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

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Summary

The maximum allowable dose level (MADL) for N-methylpyrrolidone is **3,200 micrograms/day (µg/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). 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

Saillenfait et al. (2003), and BASF (1993b), respectively. The basis for selection of these studies is discussed below.

Ten inhalation studies were available, one in Himalayan rabbits and nine 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 routes[1].

			Endpoints affected at LOEL
inhalation studies			
Staples 1990 (fetal evaluation study)	Rat (SD) M&F 12 wk prior to mating; F gd 0-20	116 ppm, 6 h/d 130 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**, 116 ppm, 6 h/d 11, **56**, 130 mg/kg/d[2]	↓ pup weight, pnd 1-21 no parental toxicity
Saillenfait et al. 2003	Rat (SD) gd 6-20	30, **60**, 121 ppm, 6 h/day (33, **65**, 132 mg/kg/d[3])	↓ fetal weight ↓ pregnancy weight gain. gd 6-13 (9%) ↓ maternal food intake, gd 13-21
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	150 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	150 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**, 1.0 mg/L, 6 h/d 20, **49**, 99 mg/kg/d[3]	↑ accessory 13th rib no maternal toxicity
dermal studies			
BASF 1993b	Rabbit (Himalayan) gd 7-19	100, **300**, 1000 mg/kg/d	↑ accessory 13th rib ↑ separated origin of carotid no maternal toxicity
Becci et al. 1982 Knickerbocker 1979	Rat (SD) gd 6-15	75, **237**, 759 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 and Sprague-Dawley rats, minute volume derived from allometric equation in U.S. EPA (1988).

Two studies in Sprague Dawley rats with inhalation exposure were reported by Staples (1990). Both studies reported intrauterine growth retardation in the 130 mg/kg/d exposure group as reflected in fetal weight at term in the prenatal evaluation study and birthweight in the postnatal evaluation study. The postnatal evaluation 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 the postnatal evaluation 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 from this study.

The recent study by Saillenfait et al. (2003) provided support for the LOEL and NOEL from Staples (1990). The study design was similar to Staples (1990) in that Sprague-Dawley rats were used and NMP vapor was generated at comparable but somewhat higher air concentrations. However, the exposure was limited to gd 6-20, while the exposure in Staples (1990) began 12 weeks prior to mating. The developmental endpoint affected by NMP in Saillenfait et al. (2003) was fetal weight at term (gd 21). The developmental toxicity LOEL was 132 mg/kg/d. Saillenfait et al. (2003) also reported maternal toxicity. Maternal food intake (g/day) was reduced from gd 13-21 in the 121 ppm exposure group and pregnancy weight gain was lower from gd 6-13 in both the 60 and 120 ppm exposure groups. The developmental toxicity NOEL of 65mg/kg/d identified for this study was higher than the NOEL of 56 mg/kg/d from Staples (1990). However, the NOEL from Saillenfait et al. (2003) would not necessarily be appropriate for the effects found in Staples (1990) because the exposure period was longer in Staples (1990).

The rabbit inhalation study (BASF 1993a) also contained a LOEL and a NOEL. The endpoints affected at the LOEL were increased incidence of accessory 13^{th} 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 cm^2 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 semiocclusive 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 13^{th} 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, Akrill et al. 2002), exposures that involve longer contact times may require special consideration (U.S. EPA 1992).

References

Akrill P, Cocker J, Dixon S (2002). Dermal exposure to aqueous solutions of N-methyl pyrrolidone. *Toxicol Lett* 134:265-269.

BASF (1993a). Study of the prenatal toxicity of N-Methylpyrrolidone in rabbits after inhalation of vapor-aerosol-mixtures. Project No. 41RO544/90100.

BASF (1993b). Study of the prenatal toxicity of N-Methylpyrrolidone (as aqueous solution) in rabbits after dermal application. Project No. 44RO544/90078.

Becci P, Knickerbocker M, Reagan E, Parent R, Burnette LW (1982). Teratogenicity study of N-methylpyrrolidone after dermal application to Sprague-Dawley rats. *Fundam Appl Toxicol* **2**: 3-4.

Knickerbocker M (1979). Teratologic evaluation of N-methylpyrrolidone after dermal application in Spargue-Dawley rats. Food and Drug Research Laboratories, Inc. #6161.

Solomon H, Burgess B, Kennedy Jr G, Staples R (1995). 1-Methyl-2pyrrolidone (NMP): Reproductive and developmental toxicity study by inhalation in the rat. *Drug Chem Toxicol* **18(4)**, 271-93.

Staples R (1990). 1-methyl-2-pyrrolidinone (NMP): Reproductive and developmental toxicity in the rat. E.I. du Pont de Nemours and Company. Haskell Laboratory Report No. 294-90. (Also published as Solomon H, Burgess B, Kennedy Jr G, Staples R (1995). 1-Methyl-2pyrrolidone (NMP): Reproductive and developmental toxicity study by inhalation in the rat. *Drug Chem Toxicol* **18(4)**, 271-93.)

Ursin C, Hansen CM, Van Dyk JW, Jensen PA, Christensen IJ, Ebbehoej J (1995). Permeability of commercial solvents through living human skin. *Am Ind Hyg Assoc J* 56:651-660.

U.S. Environmental Protection Agency (U.S. EPA 1988). Recommendations for and documentation of biological values for use in risk assessment. Environmental Criteria and Assessment Office. EPA/600/6-87/008.

U.S. Environmental Protection Agency (U.S. EPA 1992). Dermal Exposure Assessment: Principles and Applications. EPA/600/8-91/011B. Interim Report.

U.S. Environmental Protection Agency (U.S. EPA 1993). Lifecycle Analysis and Pollution Prevention Assessment for N-Methylpyrrolidone (NMP) in Paint Stripping.

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: 1788.

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(229): 61432.

Walker BR, Adams EM, Voelkel NF (1985). Ventilatory responses of hamsters and rats to hypoxia and hypercapnia. *J Appl Physiol* **59(6)**: 1955-1960.