Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Hydramethylnon for Oral Exposure

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

Summary

The maximum allowable dose level (MADL) for hydramethylnon is **120 micrograms/day (µg/d) for the oral route of exposure**. The MADL was derived as described below, based on a two generation reproduction study in rats conducted by Schroeder (1995).

Background

This report describes the derivation of a MADL for hydramethylnon (CAS No. 67485-29-4). Hydramethylnon is an insecticide used to control ants, cockroaches and termites.

Hydramethylnon 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 and male reproductive toxicity), effective March 5, 1999. The Proposition 65 listing of hydramethylnon was based on the formal identification by the U.S. Environmental Protection Agency (U.S. EPA 1994a, 1994b) of hydramethylnon as causing male reproductive and 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 human data on hydramethylnon male reproductive toxicity were located by electronic literature searches or in the references consulted. Several subchronic, chronic and multigeneration studies in rats and mice were conducted with oral administration of hydramethylnon in connection with pesticide registration requirements. These studies consistently identified testicular toxicity as manifested in impaired fertility, testicular atrophy and histopathology, depending on dose (see Table 1). Developmental toxicity

studies (Biodynamics 1979; IRDC 1982c) demonstrated hydramethylnon developmental toxicity at doses higher than those producing testicular toxicity in chronic and multigeneration studies (Tale 1). Thus, studies demonstrating testicular toxicity were reviewed for MADL development.

The study selected as the basis for MADL development was a two-generation study (Schroeder 1995) with a larger group size based on an earlier three-generation reproduction study (Bio/dynamics 1982).

In the three-generation study, hydramethylnon was administered to CD rats in diet at concentrations of 25, 50, 100 or 200 ppm. There were 12 males in each dose group. General toxicity was limited to lower body weights and body weight gains prior to mating. At the highest dose (200 ppm), no pregnancies were produced in breeding for two litters of the first generation, or in two additional matings after the breeders were removed from dosing for 30 or 60 days. Reproductive effects seen at 100 ppm included reduced male fertility (0/12 males fertile in breeding for the first litter, 5/11 fertile in breeding for the second litter, 6/11 fertile after 30-day recovery). Because of poor fertility, the 100 and 200 ppm groups were not bred for a second generation. At necropsy, gross and histopathology of the testes were reported. In the 200 ppm group, 12/12 males had small testes (gross pathology) and testicular degeneration (histopathology). In the 100 ppm group the incidence was 4/12 for small testes and testicular pathology. There were no effects on fertility or testicular pathology in the 25 or 50 ppm diet groups over three generations.

In the two-generation study (Schroeder 1995), similar doses were used (0, 25, 50 and 75 ppm diet) with a larger group size (30 males and 30 females per group) to more accurately determine a NOEL. The incidence of testicular degeneration in this study was 5/30 at 75 ppm and 1/29 at 50 ppm in the parental generation. The lowest observable effect level (LOEL) for this study was 50 ppm based on the single case of testicular degeneration, and also a lower incidence of mating and longer time to mating in the F1 generation (differences from control not statistically significant).

Both U.S. EPA (1998) and DPR (2000) identified 50 ppm diet as the LOEL for this study based on the single incidence of characteristic testicular toxicity at this diet concentration, and the dose response trend at higher doses. Thus, the 25 ppm dietary concentration was selected as the NOEL for the Schroeder study. OEHHA also selected 25 ppm as the NOEL for MADL development. Based on food intake in the study, this dietary concentration corresponded to a dose of 1.7 mg/kg body weight/d (U.S. EPA 1998).

A number of chronic and subchronic studies also demonstrated testicular degeneration (Table 1). A two-year chronic toxicity/oncogenicity study (IRDC 1982a) in rats found testicular pathology consisting of small, soft testes noted at gross pathology and testicular

Table 1. Studies relevant for development of an oral MADL for hydramethylnon

Study Reference	Species, route[1] duration	Doses: LOEL is underlined **NOEL is in bold**	Reproductive, developmental and general toxicity endpoints affected at the LOEL
male reproductive toxicity			
IRDC, 1982a	rat, CD diet two years	0, **25**, 50, 100, 200 ppmdiet(0, **1.2**, 2.4, 4.9, 10.0 mg/kg body weight/d)	bilateral testicular atrophy no general toxicity
IRDC, 1982b	mouse, CD diet 18 months	0, **25**, 50, 100, 200 ppm diet (0, **3.57**, 6.93, 14.2, 28.6 mg/kg body weight/d)`	testicular degeneration hypospermia interstitial cell hyperplasia of Leydig cells germ cell degeneration no general toxicity
MRID 00032641 (USEPA document no.)*	rat, SD diet 90 day	0, **50**, 100, 200, 400/25 ppm diet (0, **2.5**, 5, 10, 20/1.25 mg/kg body weight/d)	testicular atrophy ↓ testicular weights small, soft testes reduced body weight (5%)
Bio/dynamics Inc., 1982	rat, CD diet three generation	0, 25, **50**, 100, 200 ppm diet (one generation only for 100 and 200 ppm diet)	↓ mating ↓ pregnancy rate seminiferous tubule degeneration reduced sperm ↓ body weight premating (18%) ↓ body weight gain premating (16%)
Schroeder, 1995	rat, CD diet two generation	0, **25**, 50, 75 mg/kg diet (0, **1.66**, 3.32, 5.05 mg/kg body weight/d)	seminiferous tubule degeneration ↓ body weight gain premating (7%)
American Cyanamid Co. 1980a*	rat, immature CD diet four week + four week recovery	0, **200**, 400 ppm diet, pair fed	*at end of treatment*: spermatid giant cells cellular debris in epididymis *after recovery*: tubular atrophy decreased sperm
American Cyanamid Co. 1980b*	rat, mature CD diet four week + four week recovery	0, **200**, 400 ppm diet, pair fed	*at end of treatment*: spermatid giant cells; prostate atrophy; cellular debris in epididymis; *after recover*: tubular atrophy; decreased sperm
American Cyanamid Co. 1983*	rat, immature CD gavage one dose	0, **800** mg/kg body weight	no effects reported
American Cyanamid 1980c*	rat, CD gavage five days dominant lethal	0, **3**, 30, 90 mg/kg body weight/d	↓ fertility

*information is from summaries provided in DPR (2000) and/or U.S. EPA (1998)

Table 1. Studies relevant for development of an oral MADL for hydramethylnon (continued)

Study Reference	Species, route[1] duration	Doses: LOEL is underlined **NOEL is in bold**	Reproductive, developmental and general toxicity endpoints affected at the LOEL
developmental toxicity			
Bio/dynamics, 1979*	rat, CD gavage gd 6-15	0, 3, **10**, 30 mg/kg body weight /d	↓ fetal body weight ↓ skeletal ossification ↑ rudimentary ribs ↓ dam body weight (8%) ↓ dam thymus size ↑ dam toxic signs ↑ dam yellow body fat
IRDC, 1982c*	rabbit, NZW gavage gd 6-18	0, **5**, 10, 20 mg/kg body weight/d	↓ fetal body weight ↓ dam body weight (12%) ↑ yellow body fat ↑ dam toxic signs ↑ dam stool changes

*information is from summaries provided in DPR (2000) and/or U.S. EPA (1998)

atrophy with histopathology. These effects were found at similar dietary concentrations of hydramethylnon as in the two- and three-generation studies, thus supporting the NOEL used for MADL development. However, the LOEL and NOEL for testicular pathology in mg/kg/d calculated from food intake data (2.4 and 1.2 mg/kg body weight/d respectively) were lower than in the multigeneration studies. The NOEL of 1.7 mg/kg bodyweight/d from the two-generation study (Schroeder 1995) is based on a better characterization of reproductive toxicity than the NOEL of 1.2 mg/kg/d from the chronic study (IRDC 1982).

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 (22 CCR Section 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 Section 12803(b)). For male reproductive toxicity, the assumed body weight of the man is 70 kg (22 CCR 12803(b)). The MADL is derived by dividing the NOEL by one thousand (1,000) to arrive at the maximum allowable dose level (22 CCR Section 12801(b)(1)). Thus, the adjusted NOEL was divided by 1,000 to obtain the MADL.

NOEL = (1.7 mg × 98.2% purity)/kg body weight/d × 70 kg = 116.9 mg/d

$MADL_{oral}$ = 116.9 mg/d ÷ 1000 = **120 µg /day** (rounded to two significant figures)

References

Bio/dynamics (1982). A three-generation reproduction study with AC 217,300 in rats.

International Research and Development Corporation (IRDC 1982a). 24-month feeding study of AC217,300 to rats. Study No. 141-014. Mattawan, Michigan.

Schroeder RE (1995). A two-generation reproduction study with AC 217,300 in rats. Pharmaco LSR, Inc. Report No. 92-4046.

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.

U.S. Environmental Protection Agency (U.S. EPA, 1998). Reregistration Eligibility Decision (RED). U.S. EPA Office of Prevention, Pesticides and Toxic Substances, EPA 738-R-98-023.

Bibliography

Studies on the developmental and male reproductive toxicity of hydramethylnon that were considered in the development of the MADL are listed below. For the ones preceded by an asterisk, information was taken from summaries provided in DPR (2000) and/or U.S. EPA (1998).

*American Cyanamid Co. (1979) AC217,300: 91-day study in the dog. Pharmacopathics Research Laboratories, Inc. 5/31/79.

*American Cyanamid Co. (1980a). CL217,300: An 8-week feeding and recovery study in maturing rats. Agricultural Research Division, 6/23/80. Princeton, New Jersey.

*American Cyanamid Co. (1980b). CL217,300: An 8-week feeding and recovery study I mature rats. Agricultural Research Division. Princeton, New Jersey.

*American Cyanamid Co. (1980c). A dominant lethal test in male rats treated with CL 217,300 by gavage for 5 days. Princeton, New Jersey.

*American Cyanamid Co. (1983). "Reproductive performance of male albino rats after receiving a single oral dose with AC 217,300 (Amdro). 6/1/83. Princeton, New Jersey.

*Bio/dynamics (1979). Teratogenesis study in rats with AC 217,300. Project 79-2382, East Millstone, NJ.

Bio/dynamics (1982). A three-generation reproduction study with AC 217,300 in rats. Project 79-2412 (80-2540), East Millstone, NJ.

DPR (2000). Summary of Toxicology Data: Hydramethylnon. California Department of Pesticide Regulation. file name, t20001031.

*Hazleton Laboratories America, Inc. (1980). Twenty-six week toxicity study in dogs: AC217,300. Pharmacopathics Research Lab Inc., Report #P-981-78-142, Laurel, MD.

International Research and Development Corporation (IRDC 1982a). 24-month feeding study of AC217,300 to rats. Study No. 141-014. Mattawan, Michigan.

International Research and Development Corporation (IRDC 1982b). Eighteen-month feeding study of AC 217,300 to mice. Mattawan, Michigan.

* International Research and Development Corporation (IRDC 1982c). Teratology study with AC217,300 in rabbits. Mattawan, Michigan.

Schroeder RE (1995). A two-generation reproduction study with AC 217,300 in rats. Pharmaco LSR, Inc. Report No. 92-4046. East Millstone, New Jersey.

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.

U.S. Environmental Protection Agency (U.S. EPA, 1998). Reregistration Eligibility Decision (RED). U.S. EPA Office of Prevention, Pesticides and Toxic Substances, EPA 738-R-98-023.