u> ppm 181 mg/kg/d ³ 6 h/d	↓ birthweight ↓ postnatal weight delayed milestones ↓ maze and alternation performance no maternal toxicity
Hass et al. 1995	Rat (Mol:WIST) gd 4-20	<u>150</u> ppm 181 mg/kg/d ³ 6 h/d	↓ fetal weight ↓ ossification ↑ preimplant loss no maternal toxicity
BASF 1993a	Rabbit (Himalayan) (head-nose) gd 7-19	0.2, 0.5 , <u>1.0</u> mg/L, 6 h/d 20, 49 , <u>99</u> mg/kg/d ³	↑ accessory 13 th rib no maternal toxicity
dermal studies			
BASF 1993b	Rabbit (Himalayan) gd 7-19	100, 300 , <u>1000</u> mg/kg/d	↑ accessory 13 th rib ↑ separated origin of carotid no maternal toxicity
Becci et al. 1982 Knickerbocker 1979	Rat (SD) gd 6-15	75, 237 , <u>759</u> mg/kg/d	↓ fetal weight ↓ ossification ↓ live fetuses ↓ pregnancy weight gain (17%)

¹ abbreviations: LOEL = lowest observable exposure level, gd=gestation day; pnd=postnatal day, M=male, F=female; P0=parental generation; F1 first offspring generation of multi-generation study; SD=Sprague Dawley.

² mg/kg/d from U.S. EPA (1993)

³ conversion to mg/kg/d by RCHAS. For Wistar rat, minute volume derived Walker et al. (1985). For Himalayan rabbit, minute volume derived from allometric equation for rabbits in U.S. EPA (1988)

The Staples (1990) postnatal evaluation rat study included lower air concentrations as vapor (0, 10, 50 and 116 ppm), provided air monitoring data, and contained a NOEL as well as a LOEL. For the birth weight (pnd 1) endpoint in this study, effects were identified at both 10 and 116 ppm. However, the effect at 10 ppm was attributed by the authors to the larger litter sizes in this group. RCHAS performed a covariate analysis of the individual birthweight data from this study (Staples 1990) and found results in agreement with the interpretation of the authors. Thus the NOEL of 50 ppm (estimated as 56 mg/kg/d) by U.S. EPA (1993) for the inhalation route was identified for this study.

The rabbit inhalation study (BASF 1993a) also contained a LOEL and a NOEL. The endpoints affected at the LOEL were increased incidence of accessory 13th ribs and separated origin of the carotid. The NOEL (49 mg/kg/d) in the rabbit study was very similar to, but somewhat lower than, that of the Staples (1990) rat study (56 mg/kg/d). Thus the NOEL from Staples (1990) was selected for MADL development as the highest NOEL lower than the lowest LOEL for inhalation exposure.

Two dermal exposure studies were available, one rat and one rabbit developmental toxicity study (Becci et al. 1982; Knickerbocker 1979). In the rat study, 100% NMP was applied to an approximately 25 cm² area of shaved skin on the back of the rat. Collars were used to prevent ingestion. The N-methylpyrrolidone remained on the skin for 8 h and was then removed by washing with water. In the rabbit study, N-methylpyrrolidone diluted in distilled water (40g/100mL) was applied to a shaven skin area in a semioclusive dressing 18 x 11.5 cm. It was left on the skin for 6 h and then removed by washing. Each study contained both a LOEL and NOEL. The NOEL of 300 mg/kg/day obtained from the BASF (1993b) rabbit study was somewhat higher than the NOEL of 237 mg/kg/day from the Knickerbocker (1979) rat study, and was thus selected for MADL development. The endpoint affected at the LOEL in the rabbit study was increased incidence of accessory 13th ribs.

Calculation of the MADLs

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 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 12803(b)). For developmental toxicity, the assumed body weight is 58 kg.

MADL_{INHALATION}

NOEL = 56 mg/kg/d (estimate from U.S. EPA 1993 from 50 ppm air concentration)
NOEL (in mg/day) = 56 mg/kg/d × 58 kg = 3,248 mg/d
MADL_{INHALATION} = 3,248 mg/d ÷ 1000 = **3,200 µg/d** (rounded to two significant figures)

The inhalation MADL is an intake value appropriate for human vapor or aerosol exposures.

MADL_{DERMAL}

NOEL=300 mg/kg /d
NOEL (in mg/day) = 300 mg/kg/d × 58 kg body weight = 17,400 mg/d
MADL_{DERMAL} = 17,400 mg/d ÷ 1000 = **17,000 µg/d** (rounded to two significant figures)

Animal studies that formed the basis of the MADL used single event dermal exposures. Because of the high permeability rate of N-methylpyrrolidone in human skin (Ursin et al.

1995, Akkrill et al. 2002), exposures that involve longer contact times may require special consideration (U.S. EPA 1992).

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