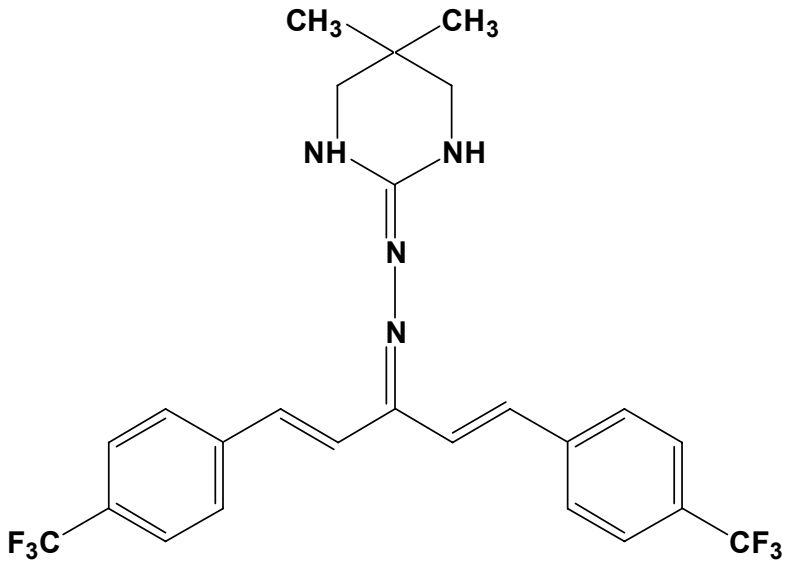
HYDRAMETHYLNON

RISK CHARACTERIZATION DOCUMENT



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I. TECHNICAL SUMMARY

A. INTRODUCTION

Hydramethylnon is an insecticide effective against ants, cockroaches, termites, and other insects and was first registered for use in 1980. The mechanism of action is the inhibition of mitochondrial function. It has both non-food (i.e. structures and turf/lawn) and food uses (range land grasses, hay, and forage). Tolerances are established for residues on pineapples (0.05 ppm), grasses (2 ppm) and grass hay (0.1 ppm). U.S.EPA has concluded that hydramethylnon is eligible for reregistration. In California, the use of hydramethylnon is limited to non-food sites. Hydramethylnon is listed as a reproductive and developmental toxicant under Proposition 65. As of May 2002, there are 42 products registered with structural pest control as the major use. The annual hydramethylnon use has increased from 145 pounds in 1992 to 2,495 pounds in 2000. There have been just two illness/injuries reported from 1982 to 1998 and neither required hospitalization.

Hydramethylnon is not expected to be of environmental concern due to its physical and chemical properties. It has low vapor pressure and low Henry's Law constant and thus unlikely to be found in the air. It has low potential to leach from the soil and reach the ground water since it is insoluble in water and adsorbs to soil. It is stable to abiotic hydrolysis but photolyzes rapidly. While hydramethylnon is lipid soluble, it is unlikely to bioaccumulate in aquatic organisms because of the low levels in the water. In soil, hydramethylnon is degraded by sunlight. Microbial degradation is low since hydramethylnon binds strongly to soil particles. Negligible hydramethylnon residues are expected in plants as it is not taken up via roots and is metabolized in foraging ruminants.

B. TOXICOLOGY PROFILE

In rats, hydramethylnon was poorly absorbed by the oral or dermal route of administration with the absorption estimated at 10% and 5%, respectively, of the administrated dose. After oral absorption, hydramethylnon associated radioactivity was detected in all tissues examined with higher levels in certain tissues (fat, liver, and kidney) than other tissues (muscle and blood). With dermal exposure, individual tissue levels were below the detection limit due to the low absorption. After oral exposure, hydramethylnon was metabolized to a small extent as less than 1% of the administrated dose was converted to metabolites. The primary route of excretion was the feces for both oral and dermal exposures with hydramethylnon excreted primarily unchanged. Low levels of hydramethylnon and metabolites were detected in the urine after oral exposure.

For acute toxicity, hydramethylnon was relatively nontoxic by the oral and dermal routes. The oral LD50s were 1131 to 1300 mg/kg for technical hydramethylnon and >5000 mg/kg for the formulations; the oral Toxicity Category is either III or IV. The dermal LD50s were all greater than 5000 mg/kg with a Toxicity Category of III. Hydramethylnon is not an eye or skin irritant at concentrations tested for the acute responses; depending on the studies, Toxicity Category of III or IV has been assigned. It is not a skin sensitizer in guinea pigs. At non-lethal

concentrations, various clinical signs have been observed in experimental animals. After acute oral exposure, the most common effects in rats were anorexia and decreased body weight gain. With dermal exposure, rabbits showed diarrhea, nasal discharge, ptosis, and lethargy. The clinical signs (decreased activity, labored breathing) observed in rats with inhalation exposure were likely caused by the dust, rather than a systemic effect of hydramethylnon.

After subchronic oral exposure, the testis was the main target organ for hydramethylnon toxicity in rats and dogs. The testicular lesions included tubular degeneration or vacuolation, presence of giant cells, cellular debris in the epididymis, and testicular atrophy. The testicular effect was not related to the decreased food consumption and body weights observed in these species. After subchronic dermal exposure, decreased food consumption and body weight, and increased relative liver weights were reported in rabbits.

With chronic exposure, hydramethylnon caused decreased food consumption in rats, mice, and dogs. In addition, kidney damage in rats (glomerulonephrosis) and in mice (kidney amyloidosis and chronic nephritis) was observed after dietary exposure. Testicular effects (degeneration) were also observed in the rodents, but not in the 26-week dog study. The only oncogenic effect found was lung tumors in female mice after dietary exposure to hydramethylnon for 18 months; however, the finding was considered equivocal. Hydramethylnon was not genotoxic in *in vitro* and *in vivo* assays.

Multiple generation reproductive toxicity studies showed that hydramethylnon caused reduced fertility in rats. This effect was apparently not reversible as reduced fertility was observed in treated rats given control diets for several weeks. The primary target organ for hydramethylnon was the testis, which showed degeneration and atrophy, aspermia, and cellular debris in the epididymides. In developmental toxicity studies, hydramethylnon caused reduced body weight gain in pregnant rats and rabbits. Both species showed similar clinical signs (soft stool, anogenital stains) and yellow body fat. Fetal body weights of rats and rabbits were reduced and may be attributed to the body weight loss of the dams. Increased ossification variation was reported in fetal rats exposed to hydramethylnon *in utero*.

C. RISK ASSESSMENT

C.1. Hazard Identification

From short-term exposure studies, the critical acute oral NOEL was 3 mg/kg/day (0.3 mg/kg/day, absorbed) for decreased body weight, clinical signs (perianal area and bloody nasal discharges), and reduced fertility at 30 mg/kg/day in rats given hydramethylnon for 5 days (Harnois, 1979). For dermal exposure, the critical acute NOEL was 50 mg/kg/day (1.8 mg/kg/day, absorbed) for decreased food consumption and was derived from a 21-day dermal toxicity study (Thompson, 1982). This study was selected because the effect was observed by day 4 in the study and the only acute dermal toxicity study was inadequate.

For subchronic exposure, the critical NOEL of 1 mg/kg/day (0.1 mg/kg/day, absorbed) was derived from results of two studies with dogs given hydramethylnon capsules. In the 13-week study, decreased food consumption and body weights were observed throughout the study

with statistical significance for some weeks with the lowest dose (3 mg/kg/day) as the LOEL (American Cyanamid Company, 1979). The results from the 26-week study (Marshall, 1980) showed that the NOEL for this endpoint was at 1 mg/kg/day as the effect at 3 mg/kg/day was consistent with those from the 13-week study. Testicular effects were observed at higher doses in both dog and rat oral subchronic toxicity studies.

For dermal exposure, the 21-day subchronic dermal toxicity study in rabbits showed reduced food consumption, decreased body weights, and increased relative liver weights at 250 mg/kg with a NOEL at 50 mg/kg (1.8 mg/kg/day, absorbed) (Thompson, 1982). This NOEL is considered the critical NOEL for dermal exposure.

For chronic exposure, the critical oral and dermal NOELs were the same, 1 mg/kg/day (0.1 mg/kg/day, absorbed), for clinical signs (soft stools, mucoid stools, diarrhea) and weight loss in dogs observed at 3 mg/kg/day (Marshall, 1980). Kidney effects (glomerulonephrosis) and testicular effects were observed at slightly higher NOELs (1.5 mg/kg/day to 3.57 mg/kg/day) in other studies. Weight of evidence of the chronic toxicity/oncogenicity data showed suggestive evidence for the oncogenicity of hydramethylnon, but the evidence was not sufficient to assess human carcinogenicity potential. The evidence was limited to tumors in one site (lung), one species (mouse), and in one gender (female). Other studies, such as pharmacokinetics and genotoxicity studies, did not show support evidence for oncogenic potential.

C.2. Exposure Assessment

For handlers, the U.S. EPA Pesticide Handlers Exposure Database (PHED) was used to derive the exposure values. The workers were assumed to be exposed 60 days per season or per year. The upper bound exposures were 0.01 *u*g/kg/day for most workers and 0.05 *u*g/kg/day for loader of aerial application. The average exposures ranged from 0.004 *u*g/kg/day to 0.023 *u*g/kg/day. The amortized exposures ranged from 0.001 *u*g/kg/day to 0.004 *u*g/kg/day. The harvesters and other fieldworkers exposures were based on foliar residue studies for other pesticides, and dermal transfer rates used in other DPR and U.S. EPA exposure assessments. For low to high exposures, the range of the upper bound and average values was 0.4 *u*g/kg/day to 2.0 *u*g/kg/day. The chronic exposure is 1/6 (60 days/365 days) of the upper bound value.

For non-agricultural uses of hydramethylnon granules, such as in homes or commercial buildings, the exposure estimates for aerial and ground applications were the same as those for agricultural uses. For use in spreaders (hand-held rotary or push-type), the exposure estimates were based on data for diazinon granules. For application by hand, the PHED was used. For use of hydramethylnon via spreaders or bare hands, the residents were assumed to have only acute exposures and the exposures were 0.003 *u*g/kg/day and 0.05 *u*g/kg/day, respectively. For the PCOs, the acute and average exposures were the same: 0.01 *u*g/kg/day (via spreader) and 0.24 *u*g/kg/day (by hand). Their amortized exposures were 0.002 *u*g/kg/day and 0.04 *u*g/kg/day, respectively. No handling exposures were expected from the application of Ready-to-use roach or ant killer bait products with minimal direct contact with hydramethylnon.

For outdoor exposures of non-user residents and passers-by (including children), the highest possible exposures were those for fieldworkers and ranged from 0.4 to 2.0 *u*g/kg/day.

The actual exposures were likely to be lower since people would unlikely be present on treated areas infested with ants. Exposure of children to hydramethylnon from indoor use was considered insignificant since the bait stations are child-resistant.

The only dietary exposure of concern was the use of hydramethylnon on pineapples. Using the tolerance as the residue for acute exposure and 100% crop treatment, the acute dietary exposures ranged from 0.299 *u*g/kg/day (females 13-19 years, not pregnant or nursing) to 1.262 *u*g/kg/day (nursing infants, <1 years old). For chronic dietary exposures based on ½ of the tolerance and 100% crop treatment, the range was 0.001 *u*g/kg/day for many of the adult groups to 0.010 *u*g/kg/day (females 13+ years, nursing).

For aggregate exposure to hydramethylnon, the population was broadly divided into workers (who work with hydramethylnon) and residents (those who come into contact with hydramethylnon treated areas). The dietary component of the workers was based on the exposure of female adults (16+ years old) and female adults (20+ years old) from individual consumption surveys for acute and chronic exposures, respectively. The dietary exposure for residents was based on the highest exposed children group, 1-6 years.

D. RISK CHARACTERIZATION

The acute and subchronic margins of exposure (MOE) for occupational exposures ranged from 900 (high activity field workers) to >100,000 (most of other workers). The chronic MOEs ranged from 303 (high activity field workers) to >100,000 (most of other workers). The acute MOEs for residential exposures ranged from 900 (high activities) to 4,500 (low activities). These MOEs were based on exposures for field workers on day 0 post-application. There were no subchronic or chronic exposures.

The MOEs for acute dietary exposure to hydramethylnon residues on pineapples ranged from 2,377 (nursing infants, <1 year old) to 10,042 (females 13-19 years, not pregnant or nursing). For chronic dietary exposure, the MOEs were all greater than 100,000.

The MOEs for aggregate acute exposure ranged from 686 (high activity residents) to >2,000 (most worker scenarios). The MOEs for aggregate chronic exposure ranged from 303 (high activity residents) to 87,608 (applicators and flaggers).

E. RISK APPRAISAL

The uncertainties associated with hazard identification included the use a subchronic dermal toxicity study to determine the critical NOEL for acute dermal exposure and the use of oral toxicity studies to extrapolate the effects for dermal exposures.

There were also uncertainties with the exposure estimates due to lack of chemical-specific exposure data for people using and potentially exposed to hydramethylnon. The use of conservative or first-tier approaches such as upper bound values and tolerance resulted in overestimation of the exposures. The risk associated with the exposure to hydramethylnon, expressed as margins of exposure, showed that the MOEs were greater than 100, the benchmark

generally used to determine the level that is protective of human health. The use of this 100-fold default factor was appropriate since there were no data to increase or reduce this factor.

With respect of issues related to the Food Quality Protection Act, there was no evidence of increased sensitivity of infants and children to the effects of hydramethylnon. Aggregate exposure was considered possible and an assessment was conducted in this document. Cumulative toxicity of hydramethylnon with other chemicals with common mechanism was considered unlikely; however, there were no data to substantiate this assumption. With respect to potential endocrine effects, the current database provided no evidence of endocrine disruption caused by hydramethylnon.

F. TOLERANCE ASSESSMENT

No tolerance assessment was performed since the tolerance for pineapple, the only food use, was already used for dietary exposure assessment.

G. CONCLUSIONS

The human health risk from potential exposure to hydramethylnon was evaluated in this Risk Characterization Document. The exposure scenarios included occupational and residential dermal exposures due to the handling of hydramethylnon during application, residential dermal exposure from direct contact to treated areas, dietary exposure from consuming treated pineapples, and the aggregate exposure from non-dietary and dietary sources. The risks associated with these exposures were assessed using toxicity endpoints from experimental animals and were calculated as margins of exposure. The critical acute oral endpoints were decreased body weight gain, clinical signs, and reduced fertility in rats. The critical acute and subchronic dermal endpoint was mainly decreased body weight gain in rabbits. The critical chronic oral and dermal endpoint was clinical signs in dogs. The database showed only suggestive evidence for oncogenicity and was insufficient to assess the human oncogenicity potential for hydramethylnon.

Overall, this assessment showed that human exposure to hydramethylnon was relatively low due to the physical and chemical properties and few uses. Worker exposures included workers involved in aerial, ground, and hand applications as well as harvesters and fieldworkers who may be in contact with treated foliage. The general public may be exposed to treated foliages. For these exposure scenarios, the margins of exposures were all greater than the benchmark of 100 for occupational, residential, dietary, or aggregate exposures to hydramethylnon. The risks associated with all current use scenarios should be considered acceptable.

II. INTRODUCTION

A human health risk assessment on hydramethylnon was conducted by the Department of Pesticide Regulation (DPR) because of adverse effects identified in chronic and reproductive toxicity studies submitted under The Birth Defect Prevention Act of 1984 (SB 950). The purpose of this risk assessment was to address these and other potential adverse health effects to workers and the general population exposed to hydramethylnon.

II.A. CHEMICAL IDENTIFICATION

Hydramethylnon (tetrahydro-5,5-dimethyl-2(1H)-pyrimidinone [3-[4-(trifluoromethyl)phenyl]-1-[2-[4-trifluormethyl)phenyl]ethenyl]-2-propenylidene]hydrazone) is an insecticide used to control ants (including imported fire ants), cockroaches, termites, and other insects (Hollingshaus and Little, 1984a and b). The use sites include food uses (pineapple and rangeland grasses and hay) and non-food uses (lawns, turfs, golf courses, non-bearing nursery stocks, right-of-ways, houses and other structures). However, the use of hydramethylnon on pasture and rangeland grass is not permitted in California.

In insects, hydramethylnon is toxic to species that ingest food, as opposed to other modes of feeding (Hollingshaus and Little, 1984a). With ingestion, 45-55% of the administered dose is found in the tissues compared to ≤11% after dermal application on the cuticle. Hydramethylnon is the active compound and known metabolites do not have insecticidal activity (Hollingshaus and Little, 1984b). Hydramethylnon causes a decrease in feeding and general lethargy observed 24 hours after exposure (Hollingshaus and Little, 1984b; Hollingshaus, 1987). The insects are moribund within 72 to 96 hours and are dead several days later. Experiments with Chinese Hamster Ovary cells *in vitro* showed that hydramethylnon is a specific inhibitor of site II of the electron transport chain in mitochondria. Metabolic and environmental degradation products[1] did not have any effects (Hollingshaus, 1987).

II.B. REGULATORY HISTORY

Hydramethylnon was developed by American Cyanamid Company and was first registered with the U.S. EPA for use as a pesticide in 1980. Tolerances were established for residues on grasses at 0.05 ppm (Code of Federal Regulations 40 Part 180.395). Since hydramethylnon is completely metabolized in foraging ruminants, U.S. EPA exempted the requirement of tolerances for meat, milk, and meat byproducts. From 1998-2002, there was a Section 18 emergency exemption for potential residues in or on pineapple in Hawaii with a time-limited tolerance of 0.05 ppm (U.S. EPA, 2002). A permanent tolerance for this use was established this year (U.S. EPA, 2003).

During U.S. EPA's reregistration process, the registrant submitted additional data during Phase 2 Data Call-In of 1989, Phase 3 Data Call-In of 1991, and comprehensive Outdoor

[1] 1,5-bis(",","-trifluoro-*p*-tolyl)-1,4-pentadien-3-one; p-(trifluoromethyl)-cinnamic acid; 2-hydrazino-1,4,5,6-tetra-hydro-5,5-dimethyl pyrimidine hydroiodide; tetrahydro-5,5-dimethyl-2(1*H*)-pyrimidinone; and 1,6,7,8-tetra-hydro-7,7-dimethyl-3-(*p*-(trifluoro-methyl)styryl)-4*H*-pyrimido-(2,1-c)*as*-triazin-4-one; trifluoro-*p*-toluic acid.

Residential (Turf) and Agricultural Reentry Data Call-Ins of 1995. In 1998, U.S. EPA completed the Reregistration Eligibility Document (RED) for hydramethylnon and concluded that the use was eligible for reregistration (U.S. EPA, 1998a and b). Due to its physical and chemical properties, hydramethylnon exposure was considered relatively low with negligible food residues from grass and rangeland uses, and minimal exposure from residential and occupational uses. Residue in the drinking water was considered unlikely and thus poses minimal risk to freshwater and terrestrial non-target organisms and water resources. While the U.S. EPA did not make a determination of whether hydramethylnon has a common mode/mechanism of toxicity with other chemicals, hydramethylnon was not expected to have any significant contribution toward the total exposure of other chemicals. For reregistration, the U.S. EPA required the submission of additional product specific data, confirmatory ecological effects and environmental fate data, revised Confidential Statements of Formula, and revised labeling. In terms of regulatory levels, the chronic reference concentration was 0.01 mg/kg/day in the 1998 RED; however, it was 0.001 mg/kg/day (dated 1987) in the U.S. EPA Integrated Risk Information System. The latter reference concentration was used in the evaluation of the time-limited tolerance for pineapples (U.S. EPA, 1998c). In 2003, U.S. EPA established a tolerance of 0.05 ppm for hydramethylnon residues on pineapples based on acute and chronic dietary reference concentrations of 0.05 mg/kg/day and 0.017 mg/kg/day, respectively (U.S. EPA, 2003). There are no other federal regulatory limits such as water advisory levels, or occupational exposure limits.

In California, the Proposition 65 Science Panel discussed the proposal to list hydramethylnon as a carcinogen (lung tumors in mice) (Whatley, 1989). Due to lack of clear evidence in animal studies, the Panel concurred with the DPR (then California Department of Food and Agriculture) recommendation not to list hydramethylnon as a carcinogen. On March 5, 1999, hydramethylnon was listed as a chemical with reproductive toxicity under the authoritative bodies mechanism of Proposition 65. The U.S. EPA had determined that hydramethylnon caused developmental effects (decreased fetal body weight, increased post-implantation loss, and vertebral abnormalities) and male reproductive toxicity (testicular atrophy and infertility). The Maximum Allowable Dose Level (MADL), under Proposition 65, for hydramethylnon is 120 *u*g/day for the oral route exposure (Office of Environmental Health Hazard Assessment, 2003). It was based on a NOEL of 25 ppm (1.7 mg/kg/day; 1.2 mg/kg/day when corrected for purity) for testicular toxicity in the 50-ppm male rats in a two-generation reproductive toxicity study (Schroeder, 1995) and a 1000-fold safety factor.

II.C. TECHNICAL AND PRODUCT FORMULATIONS

As of May, 2002, 42 products are registered for use in California. They are sold as granules/flake, pellet/tablet/cake/briquet, gel/paste/cream, impregnated material, or dry material. Hydramethylnon is also placed inside bait boxes that contain 0.73% to 2.15% hydramethylnon as the active ingredient. The product registrants are: American Cyanamid Company, Micro-Flo Company, Combat Insect Control Systems, and MaxForce Insect Control Systems.

II.D. USAGE

In California, hydramethylnon use has increased from 145 pounds in 1992 to 2,378

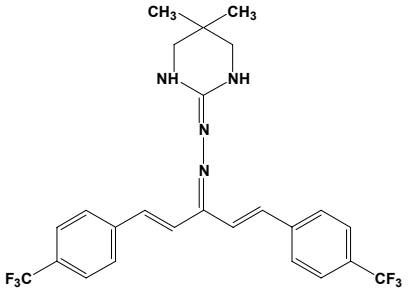
pounds in 2001 (DPR, 2002a). The major use is for structural pest control, accounting for 90% of the total. Other uses include landscape maintenance, outdoor nursery plants, and rights of way. The actual number of pounds used is higher because the use report does not include homeowner uses. In 2001, 7,820 pounds were sold for agricultural and home uses (DPR, 2002b).

II.E. ILLNESS REPORT

From 1982 to 1998, there were 2 illnesses/injuries reported in the California Illness Report as probably associated with hydramethylnon exposure alone (see Appendix A). Both cases were due to structural pest control use. In the 1996 case, a bystander office worker complained of respiratory symptoms. In the 1998 case, a bystander convalescent hospital employee reported skin and systemic effects. Neither bystander was hospitalized.

II.F. PHYSICAL AND CHEMICAL PROPERTIES

Chemical name:	Tetrahydro-5,5-dimethyl-2(1H)-pyrimidinone [3-[4-(trifluoromethyl) phenyl]-1-[2-[4-trifluormethyl)phenyl]ethenyl]-2-propenylidene]hydrazone
CAS Registry number:	67485-29-4
Common name:	Hydramethylnon
Trade name:	Amdro, Combat, Maxforce, Siege, Subterfuge, CL 217,300, AC 217,300
Molecular formula:	$C_{25}H_{24}F_6N_4$
Molecular weight:	494.50 g/mole
Chemical structure:	



Physical appearance:	yellow to tan crystalline solid, vegetable oil odor
Solubility:	insoluble in water (0.005-0.007 mg/L at 25EC, pH 7.4), slightly soluble in alcohols, and soluble in acetone, chlorobenzene, and 1,2-dichloroethane.
Melting point:	189 ^{o}C to 191°C
Vapor pressure:	6 x 10^{-8} mm Hg at 25°C
Henry's Law constant:	1.95 x 10^{-7} atm m^3/g mole
Partition coefficient:	Kow = 27,965 (n-octanol and water), log Kow=4.45

a/ References: U.S. EPA, 1998b; Bacey, 2000 (Appendix B).

II.G. ENVIRONMENTAL FATE

The environmental fate of hydramethylnon was prepared by the DPR Environmental Monitoring Branch and is included as Appendix B of this document. In summary, hydramethylnon is not expected to be of environmental concern due to its physical and chemical properties. It has low vapor pressure and low Henry's Law constant and thus unlikely to be found in the air. It is not expected to leach from the soil and reach the ground water since it is insoluble in water and adsorbs to soil. It is stable to abiotic hydrolysis with a half-life of 30 days. It is photolyzed rapidly with an aqueous photolysis half-life of less than 1 hour and 5 photoproducts have been detected. While hydramethylnon is lipid soluble, it is unlikely to bioaccumulate in aquatic organisms because of low concentrations in the water. In soil, hydramethylnon is degraded by sunlight with a soil photolysis half-life of 5 days. Microbial degradation is low since hydramethylnon binds strongly to soil particles. Negligible hydramethylnon residue is expected in plants grown on/near treated ground as it is not taken up via roots. Hydramethylnon residue on plant material, when ingested, is metabolized in foraging ruminants.

III. TOXICOLOGY PROFILE

The toxicological database of hydramethylnon consists primarily of oral and dermal studies. Inhalation exposure is considered negligible since hydramethylnon is a solid at room temperature with low vapor pressure. All studies required under SB 950[2] have been submitted to DPR. The acceptability of these required studies (except genotoxicity studies), where noted in this document, is based on the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. The acceptability of the genotoxicity studies is based on the Toxic Substances Control Act guidelines (Federal Register, 1985 and 1987). A study is considered supplemental information if the study type requirement under SB 950 is fulfilled by an acceptable study or if the study is not part of the SB 950 data requirement. The toxicology summaries for SB 950 required and other studies submitted to DPR are included in Appendix C. In these toxicity studies, the no-effect levels may be expressed as No-Observed-Effect Levels (NOELs) or No-Observed-Adverse Effect Levels (NOAELs). The NOELs/NOAELs established by the U.S. EPA are noted when they are available (U.S. EPA, 2003). For the purpose of this document, endpoints under either designation are considered relevant for hazard identification.

Summary tables for selected toxicity studies considered for critical NOELs and lowest-observed-effect levels (LOELs) for hazard identification are presented in Tables 7, 14, and 19 for acute, subchronic, and chronic exposures, respectively. For comparison between studies, the NOELs are also presented as dosage (mg/kg/day) (calculations in Appendix D). This dosage expression takes into consideration the feed concentration and consumption rate. This approach follows the dose calculation methods outlined in the 1992 U.S. EPA Exposure Assessment guidelines, where the potential dose is a function of the concentration and intake rate (U.S. EPA, 1992). For comparison of systemic effects between routes, the dosages are converted to absorbed doses using absorption factors of 10% and 5% for oral and dermal exposures, respectively (**III.A.1. Absorption** on absorption factors).

III.A. PHARMACOKINETICS

Summary: In rats, hydramethylnon was poorly absorbed by the oral or dermal route of administration with the absorption estimated at 10% and 5%, respectively, of the administrated dose. After oral absorption, hydramethylnon-associated radioactivity was detected in all tissues examined with higher levels in certain tissues (fat, liver, and kidney) than other tissues (muscle and blood). With dermal exposure, individual tissue levels were below the detection limit due to the low absorption. After oral exposure, hydramethylnon was metabolized to a small extent as less than 1% of the administrated dose was converted to metabolites after oral exposure. The primary route of excretion was the feces for both oral and dermal exposures with hydramethylnon excreted primarily unchanged. Low levels of hydramethylnon and metabolites were detected in the urine after oral exposure.

III.A.1. Absorption

Hydramethylnon was poorly absorbed after gavage administration in rats. Sprague-

[2] The required studies are: chronic toxicity (in two species), oncogenicity (in two species), reproductive toxicity (rats), developmental toxicity (in two species), genotoxicity, and neurotoxicity studies.

Dawley rats (5/sex/group) were dosed with hydramethylnon by gavage in corn oil as a single dose (3 mg/kg or 100 mg/kg) or multiple-doses (14 consecutive daily treatment of 3 mg/kg, followed by 3 mg/kg of ^{14}C-hydramethylnon; >95% radiopurity) (Zdybak and Robinson, 1992). Both phenyl and pyrimidinyl ring-labeled hydramethylnon were used. Urine and feces samples were collected during exposure and for 7-days after exposure. Tissues radioactivity was also determined 7 days after exposure. There were no substantial differences associated with gender, dose level, or duration of treatment in the amount absorbed. The absorption was low as most of the dose was rapidly excreted in the feces within 36 hours with the parent compound as the major component found in the feces. The absorption ranged from 5.07% to 11.35% of the administered dose for the phenyl-^{14}C label (Table 1) and from 4.58% to 7.96% for the pyrimidinyl-^{14} C label (data not shown). Based on these values, the oral absorption (sum of % dose in the urine and tissues) was established as 10% (Table 1); this value is used to calculate the absorbed doses in this document.

Table 1. The disposition of hydramethylnon in the rat 7 days after oral exposure.[a]

Compartments	**% of Administered Dose[a]**					
	3 mg/kg Single dose		**10 mg/kg Single dose**		**3 mg/kg For 14 days**	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**
Total in Tissues	3.20	5.38	3.62	9.87	5.64	8.01
Total Excreted						
Feces	85.44	86.99	91.77	93.27	93.93	88.45
Urine	4.25	2.33	1.45	1.48	2.49	2.09
Total Absorbed[b]	7.45	7.71	5.07	11.35	8.13	10.10
Overall Recovery	92.89	94.70	96.84	104.62	102.06	98.55

a/ Data from Zdybak and Robinson, 1992. % of administered dose includes radioactivity for the parent compound and metabolites in the compartments. Only results for the phenyl-^{14}C label are presented in this table. Total absorbed for the pyrimidinyl-^{14}C label was similar (4.58% to 7.96% of administered dose).

b/ Total absorbed is the sum of % dose in the tissues and urine.

In rats, the dermal absorption of hydramethylnon was lower than the oral absorption. Based on the results of the following two studies, the DPR Worker Health and Safety Branch determined a dermal absorption factor of 5% (see Appendix A). This factor included the amounts found in the skin after washing and in the tissues and excreta after 10-hours of exposure as well as a doubling factor. A doubling factor was used to account for potential higher absorption at low concentrations as in human exposure, and with the use of granules compared to gels used in the studies. In the U.S. EPA Reregistration Eligibility Document, U.S. EPA established a dermal absorption factor of 1% based on the results of the same two studies (U.S. EPA, 1998a). The total absorbed doses reported in the RED were 0.414% for Maxforce gel (2% a.i.; Frantz and Beskitt, 1993) and 0.97% for Siege (2.16% a.i.; Sharp, 1993) but no details were provided on the calculation.

In the study by Sharp (1993), hydramethylnon (^{14}C-, gel; 2.16% a.i., 97.1% radiopurity; 2

mg of hydramethylnon/animal or 7.1 to 7.4 mg/kg based on body weights of 269 to 282 grams before dosing) was applied to the shaved skin (12.5 cm^2) of 8 male Sprague-Dawley rats for 10 hours and covered with a nonocculsive cover. Urine and feces were collected throughout the experimental period. Radioactivity in blood and tissues (skin, fat, kidneys, liver, lungs, and testes) were less than the detection limit after the 10-hour exposure and at 336 hours post-exposure (Table 2). Over 93% of the radioactivity was recovered in the skin wash. In the report, the total amount absorbed (carcass, feces, urine, and cage wash/wipe) was 0.83% of the dose over a 336-hour period.

Table 2. The disposition of hydramethylnon in the rat after 10 hours of dermal exposure.[a]

Compartments	**% of Administered Dose**	
	After 10 hours of exposure	**336 hours postdose**
Total in Carcass	0.46%	0.16%
Feces	ND	0.41%
Urine	<0.01%	<0.01%
Cage wash/wipe	<0.01%	0.25%
Total Absorbed	0.46%	0.83%
Amount Remaining on Skin	2.36%	0.75%

a/ Data from Sharp, 1993. ND=non-detected. The dosage was 7 mg/kg.

In another study with rats, dermal absorption was also low after longer exposure at a higher concentration than the previous study. The skin of male Sprague-Dawley rats (4/group) was exposed to hydramethylnon (^{14}C-, Maxiforce gel with 2% a.i., 98.3% radiopurity; 113.9-151.9 mg/kg) 10 hours each day for 10-hours, 24-hours, 1-week or 2-weeks (Frantz and Beskitt, 1993). The application site (10 cm^2) was covered with a nonocculsive covering. For the 10-hour and 24-hour groups, samples were collected at termination (blood), 0-10 hours (urine and feces for both groups), and 10-24 hours (urine and feces for the 24-hour group). For the 1-week and 2-week groups, urine and feces were collected at 24-hour intervals. For 10-hours and 24-hours groups, radioactivity was found primarily in the skin (0.90% to 0.93%) with lower levels in the urine and feces (Table 3). With prolonged exposure (1 to 2 weeks), radioactivity in the feces increased and accounted for 0.30% to 0.56% of the administered dose. No radioactivity was detected in the carcass, except for the 24 hours exposure group (0.31% of administered dose). In the report, the amounts absorbed (sum of carcass, dose site skin, feces, urine, and cage wash) were 1.07% (10-hour), 1.48% (24-hours), and 0.57% (1-week), and 0.62% (2-weeks) of the administered dose. Additional studies showed that 24% of the radioactivity was in the stratum corneum with the remaining in the deeper layers of the skin.

Table 3. The disposition of hydramethylnon in the rat after 10 hours to 2 weeks of dermal exposure.[a]

Compartments	% of Administered Dose[b]			
	10 hours	24 hours	1 week	2 weeks
Total in Carcass	0.00%	0.31%	0.00%	0.00%
Dose Site Skin	0.90%	0.93%	0.22%	0.04%
Feces	0.01%	0.15%	0.30%	0.56%
Urine	0.11%	0.02%	0.03%	0.02%
Cage wash/wipe	0.05%	0.07%	0.02%	0.00%
Total Absorbed	1.07%	1.48%	0.57%	0.62%
Amount Remaining on Skin	0.20%	0.31%	0.06%	0.01%

a/ Data from Frantz and Beskitt, 1993. The dosage was 113.8 to 151.9 mg/kg.
b/ Values were for the entire exposure period. The remaining dose was in gel removed from the site and skin/water rinses.

III.A.2. Distribution

After oral absorption, radioactivity was detected in all the tissues examined with relatively higher levels in some tissues. In the study by Zdybak and Robinson (1992), the total amount in the tissues was less than 10% of the administered dose (Table 1). Total tissue radioactivity remaining in the tissues after 7 days ranged from 3-6% of dose in males and from 5-10% of dose in females.

Hussain (1980) showed that liver, fat and kidneys contained higher tissue radioactivity than other tissues after oral exposure. Sprague-Dawley male rats (3/group) were given hydramethylnon in corn oil (^{14}C-benzylic or pyrimidinyl position; >96% radiopurity; equivalent to 10 ppm or 74-79 ppm in the diet, 260 *u*g/160 g animal for 10 ppm). There were 5 treated groups for sacrifices at 24 hours, 48 hours, 96 hours, 144 hours, or 216 hours after dosing. One rat from the control group was sacrificed at 24, 96, or 216 hours. Urine and feces samples were collected every 24 hours. At the specified termination time, blood, liver, kidney, muscle tissue and fat tissue were sampled. The highest level of radioactivity was found in the liver for all time points with much lower levels in the muscle and blood (Table 4). In the 10 ppm group, peak tissue level was at 24 hours for all tissues and the half-lives were: 2.1 days in the blood, 2.2 days in the kidney, 2.7 days in the liver, 2.8 days in the muscle, and 4.8 days in the blood. The tissue levels for the 74-ppm/ 79-ppm groups were 4-7 fold higher than that for the 10-ppm group.

With dermal exposure, hydramethylnon was generally not detected in the rat tissues examined (fat, kidneys, liver, lungs and testes) due to low absorption (less than 1% of the administered dose (Sharp, 1993). Radioactivity was detected (0.46% of dose after 10 hours and 0.16% after 336 hours) only in the residual carcass after the 10-hour exposure (Table 2).

Table 4. The distribution of hydramethylnon in the rat after 1 to 9 days of oral exposure.[a]

Compartments	24 hours	48 hours	96 hours	144 hours	216 hours
10 ppm Tissues	**Total Radioactivity (mean, ppm)**				
Liver	0.61	0.44	0.30	0.17	0.13
Fat	0.35	0.25	0.13	0.07	0.05
Kidney	0.28	0.27	0.21	0.13	0.10
Muscle	0.10	0.06	0.05	0.03	0.03
Blood	0.03	0.01	0.01	<0.01	<0.01
10 ppm Excreta	**Cumulative % of Administered Dose (mean)**				
Feces	71.5	81.8	85.0	86.6	88.4
Urine	0.6	0.9	1.2	1.4	1.7
74 ppm Tissues	**Benzylic label-Total Radioactivity (mean, ppm)**				
Liver	2.16	1.97	1.42	NA	NA
Fat	1.16	1.64	NA	NA	NA
Kidney	1.34	1.18	NA	NA	NA
79 ppm Tissues	**Pyrimidinyl label-Total Radioactivity (mean, ppm)**				
Liver	3.45	2.15	NA	NA	NA
Fat	2.13	2.16	NA	NA	NA

a/ Data from Hussain, 1980. NA=% of administered dose for tissues was not provided in the report. Data presented were for the benzylic label.

III.A.3. Metabolism and Excretion

Hydramethylnon was metabolized to a small extent, as less than 1% of the administered dose was converted to metabolites after oral exposure. From the tissues (fat, kidneys, lung and liver) of the high dose group (10 mg/kg), the major labeled component of tissues was parent compound with <1% of the dose as a number of polar, moderately polar, and nonpolar metabolites (Zdybak and Robinson, 1992). The minor metabolites identified were a ketone metabolite (CL 98,724), a benzoate metabolite (CL 71,640), and a pyrimidinone derivative (CL 89,466) (Figure 1).

Hussain (1980) used a 10 ppm (benzylic and pyrimidinyl labels) and a 74-79 ppm dose of hydramethylnon (equivalent to 74 ppm in the diet for the benzylic label, and 79 ppm for the pyrimidinyl label) to study the metabolism of hydramethylnon in rats. Analysis of the tissue samples showed hydramethylnon was the major compound (40-50%) in the liver, fat, and kidneys (Table 4). In the liver, one of the metabolite was CL 98,724 and accounted for 4.7% of the total radioactivity in the tissue. At 48 hours, relatively more CL 98,724 was found (32.2% of total in tissue) as hydramethylnon decreased to 23.6% of the total in tissue. At 96 hours, CL 98,724 continued to decline probably due to elimination since there was no proportional increase in other metabolites. Several unidentified polar metabolites were detected in the fat and kidneys.

Hydramethylnon was excreted primarily unchanged in the feces after either oral (Zdybak and Robinson, 1992) or dermal absorption (Sharp, 1993; Frantz and Beskitt, 1993). In the Hussain study (1980) with rats after oral exposure, the 10-ppm group feces contained 71.5% of

the administered radioactivity (Table 4) with hydramethylnon as 63.5% of the dose and polar metabolites as 5.0% of the dose (Hussain, 1980). Zdybak and Robinson (1992) showed that the elimination of hydramethylnon in the rat was relatively rapid. Most of the label (90% of the radioactivity) was excreted in the feces within 36 hours. Hydramethylnon was the only labeled compound identified in the feces (70-85% of administered doses).

Urinary elimination was about 1-4% of total administered compound. In the rat (10-ppm group), urine (0.6% of the dose) showed no hydramethylnon but several unidentified metabolites by thin-layer chromatography (Hussain, 1980). Zdybak and Robinson (1992) identified two main urinary metabolites: a substituted cinnamic acid (p-trifluoromethyl-, CL 243, 236) and a substituted p-toluic acid (alpha, alpha, alpha-trifluoro, CL 71,640). A slightly lower amount of another metabolite (1(1H)-pyrimidinone, tetrahydro-5,5-dimethyl-, CL 89,466) was detected. The analysis for metabolites was not conducted in the dermal pharmacokinetic study due to low absorption.

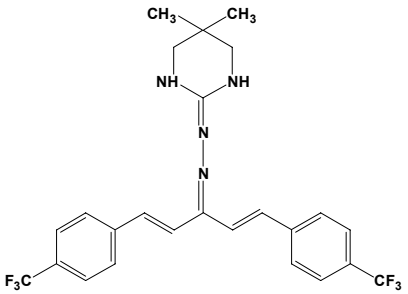
In a study on antidotes and excretion of hydramethylnon (1.8 mg/kg, gavage) in rats, neither the "universal antidote" of charcoal:magnesium oxide:tannic acid (2:1:1) nor magnesium oxide:tannic acid enhanced the excretion (Reichert, 1983). At 12 hours after dosing, the average amount of radioactivity excreted in the feces was 16.4% for no antidote, 21.4% for the universal antidote, and 11.8% for the magnesium and tannic acid mixture. At 24 hours after dosing, the respective percentages in the feces were 92.7%, 69.3%, and 77.4% for the three regiments.

The potential efflux of hydramethylnon from cells via the P-glycoproteins (P-gp)[3] was studied in B16/F10 murine melanoma cells transfected with the human MDR1 gene, which codes for P-gp (Bain and LeBlanc, 1996). Hydramethylnon was shown to bind to P-gp strongly as it caused a greater than 80% inhibition of efflux of the P-gp substrate, doxorubicin. However, additional experiments with cells loaded with hydramethylnon showed that the binding did not enhance transport of hydramethylnon out of the cells (efflux ratio of 1.47 compared to doxorubicin at 7.05).

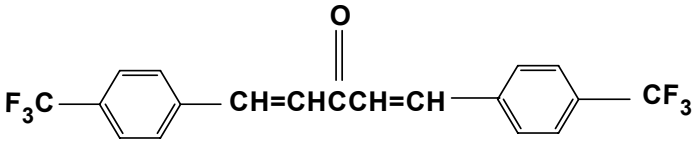
[3] P-glycoproteins are hypothesized to have a role in hormone transport and xenobiotic clearance since these proteins are found in hormone-producing and in hormone-responsive organs as well as in organs of elimination, respectively.

Figure 1. Hydramethylnon and metabolites in rats. [4]

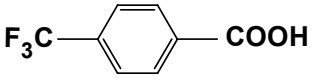
Hydramethylnon



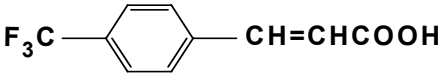
CL 98,724 (1,5-bis (",","-trifluoro-*p*-tolyl)-1,4-pentadien-3-one)- tissues



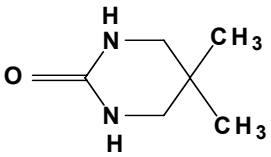
CL 71,640 - tissues, urine



CL 243,236 - urine



CL 89,466 – tissues, urine



[4] Data from Zdybak and Robinson, 1992; Hussain, 1980

III.B. ACUTE TOXICITY

Summary: Hydramethylnon was relatively nontoxic by the oral and dermal routes. The oral LD50s were 1131 to 1300 mg/kg for technical hydramethylnon and >5000 mg/kg for the formulations; the oral Toxicity Category is either III or IV. The dermal LD50s were all greater than 5000 mg/kg with a Toxicity Category of III. Hydramethylnon was not an eye or skin irritant at concentrations tested for the acute responses with the Toxicity Category of III or IV. It was not a skin sensitizer in guinea pigs. After acute oral exposure to non-lethal concentrations, the most common effects in rats were anorexia and decreased body weight gain. With dermal exposure, rabbits showed diarrhea, nasal discharge, ptosis, and lethargy. The clinical signs (decreased activity, labored breathing) observed in rats with inhalation exposure were likely caused by the dust, rather than a direct effect of hydramethylnon.

The following are summaries of acute toxicity studies. Only studies with clinical signs reported by the investigators are described. A list of acute toxicity studies for the technical hydramethylnon and formulations is presented in Tables 6 and 7 (with NOEL/LOEL).

III.B.1. Oral - Rat

Wistar rats (5/sex/dose) were exposed to Combat Ant Control System (1% purity; 5000 mg hydramethylnon/kg by gavage (Moreno, *et al*. 1983a). There were no deaths. Chromorhinorrhea, ptosis, and chromodacryorrhea were observed in 3 males; females were reported to appear normal. The Toxicity Category was IV and this study was considered acceptable to DPR under FIFRA guidelines.

Charles River rats (5/sex/dose) were given a single dose of technical hydramethylnon (91.6% purity; 0, 400, 800, 1600, or 3200 mg/kg) (Fischer, 1979a). The numbers of deaths in each group (from control to the highest dose) were 0/5, 0/5, 0/5, 5/5, and 5/5 for males, and 0/5, 0/5, 0/5, 4/5, and 5/5 for females. Treatment-related effects were reported for all treated groups and included anorexia; decreased weight gain in 2 weeks following exposure; congestion in the liver, kidney, and lungs; and yellow abdominal fat. The acute NOEL was <400 mg/kg. The LD_{50}s were 1131 mg/kg (no 95% limits calculable) for males and 1300 (985-1715) mg/kg for females. The Toxicity Category was III, and this study was considered acceptable to DPR under FIFRA guidelines.

III.B.2. Dermal - Rat

The shaved skin of Charles River rats (4/sex/dose) was exposed to a single dose of technical hydramethylnon (91.6% purity; 5000 mg/kg) for 24 hours (Fischer, 1979a). There were no deaths, and some animals were anorexic. Necropsy showed dark or necrotic livers, congested kidneys, black spots on kidney surface, and yellow abdominal fat. The LD_{50} was > 5000 mg/kg. The Toxicity Category was not determined. This study was not acceptable to DPR because the number of animals tested was less than that required under FIFRA guidelines.

The shaved skin of Sprague-Dawley rats (5/sex/dose) was exposed to a single dose of AC 217,300 Termite Bait Formulation (0.61% hydramethylnon, 4000 mg hydramethylnon/kg) moistened with water for 24 hours (Bradley, 1994a). The application site was occluded. One

animal died, and necropsy showed dark lungs and intestinal tract in this animal. Blood around the nose was observed in the survivors, and 1 survivor showed distended urinary bladder. No gross pathological changes were observed in any animal. The LD_{50} for both genders was greater than 4000 mg/kg and the Toxicity Category was III. This study was considered acceptable to DPR under FIFRA guidelines.

III.B.3. Inhalation - Rat

There were few acute inhalation studies conducted with hydramethylnon since the exposure is expected to be minimal due to its physical-chemical properties (e.g. a solid at room temperature) and the formulation (e.g. in baits and traps).

Sprague-Dawley rats (5/sex/dose) were treated with technical hydramethylnon dust (92% purity; actual concentration 0.6 mg/L) by whole-body inhalation for 4 hours (Voss and Becci, 1982). There were no deaths. Various effects observed were: nasal discharge, pigmented material around nose and eyes, lacrimation, eyelid swelling, decreased activity, urinary incontinence, ataxia, emaciation, and yellow adipose tissue surrounding the ductus deferens and epididymis. The Toxicity Category was not determined, and this study was not acceptable to DPR because the number of doses tested was less than that required under FIFRA guidelines.

Sprague-Dawley rats (5/sex/dose) were exposed to hydramethylnon (98.2% purity) as a dust by whole-body inhalation for 4 hour (Hoffman, 1993). The nominal concentrations were 0, 1.5, 4.9, and 9.7 mg/L with MMAD (GSD) determinations ranging between 1.8-2.2 *u*m (2.6-3.3). The analytical chamber concentrations were 0, 0.98, 2.9, and 4.3 mg/L. The death rates for control to the highest dose were: 0/5, 0/5, 2/5, and 5/5 for males, and 0/5, 0/5, 1/5, 5/5 for females. The deaths occurred from day 2 (one day after dosing) to day 14. During exposure, the animals were observed at 0.25, 0.5, 0.75, 1, 2, 3, and 4 hours into the exposure. For the 2.9 and 4.3 mg/L groups, some animals could not be observed because the chamber was too clouded with the dust. Clinical signs observed during and post-exposure included closed eyes, labored breathing or gasping, decreased activity, and others (rales, excessive salivation, emaciation, anogenital staining, decreased fecal volume, soft stool) (Table 5). Yellow/brown material (likely due to the dust) was noted on the fur and on the face. The signs were observed primarily during the first week after exposure with fewer signs reported in the second week. All treated groups showed weight losses or decrements in weight gain during the first week post dose. All survivors gained weight during the second week. No treatment-related findings were evident upon necropsy. The LC_{50} were 3.1 (2.0-4.6) mg/L for males, and 3.4 (2.2-5.2) mg/L for females. The combined LC_{50} was 2.9 (2.3-3.7) mg/L. The acute NOEL was <0.98 mg/L, but the effects were likely to be due to the dust rather than hydramethylnon itself. The toxicity category was IV, and the study was considered acceptable to DPR according to FIFRA guidelines.

Table 5. Effects of hydramethylnon dust in rats after acute inhalation exposure.

Signs	Analytical Concentration in mg/L			
	0	0.98	2.9	4.3
During Exposure[b]				
Eyes closed	0/10	0/10	4/5**	0/5
Labored breathing	0/10++	0/10	5/5**	5/5**
Decreased activity	0/10	10/10	0/5	5/5
Yellow material on fur	0/10	10/10	5/5	0/5
Gasping	0/10	3/10	2/5	2/5
1 Day After Exposure[c]				
Eyes closed	0/10++	0/10	2/10	6/10**
Labored breathing	0/10++	2/10	10/10**	10/10**
Decreased activity	0/10++	0/10	5/10**	7/10**
Yellow material on fur	0/10++	10/10**	10/10**	10/10**
Yellow anogenital stain	0/10++	0/10	7/10**	8/10**
Decreased fecal volume	0/10++	0/10	0/10	9/10**

a/ Data from Hoffman, 1993. *,** significance of $p<0.05$ and $p<0.01$ by the Fisher's exact test; ++, significance at $p<0.01$ by the Cochran-Armitage trend test.

b/ Incidences were for both genders and expressed as the maximum number of animals affected/ total examined during observation period. During exposure, the animals were observed at 0.25, 0.5, 0.75, 1, 2, 3, and 4 hours during exposure. For 2.9 and 4.3 mg/L, the number of animals observed was 5 instead of 10 because some could not be observed because the chamber was too clouded with hydramethylnon dust.

c/ The animals were observed daily for 14 days after exposure. Only the data for day 1 post exposure is presented in this Table.

III.B.4. Dermal - Rabbit

Albino rabbits (strain not specified, 5/sex/dose) were dermally exposed to Combat Ant Control System (1% hydramethylnon; at 2 g hydramethylnon/kg body weight) for 24 hours (Moreno *et al*., 1983b). There were no deaths. The females were more affected than the males and were observed to have diarrhea, few feces, yellow nasal discharge, ptosis, and lethargy. Only one male was affected and had yellow nasal discharge. One female with diarrhea and few feces for 7 days also had weight loss. Anogenital area soiling (females) and yellow coloration (both genders) of treated skin were also noted. The Toxicity Category was III and this study was considered acceptable to DPR under FIFRA guidelines.

Table 6. The acute toxicity of technical hydramethylnon and formulations.[a]

Study/ Species	Gender	LD_{50} Concentration (mg/kg)	Category	Other Effects	References
Technical (92-98% hydramethylnon)					
Oral/Rat	M&F	1131-1300 mg/kg	III	Anorexia; decreased weight gain; congestion in liver, kidney, and lungs; yellow abdominal fat.	*Fischer, 1979a
Dermal/ Rat	M&F	> 5000 mg/kg	(not enough animals tested)	Anorexia, dark or necrotic livers, congested and spotted kidneys, yellow abdominal fat.	Fischer, 1979a
Inhalation/ Rat	M&F	> 0.6 mg/L M:3.1 (2.0-4.6)mg/L F: 3.4 (2.2-5.2)mg/L	(only 1 dose tested) IV	Irritation, decreased activity, urinary incontinence, ataxia, yellow fat, and others Eyes closed, labored breathing, decreased activity, and other effects	Voss and Becci, 1982 *Hoffman, 1993
Eye irritation/ Rabbit	M	NA	III	Corneal opacity and conjunctivitis clearing completely by 48 hours, no iritis	*Fischer, 1979a
Dermal irritation/ Rabbit	M	NA	IV	Erythema cleared by 72 hours	*Fischer, 1979a
Dermal sensitization/ Guinea pig	M	NA	NA	Not a sensitizer	Siglin and Becci, 1982
Hydramethylnon - 3.2% concentrate					
Dermal sensitization/ Guinea pig	M	NA	NA	Not a sensitizer	Siglin and Becci, 1982
Amdro Fire Ant - 2.93% oil concentrate					
Oral/Rat	M&F	> 5000 mg/kg	IV	No effect	*Fischer, 1980e
Eye irritation/ Rabbit	M	NA	IV	Conjunctival irritation, cleared	* Fischer, 1980e
Dermal irritation/ Rabbit	M	NA	(need more data)	Erythema, cleared	Fischer, 1980e

a/ *after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines.

Table 6 (continued). The acute toxicity of technical hydramethylnon and formulations.[a]

Study/ Species	Gender	LD_{50} Concentration (mg/kg)	Category	Other Effects	Reference
Hydramethylnon 2.5% in oil					
Eye irritation/ Rabbit	M	NA	IV	No effect	*Fischer, 1979b
Dermal irritation/ Rabbit	M	NA	IV	No effect	*Fischer, 1979b
Maxforce 2% gel					
Oral/Rat	M&F	> 5000 mg/kg	IV	No effect	*Fischer, 1985a
Dermal/ Rabbit	M&F	> 2000 mg/kg	III	No effect	*Fischer, 1985b
Eye irritation/ Rabbit	M&F (not specified)	NA NA	IV (0bservation too short)	Conjunctivitis, cleared by 24 hours No irritation	*Glaza, 1993 Fischer, 1985c
Dermal irritation/ Rabbit	M	NA	IV	Intact- no irritation abraded-edema, erythema and cleared by 144 hours	*Fischer, 1985d
Dermal sensitization/ Guinea Pig	M	NA	NA	Not a sensitizer	Reilly, 1988
Maxforce Pharaoh Ant Killer (1-0.9% hydramethylnon)					
Oral/Rat	M&F	> 5000 mg/kg	IV	No effect	*Gabriel, 1987
Dermal/ Rabbit	M&F	> 2000 mg/kg	III	Local irritation	*Minton, 1987
Eye irritation/ Rabbit	(not specified)	NA	IV	Redness	*Reilly, 1987a
Dermal irritation/ Rabbit	(not specified)	NA	(chemical not moistened)	No effect	Reilly, 1987b
Combat Fir Ant Killer (0.88% hydramethylnon)					
Oral/Rat	M&F	> 5000 mg/kg	IV	No effect	Fischer, 1980a
Dermal/ Rabbit	M&F	> 2000 mg/kg	III	No effect	Fischer, 1980b
Eye irritation/ Rabbit	M	NA	IV	No effect	Fischer, 1980c
Dermal irritation/ Rabbit	M	NA	IV	No effect	Fischer, 1980d

a/ *after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines.

Table 6 (continued). The acute toxicity of technical hydramethylnon and formulations.[a]

Study/ Species	Gender	LD_{50} Concentration (mg/kg)	Category	Other Effects	Reference
Combat Ant Control System (1% hydramethylnon)					
Oral/Rat	M&F	> 5000 mg/kg	IV	Chromorhinorrhea, ptosis, chromodacryorrhea	*Moreno *et al*., 1983a
Dermal/ Rabbit	M&F	> 2000 mg/kg	III	Diarrhea, few feces, yellow discharge, ptosis, lethargy	*Moreno *et al*., 1983b
Eye irritation/ Rabbit	(not specified)	NA	III	Irritation, cleared	*Moreno *et al.*, 1983c
Dermal irritation/ Rabbit	M&F	NA	IV	Erythema, cleared	*Moreno *et al.*, 1983d
Termite bait formulation					
Oral/Rat	M&F	> 5000 mg/kg	IV	No effect	*Bradley, 1994b
Dermal/Rat	M&F	> 4000 mg/kg	III	Blood around nose, darkened lungs and intestinal tract	*Bradley, 1994a
Eye irritation/ Rabbit	M	NA	III	Iritis, conjunctival irritation, both cleared later	*Boczon, 1994a
Dermal irritation/ Rabbit	M	NA	IV	No effect	*Boczon, 1994b

a/ *after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines.

Table 7. The No-Observed-Effect Level (NOEL) and Lowest-Observed-Effect Level (LOEL) for nonlethal acute toxicity of technical hydramethylnon.[a]

Species/ Route	Duration	NOEL/ LOEL (ppm)	NOEL/ LOEL (mg/kg/day)	NOEL/ LOEL (absorbed mg/kg/day)[b]	Effects at LOEL	Ref
Oral (technical hydramethylnon)						
Rat/ gavage	single dose	NA	<400/400	<40/40	Anorexia, ↓weight gain, congestion in liver, kidney, and lung	1*
Rat/ gavage	**daily x 5 doses**	**NA**	**3/ 30**	**0.3/ 3**	**↓ Body weight gain (61% of control), perianal area and bloody nasal discharges, ↓ fertility (↓ testes weight at 90 mg/kg/day)**	**2**
Rat/ gavage	daily gd 6-15	NA	10/ 30 3/ 10	1/ 3 0.3/ 1	Fetal: ↓ body weight and ossification variations Maternal: ↓ body weight, clinical signs (red nasal mucous, alopecia, soft stools and anogenital staining at 30 mg/kg/day)	3*
Rabbit/ gavage	daily gd 6-18	NA	10/ 20 5/ 10	1/ 2 0.5/ 1	Fetal:↓ body weight Maternal:↓ body weight, abortion, and clinical signs (reduced or soft stools, matting and/or discharge in anogenital region)	4*
Dermal (formulation: ant control system)						
Rabbit	24 hours	NA	<2000/2000	<100/ 100	Diarrhea, nasal discharge, ptosis, and lethargy	5*
Rabbit	**6 h/d, 5d/w x 21 days**	**NA**	**50/250**	**1.8/8/9**	**↓ food consumption by day 4 (females)**	**6***
Inhalation (dust)						
Rat	4 hours (whole body)	<0.98 mg/L / 0.98 mg/L	NA	NA	↓Activity, labored breathing	7*

a/ * indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Fischer, 1979a; 2. Harnois, 1979 under **III.E.GENOTOXICITY**; 3. Bio/dynamics, Inc., 1979; 4. IRDC, 1982d; 5. Moreno *et al*., 1983b; 6. Thompson, 1982; 7. Hoffman, 1993. Bio/dynamics, Inc., 1979 and IRDC, 1982 d are described under **III.G. DEVELOPMENTAL TOXICITY**. NA=not applicable, gd=gestational day. Bolded study is selected as the critical study for risk characterization.

b/ The absorbed doses were based on 10% and 5% oral and dermal absorption factors, respectively, and amortized for daily dosing.

III.C. SUBCHRONIC TOXICITY

Summary: After subchronic oral exposure, the testis was the main target organ for hydramethylnon toxicity in rats and dogs. The testicular lesions included tubular degeneration or vacuolation, presence of giant cells, cellular debris in the epididymis, and testicular atrophy. The testicular effect was not related to the decreased food consumption and body weights observed in these species. After subchronic dermal exposure, decreased food consumption and body weight, and increased relative liver weights were reported in rabbits. A summary of the subchronic toxicity studies is presented in Table 14.

III.C.1. Oral - Rat

Charles River rats (3/sex/dose) were given hydramethylnon (91.6% purity; 0, 50, 100, 200, 400 or 800 ppm) in the diet for 28 consecutive days (Fischer, 1979c). The average dosages for both genders (male/female) were: 0, 5.6/5.8, 10.3/11.4, 18.7/18.9, 31.5/30.4, and 46.9/46.8 mg/kg/day. The 800-ppm group was moribund and was sacrificed at the end of the second week. The 200-ppm to 800-ppm groups were anorexic and had significantly decreased food consumption all through the study (Table 8). As a result, the body weights and body weight gains of these animals were significantly reduced for some weekly measurements. At 200 ppm and at week 1, the body weights were 90% (males, $p<0.05$) and 88% (females) of controls (Table 8). At the same time period, the body weights of the 400-ppm group were 67% (males, $p<0.05$) and 72% (females, $p<0.05$) of controls. At four week, only the body weight for the 400-ppm group was significantly different from the controls. The body weight of the 200-ppm level recovered in the later weeks. The 100-ppm male group showed slight reduction in food consumption (85% of control, statistically significant only for week 2), associated with a slight but non-significant reduction in body weights.

The liver (males) and kidney (both genders) organ weights of the 400-ppm and 800-ppm groups were decreased ($p<0.05$) (Table 8). Microscopic examination showed the testis with dose-related increase in incidences for focal tubular degeneration and the presence of giant cells[5] in the 200 to 800 ppm males (Table 8). Tubular atrophy and aspermiogenesis were noted in one male at 400 ppm, and one male at 800 ppm, respectively.

For this study, the NOEL for decreased food consumption was 50 ppm (5.6 mg/kg/day) for slight but statistically significant reduction for the 100-ppm males on week 2. For other effects, the NOEL was 100 ppm (10.3 mg/kg/day) for testicular effects at the LOEL of 200 ppm (18.7 mg/kg/day) and higher concentrations. This study pre-dated modern guidelines, and did not address standard data requirements. This study was considered by DPR as a supplemental study, suitable mainly as a range-finding study.

[5] Multinucleated giant cells represent fused spermatid nuclei and are presented in affected tubules particularly in the early stage of degeneration.

Table 8. Effects of hydramethylnon (50 to 800 ppm) in rats after dietary exposure for 4 weeks.[a]

Effects	Concentration in ppm (*mg/kg/day, male/female)*					
	0 *(0)*	**50** *(5.6/5.8)*	**100** *(10.3/11.4)*	**200** *(18.7/18.9)*	**400** *(31.5/30.4)*	**800[b]** *(46.9/46.8)*
Males						
Food consumption (g/day)						
Week 1	22	22	19 (86%)	17* (77%)	10* (45%)	7* (32%)
Week 2	26	26	22* (85%)	19* (73%)	11* (42%)	6* (23%)
Week 3	29	29	25 (86%)	23* (79%)	13* (45%)	NA
Week 4	27	29	24 (89%)	23 (85%)	13* (48%)	NA
Body weight (g)						
Week 1 (% control)	193	193	182	173* (90%)	129* (67%)	103* (53%)
Week 2 (% control)	243	247	228	223 (92%)	149* (61%)	99* (41%)
Week 3 (% control)	296	303	274	272 (92%)	167* (56%)	NA
Week 4 (% control)	330	348	312	321 (97%)	189* (57%)	NA
Liver weight (g)	10.62	13.11	10.79	10.06	7.15*	4.92*
Kidney weight (g)	2.48	2.71	2.21	2.41	1.57*	1.13*
Testis-						
Degeneration	0/3++	0/3	0/3	2/3	3/3*	2/3
Giant cells present	0/3++	0/3	0/3	3/3*	3/3*	2/3
Tubular atrophy	0/3	0/3	0/3	0/3	1/3	0/3
Focal aspermiogenesis	0/3	0/3	0/3	0/3	0/3	1/3
Females						
Food consumption (g/day)						
Week 1	17	16	16	12* (71%)	8* (47%)	5* (29%)
Week 2	20	18	16	14* (70%)	9* (45%)	6* (30%)
Week 3	20	21	19	14* (70%)	9* (45%)	NA
Week 4	19	19	18	15* (79%)	9* (47%)	NA
Body weight (g)						
Week 1 (% control)	147	143	137	129 (88%)	106* (72%)	88* (60%)
Week 2 (% control)	169	159	154	146 (86%)	115* (68%)	86* (51%)
Week 3 (% control)	188	181	174	167 (89%)	119* (63%)	NA
Week 4 (% control)	206	200	187	182 (88%)	131[c] (64%)	NA
Liver weight (g)	6.37	7.33	6.84	5.85	5.72	5.45
Kidney weight (g)	1.55	1.64	1.51	1.46	1.15	0.98*

a/ Data from Fischer, 1979c. * denotes significance at $p<0.05$ based on analysis from the report. ++ denotes significance at $p<0.01$ based on Cochran-Armitage Trend test.

b/ NA=data not available because the animals were sacrificed after 2 weeks of exposure.

c/ In the report, this result was considered significant in one page but not in another page depending on the tests used. The means were quite different, but one 400-ppm female had nearly normal body weight, hence group differences were near to significance at the 95% confidence interval. A treatment effect was assumed by DPR.

Charles River rats (6/sex/dose) were given hydramethylnon (91.6% purity; 0, 25, 50, 75, or 100 ppm) in the diet for 28 consecutive days (Fischer, 1979d). The average dosages for both genders (male/female) were: 0, 3.2/3.3, 6.4/6.6, 9.2/9.5, and 12.3/12.7 mg/kg/day. There were no effects reported for the 25 ppm to 75-ppm groups. The weekly food consumption of the 100-ppm groups was in general lower than the controls but statistically significant only during some weeks (Table 9). While the absolute body weights showed no treatment effect, the body weight gains of the female rats were lower (statistically significant on weeks 1 and 2 but not other weeks) than the control (Table 9). For the 100-ppm females, the average gains were 35g and 30 g for weeks 1 and 2, respectively, compared to 41 g for controls for the same weeks. There were no histological effects in any of the organs (including the testes) examined. The NOEL was 75 ppm (average of 9.4 mg/kg/day for both genders) based on decreased food consumption and body weight gain at 100 ppm (average, 12.4 mg/kg/day). This study pre-dated modern guidelines, and did not address standard data requirements.

Table 9. Effects of hydramethylnon (25 to 100 ppm) in rats after dietary exposure for 4 weeks.[a]

Effects	**Concentration in ppm *(mg/kg/day, male/female)***				
	0 *(0)*	**25** *(3.2/3.3)*	**50** *(6.4/6.6)*	**75** *(9.2/9.5)*	**100** *(12.3/12.7)*
Males					
Food consumption (g)					
Week 1	17	18	18	17	16 (94%)
Week 2	22	21	20	20	19* (86%)
Week 3	26	24	24	23	22 (85%)
Week 4	28	26	27	24	25 (89%)
Body weight gain (g)					
Week 1	50	52	51	51	47
Week 2	53	53	51	52	49
Total	183	208	198	200	194
Females					
Food consumption (g)					
Week 1	15	15	16	14	15 (100%)
Week 2	18	18	17	16	15 (83%)
Week 3	19	19	19	18	16* (84%)
Week 4	18	19	19	17	16 (89%)
Body weight gain (g)					
Week 1	41	41	42	39	35* (85%)
Week 2	41	41	34	34	30* (73%)
Total	118	128	119	112	102 (86%)

a/ Data from Fischer, 1979d. * denotes significance at $p<0.05$ based on analysis from the report.

The possible association between food consumption and testicular effects after hydramethylnon exposure was studied in maturing (Fischer, 1980f) and mature rats (Fischer, 1980g). Maturing Charles River male rats (12/group; body weight 94-101 g) were given hydramethylnon (91.6% purity; 0, 200, or 400 ppm) in the diet for four weeks (Fischer, 1980f). The mean dosages were 0, 20.3 mg/kg/day or 34.8 mg/kg/day. There were 3 control groups: unrestricted diet control, restricted diet at the level as the 200-ppm group, and restricted diet at the 400-ppm group. After treatment, 6 rats per group were sacrificed for histological studies, and the other 6 were allowed to recover in unrestricted diet for 4 weeks before sacrifice. By the first week, there were marked, dose-related decreases in food consumption and reduced body weight and body weight gains in the restricted diet controls and treated groups (Table 10). During the treatment phase, food consumption rates were 77% and 53% of control for 200 ppm and 400-ppm groups, respectively. The bodyweight gains were 81% and 45% of controls for the 200-ppm and 400 ppm groups. Paired-feeding controls (noted as 0 and 200 ppm diet, and 0 and 400 ppm diet) had comparable weight gain decrements. During recovery, these treated rats consumed similar amounts as the controls, and the body weights for all groups were similar. The absolute weights of some organs (liver, kidney, and testes) were significantly reduced in the treated groups and dietary restricted groups; this finding was associated with the decreased body weights and reduced food consumption (Table 10).

Lesions observed at the end of the treatment period included the presence of spermatid giant cells in testes and cellular debris within epididymal tubules in 200 and 400 ppm groups, and focal hepatic cell cytoplasmic degeneration in 400 ppm rats (Table 10). There was no corresponding pathology in two restricted feed groups. After the recovery period (4 weeks untreated and on unrestricted diet), there was no residual hepatic effect, but gonadal toxicity progressed to dose-related testicular tubular atrophy and altered or damaged germ cells. While focal tubular vacuolation of the spermatocytes was only observed in the 200-ppm rats, the 400-ppm group showed seminiferous tubules lined by early germinal and/or Sertoli cells only. Additional finding at 400 pm was aspermiogenesis (1/6). These results showed that the gonadal effects were not related to decreased food consumption and lower body weight gain. In addition, these effects elicited during the treatment phase progressed beyond the period of treatment. Recovery of the livers appeared to be complete after 4 weeks on the unrestricted diet (Table 10). The NOEL was <200 ppm (<20.3 mg/kg/day) for reduction in food consumption and body weights, and testicular effects at 200 ppm (20.3 mg/kg/day).

Table 10. Effect of hydramethylnon in maturing rats after dietary exposure for 4 weeks.[a]

Effects	**Concentration in ppm *(mg/kg/day)***				
	0 and diet unrestricted	**0 and 200 ppm diet[a]**	**0 and 400 ppm diet[a]**	**200 ppm *(20.3)***	**400 ppm *(34.8)***
Food Consumption (mean for all weeks, g/rat/day)					
Treatment phase (% control)	22.8	17.6	12.1	17.5 (77%)	12.0 (53%)
Recovery phase	26.5	27.6	26.8	27.6	24.5
Body Weight during treatment phase					
Body weight gain Week 1 Total for 4 weeks (% of control)	 54±5.3 206.0±17.8	 39.2±4.5* 148.0±10.6* (72%)	 18.0±3.6* 86.5±16.4* (42%)	 40.6±6.6* 167.1±22.4* (81%)	 18.4±3.6* 91.8±25.0* (45%)
Terminal body weight (g) during treatment phase	304.3±20.2	241.5±8.7*	173.2±8.4*	255.7±17.4*	195.2±33.1*
Organ Weights (g) during treatment phase					
Liver	14.127±1.839	8.804±0.911*	6.241±0.597*	11.781±1.348*	8.929±1.362*
Kidney	2.390±0.267	1.961±0.292*	1.378±0.100*	2.231±0.329	1.807±0.297*
Testes	2.614±0.365	2.808±0.224	2.529±0.146	1.807±0.297*	2.529±0.146
Microscopic Lesions after Treatment					
Testis Spermatid giant cells	 0/6++	 0/6	 0/6	 4/6**	 4/6**
Epididymis Cellular debris	 2/6++	 0/6	 0/6	 6/6**	 6/6**
Liver Cytoplasmic degeneration	 0/6++	 0/6	 0/6	 0/6	 6/6**
Microscopic Lesions after Recovery Phase[b]					
Testis Tubular atrophy Spermatid giant cells Focal tubular vacuolation Aspermiogenesis	 0/6++ 0/6++ 0/6 0/6+	 0/6 0/6 0/6 0/6	 0/6 0/6 0/6 0/6	 1/6 5/6** 5/6** 0/6	 6/6** 5/6** 0/6 1/6
Epididymis Cellular debris Spermatozoa in tubules	 0/6++ 6/6	 0/6 6/6	 0/6 6/6	 6/6** 6/6	 6/6** 2/6
Liver Cytoplasmic vacuolation	 1/6	 1/6	 0/6	 2/6	 0/6

a/ Data from Fischer, 1980f. 200 ppm diet= controls were restricted to the same food intake as the 200 ppm treatment group. 400 ppm diet= controls were restricted to the same food intake as the 400 ppm treatment group. *,** denote significance at $p<0.05$ and $p<0.01$, respectively, based on Fisher's Exact test. +,++ denote significance at $p<0.05$ and $p<0.01$, respectively, based on Cochran-Armitage trend test.

b/ During recovery, the animals were not treated and were placed on unrestricted diet for 4 weeks.

Fischer (1980g) conducted another experiment with mature rats (351 to 368 g) using the same protocol (Fischer, 1980f). The dosages were 11 and 17 mg/kg/day for the 200 and 400-ppm groups. Body weight decrements were dose related but generally not as marked as those for the maturing rats shown in Table 10. The 200-ppm and 400-ppm group mean weights at the end of treatment were 427 g and 359 g compared to 461 g for controls. Restricted feed control body weights were similar to the respective treatment groups. Other effects such as organ weight changes and gonadal effects were limited to the 400-ppm group. The microscopic lesions observed in the 400-ppm males were spermatid giant cells in testes, cellular debris (composed of spermatids and spermatocytes) in the epididymides, prostate atrophy, and focal hepatic cell cytoplasmic eosinophilic degeneration. Lesions observed at the end of the recovery phase were tubular atrophy (400-ppm group) and cellular debris (composed of spermatids and spermatocytes) in the epididymides (200 and 400-ppm groups, slightly greater degree in the latter group). Livers appeared normal after the recovery period. These results from mature rats confirmed previous findings (Fischer, 1980f) that gonadal effects were irreversible and a direct effect of hydramethylnon, not a secondary effect due to decreased food consumption. The LOEL was 200 ppm (11 mg/kg/day) for testicular effects.

Sprague-Dawley rats (20/sex/group except for 19 for 100 ppm males, and 21 for 100 ppm females due to misidentification) were given hydramethylnon (92% purity; 0, 50, 100, 200 or 400/25 ppm) in the diet for 91 days (Tegeris, 1979). The estimated achieved dosages for the 50, 100, and 200-ppm groups were 4.5, 8.6, and 17.0 mg/kg/day in males, and 5.0, 9.6, and 19.1 mg/kg/day in females. The dosage for the 400/ 25-ppm group was not calculated because this group was initially fed 400 ppm but was reduced to 25 ppm after 2 weeks. No treatment-related clinical signs or effects in the clinical chemistry, hematology, or urinalysis were observed in the treated groups at 200-ppm to 400/25-ppm diets. Food consumption and body weight were consistently decreased, although not for all weeks, in the 200-ppm group (Table 11). After 13 weeks at 200 ppm, body weight decrements were 88% (male) and 86% (female) of controls. Food consumption and body weights (week 1 data) were markedly affected at 400 ppm, but showed recovery when the dose was reduced to 25 ppm (week 7 and 13 data).

All organ weights were similar to the controls, except for ovary and testes. The ovarian weights were statistically significantly elevated at 100-200 ppm, with no associated histopathology. In the treated males, the absolute testicular weight (statistically significant at $p<0.05$), testicular weight relative to body weight ratios, and testicular weights relative to brain weight ratios were all reduced (Table 11). Except for the 400/25-ppm group, the reduction was dose-related with testicular weight at 89%, 66%, and 57% of control for 50 ppm, 100 ppm, and 200 ppm, respectively. Histopathological examination showed testicular atrophy in all treated groups. The relatively high incidence in the 400/25-ppm group was likely due to the higher exposure (400 ppm during the first two weeks). The Medical Toxicology Data Reviewer concurred with the author's conclusion of congenital atrophy in the 50 ppm male. The NOEL was <50 ppm with a LOEL at 50 ppm (4.5 mg/kg/day) based on decreased testicular weight at this dose and testicular atrophy at the higher doses. While this study did not meet current guidelines for a subchronic study, it did provide useful data for DPR. The U.S. EPA established 50 ppm as the NOEL for this study based on decreased testicular weight, and testicular atrophy in males at 100 ppm. The dosages calculated by the U.S. EPA were 2.5, 5.0, 10, and 20/1.25 mg/kg/day for 50, 100, 200, and 400/25 ppm, respectively.

Table 11. Effects of hydramethylnon in rats after dietary exposure for 91 days.[a]

Effects	**Hydramethylnon Concentration in ppm *(mg/kg/day, male/female)***				
	0 *(0)*	**50** *(4.5/5.0)*	**100** *(8.6/9.6)*	**200** *(17.0/19.1)*	**400/25[b]** *(NA)*
Males					
Food consumption in g/rat/week					
Week 1 (% control)	122	120 (98%)	118 (97%)	99* (81%)	79* (65%)
Week 7	190	190	185	168*	198
Week 13 (% control)	165	180*(109%)	182*(110%)	157 (95%)	183*(111%)
Body weight (g)					
Week 1	137	133	133	122*	97*
Week 7	365	337*	353	312*	318*
Week 13	440	435	454	385* (88%)	439
Testicular weight, g (% control)	3.37	3.00* (89%)	2.24* (66%)	1.25* (57%)	2.21* (66%)
Testes/brain ratio	1.56	1.442	1.077	0.576	1.028
Testes/body weight ratio	7.659	7.299	5.234	3.333	5.300
Testicular, bilateral atrophy (all grades)	0/20++	1/19[c]	5/19*	20/20**	5/20
Females					
Food consumption in g/rat/week					
Week 1 (% control)	126	118 (94%)	118 (94%)	108*(86%)	91* (72%)
Week 7	129	136	128	128	149*
Week 13 (% control)	114	128*(112%)	128*(112%)	114(100%)	135*(118%)
Body weight (g)					
Week 1	127	126	124	113*	97*
Week 7	212	210	215	185*	203
Week 13	242	249	247	209* (86%)	243
Ovary weight, g (% control)	0.06	0.07	0.09* ((150%)	0.08*(133%)	0.07

a/ Data from Tegeris, 1979. Food consumption was measured weekly but only data for weeks 1, 7 and 13 are shown in this Table. * denotes significance at $p<0.05$ based on analyses in the report. *,** denote significance at $p<0.05$ and $p<0.01$, respectively, by Fisher's Exact test; ++ denotes significance at $p<0.01$ by Cochran-Armitage trend test but does not include the incidence at 400/25 ppm.

b/ This group was given a 400-ppm diet for the first 2 weeks and then 25 ppm for the rest of the study. NA=dosages were not determined.

c/ This incidence included the animal with severe, unilateral, congenital testicular atrophy with calcification.

III.C.2. Dermal - Rabbit

New Zealand rabbits (10/sex/group) were exposed to hydramethylnon (91.6% purity; in oleic acid, 10, 50, or 250 mg/kg) dermally 6 hours per day, 5 days per week, for 21 days (Thompson, 1982). The application area was approximately 10-15% of the total body surface, and the site for half of the animals per group was abraded weekly. One animal (10 mg/kg) died on day 11. There were no treatment-related effects in clinical observations. By day 4, feed consumption was reduced in the 250 mg/kg/day groups (96% of control for males, and 78% of control for females and significant at $p<0.05$) (Table 12). For days 19 to 21, the consumption rates were 71% (male) and 58% (female) of the controls. The average body weights for each group, including the controls, showed some fluctuation during the study. Most of them showed decreased body weights from pre-test to day 4, and day 19 to day 22. The final body weight of the 250 mg/kg groups were about 90% of control for two time periods (day 19 and day 22). The occasional decrease in food consumption in the 50 mg/kg/day female was considered a reflection of an unusually high control value (480 g for days 7 to 9) compared to other days.

Clinical chemistry and hematology showed a statistically significant decrease of platelet counts (females) and increase of cholesterol levels (males) in the 250 mg/kg/day; these were considered incidental findings. Relative liver organ weights were significantly ($p<0.05$) increased at the high dose (Table 12). The only treatment-related lesions were those found in the skin, and they included erythema, edema, atonia, coriaceousness, desquamation, fissuring, blanching, and subcutaneous hemorrhage. These skin effects might have been due to the vehicle as dermal irritation with various degrees of severity was found in all groups, including the control. Macroscopic examinations showed the application area as thickened, crusted, matted, and reddened. Microscopic examination of the skin showed acanthosis, hyperkeratosis, sloughing, degeneration/necrosis, edema, and inflammation. The incidences and severity of these effects were considered not dose-related as they were lower and milder at the highest dose. No histopathological lesions were found in non-dermal tissues (including the gonads); the finding of splenic congestion (5 high dose females versus 0 control females) was considered incidental. The NOEL was 50 mg/kg/day based on reduced food consumption and body weights, and increased relative liver weights. This study was considered acceptable to DPR. The U.S. EPA determined a NOAEL of 250 mg/kg/day for the study and noted the decreased food consumption (38% and 45% in males and females, respectively) and body weights (8% and 9% less than controls, respectively) at this dose, the high dose tested.

Table 12. Effects of hydramethylnon in rabbits after dermal exposure for 21 days.[a]

Effects	Concentration in mg/kg							
	Males				Females			
	0	10	50	250	0	10	50	250
Food consumption (g)								
Day 1-3	481	423	430	468	433	434	408	413
(% control)	(100%)	(88%)	(89%)	(97%)	(100%)	(100%)	(94%)	(95%)
Day 4-6	419	433	451	402	437	432	395	341*
(% of control)	(100%)	(103%)	(108%)	(96%)	(100%)	(99%)	(90%)	(78%)
Day 7-9	463	424	453	401	480	433	403*	324**
(% control)	(100%)	(92%)	(98%)	(87%)	(100%)	(90%)	(84%)	(68%)
Day 13-15	477	486	463	297**	475	431	400	298**
(% control)	(100%)	(102%)	(97%)	(62%)	(100%)	(91%)	(84%)	(63%)
Day 19-21	339	327	325	242**	312	262	279	180*
(% control)	(100%)	(96%)	(96%)	(71%)	(100%)	(84%)	(89%)	(58%)
Body weight (g)								
Pre-test	2785	2767	2742	2743	2743	2722	2649	2679
Day 4	2778	2733	2738	2753	2709	2713	2622	2648
Day 19	2998	2912	2956	2766*	2907	2908	2777	2666*
(% of control)	(100%)	(97%)	(99%)	(92%)	(100%)	(100%)	(96%)	(92%)
Day 22	2944	2896	2891	2721*	2846	2846	2726	2586*
(% of control)	(100%)	(98%)	(98%)	(92%)	(100%)	(100%)	(96%)	(91%)
Organ weight								
Liver weight (absolute, g)	83	88	88	93	85	82	82	91
Liver weight (relative, % body weight)	2.82	3.04	3.04	3.44*	2.99	2.87	3.00	3.52**

a/ Data from Thompson, 1982. *,** Significant, $p<0.05$ and $p<0.01$, respectively from the report. Body weight was measured on day 4, 7, 10, 13, 16, 19, and 22. There were no statistically significant changes ($p<0.05$) in the measurements for days 4 to 16 and data were not shown in this Table.

III.C.3. Oral - Dog

Purebred beagles (4/sex/group) were given hydramethylnon (92% purity; 0, 3, 6, or 12 mg/kg/day) daily in gelatin capsules for 91 days (American Cyanamid Company, 1979). Clinical chemistry, hematology, and urinalysis were not affected by the treatment. There were several deaths during the study (Table 13). In the 6 mg/kg/day groups, there were only one male and one female survivors at week 11. At 12 mg/kg/day, there were also only one male and one female survivor at weeks 6 and 7, respectively.

Males and females in the 3 mg/kg/day group generally consumed less food than controls (Table 13). Occasionally statistically significant decrements were observed in this group when evaluated on a weekly basis. By week 2, females dosed with 6 or 12 mg/kg/day were consuming far less than other groups. Males dosed with 6 mg/kg/day consumed significantly less than controls on week 4, and generally consumed less (some statistically significant) from that point on. The 12 mg/kg/day males consumed significantly less than controls on week 3, and by week 5 were consuming only 4% of the amount by the controls. Body weights of the 3 mg/kg/day groups did not vary significantly from controls. Higher dose groups lost weight until moribund sacrifices. Clinical signs reported for the 6 and 12 mg/kg/day groups included deteriorating conditions marked by mild tremors, occasional convulsions in moribund animals, inactivity, and emaciated appearance (Table 13). The earliest sign reported was inactivity and emaciated on day 15 in a 12 mg/kg/day female.

Histopathological examination showed all 6 and 12 mg/kg/day males with mild to moderate bilateral testicular atrophy (Table 13). This was considered by investigators to be a result of starvation rather than a primary toxic effect. However, this hypothesis was proved incorrect, at least in rats, since experiments with restricted diets showed testicular effects was not related to reduced food consumption (Fischer, 1980 f and g). The LOEL was 3 mg/kg/day based on decreased food consumption and body weight gain, and testicular effect at higher doses. The study was considered acceptable to DPR under FIFRA guidelines. In the 1988 RED, U.S. EPA designated 3 mg/kg/day, the lowest dose tested, as the LOAEL based on decreased food consumption and body weight gain, and stated that a NOAEL was not established (U.S. EPA, 1988a). However in the notice for pesticide tolerance (U.S. EPA, 2003), the 3 mg/kg/day dose was considered the NOAEL with the LOAEL as undefined. U.S. EPA noted that the 6 mg/kg/day was the lethal dose with the following effects: decreased food consumption, body weight gain; increased SGPT, cachexia, wasting of muscles and subcutanteous fat, testicular atrophy, and death.

Table 13. Effects of hydramethylnon in dogs after oral exposure for 91 days.[a]

Effects	Concentration in mg/kg/day							
	Males				Females			
	0	3	6	12	0	3	6	12
Survival								
Week 7	4/4	4/4	3/4	0/4*	4/4	4/4	4/4	1/4
Week 13	4/4	4/4	1/4	0/4*	4/4	4/4	1/4	0/4*
Food consumption (g/dog/week)								
Week 1	239	233	235	239	197	205	196	180
Week 2	308	268	236	223	259	255	178*	89*
Week 3	323	279	227	155*	244	218	82*	55*
Week 4	295	198*	183*	172	243	223	146*	161
Week 5	304	263	200	11*	260	227	62*	154
Week 7	339	297	159	NA	268	213	4*	168
Week 12	266	229	NA	NA	229	176*	NA	NA
Body weight (kg/dog)								
Week 1	8.9	8.4	7.8	8.5	7.3	7.1	7.7	6.6
Week 7	10.7	9.8	6.8*	NA	8.1	7.4	5.6*	NA
Week 13	11.7	10.5	NA	NA	8.4	7.7	NA	NA
Clinical signs[b]								
Inactivity/emaciated	0/4++	0/4	3/4	4/4**	0/4++	0/4	4/4**	4/4**
Tremors	0/4	0/4	2/4	1/4	0/4	0/4	3/4	2/4
Convulsion	0/4	0/4	1/4	1/4	0/4	0/4	0/4	0/4
Testicular atrophy bilateral, moderate	0/4	0/4	4/4*	4/4*	NA	NA	NA	NA

a/ Data from American Cyanamid Company, 1979. NA= not applicable due to death of animal or gender-specific effect. *, **denote significance at $p<0.05$, and $p<0.01$, respectively based on Fisher' Exact test. +,++ denote significance at $p<0.05$ and $p<0.01$, respectively based on Cochran-Armitage trend test. Only representative food consumption and body weight data were represented.

b/ Some dogs showed multiple signs. For example, in the 6 mg/kg/day males, one dog showed: inactivity and emaciated (after day 46), mild tremors (day 49, 68, and 70 through 74), convulsion (day 75), vomiting (days 46 and 49). The earliest sign was day 46 for the 6 mg/kg/day males, day 23 for 12 mg/kg/day males, day 28 for 6 mg/kg/day females, and day 15 for 12 mg/kg/day females.

Table 14. The No-Observed-Effect Level (NOEL) and Lowest-Observed-Effect Level (LOEL) for subchronic toxicity of technical hydramethylnon.[a]

Species/ Exposure duration	NOEL/ LOEL (ppm)	NOEL/ LOEL (mg/kg/day)	NOEL/LOEL (absorbed mg/kg/day)[b]	Effects	Ref
Oral					
Rat/28 days/diet daily	50/100 100/200	5.6/10.3 10.3/18.7	0.56/ 1.03 1.03/ 1.87	Slight ↓ Food consumption and body weight gain (male only) Testicular effects (tubular degeneration, giant cells)	1
Rat/28 days/diet daily	75/100	9.4/12.4	0.94/ 1.24	↓ Food consumption and body weight gain on week 2 (no testicular effects at 100 ppm)	2
Rat/28 days/diet daily (maturing rats)	<200/200	<20.3/20.3	<2.03/ 2.03	↓ Food consumption and body weights by week 1, testicular effects (giant cells, cellular debris, tubular vacuolation, atrophy)	3
Rat/28 days/diet daily (mature rats)	<200/200	<11/11	<1.1/ 1.1	Testicular effects (cellular debris in epididymis)	4
Rat/91 days/diet daily	<50/50	<4.5/4.5	<0.45/ 0.45	↓ Testicular weight (testicular atrophy at 100 ppm)	5
Dog/ 91 days/capsule daily	**NA**	**<3/3**	**<0.3/ 0.3**	**↓ Food consumption and body weight gain (clinical signs as inactivity, tremors, and convulsion; and testicular atrophy at 6 mg/kg/day)**	**6***
Dog/ 26 weeks/capsule daily	**NA**	**1/3**	**0.1/ 0.3**	**↓ Food consumption and body weight gain and clinical signs as soft or mucoid stools and diarrhea. (no testicular effect at 3 mg/kg/day, highest dose tested)**	**7***
Dermal					
Rabbit/21 days 5 days/week	NA	50/250	1.8/ 8.9	↓ Food consumption and body weight; increased relative liver weight (no testicular effect at 250 mg/kg)	8*

a/ Abbreviations: hr=hour, d=day, w=week. * Study was acceptable to DPR under FIFRA guidelines. References: 1. Fischer, 1979c; 2. Fischer, 1979d; 3. Fischer, 1980f; 4. Fischer, 1980g; 5. Tegeris, 1979; 6. American Cyanamid Company, 1979; 7. Marshall, 1980 under **III.D. CHRONIC TOXICITY**; 8. Thompson, 1982. Bolded studies are selected for the consideration of critical subchronic NOEL for risk characterization.

b/ The absorbed doses were based on 10% and 5% oral and dermal absorption factors, respectively, and amortized for 7 days of exposure

III.D. CHRONIC TOXICITY AND ONCOGENICITY

Summary: With chronic exposure, hydramethylnon caused decreased food consumption in rats, mice, and dogs. In addition, kidney damage in rats (glomerulonephrosis) and in mice (kidney amyloidosis and chronic nephritis) were observed after dietary exposure. Testicular effects (degeneration) were also observed in the rodents, but not in the 26-week dog study. The only oncogenic effect observed was lung tumors in female mice after dietary exposure to hydramethylnon for 18 months; however, the finding was considered equivocal. A summary of the chronic toxicity studies is presented in Table 19.

III.D.1. Oral - Rat

CD rats (50/sex/dose) were given hydramethylnon (92% purity; 0, 25, 50, 100, or 200 ppm) in the diet for 2 years (International Research and Development Corporation, IRDC, 1982a). Calculated mean hydramethylnon dosages were 1.2, 2.4, 4.9, and 10.0 mg/kg/day for males; and 1.5, 3.0, 6.2, and 12.1 mg/kg/day for females. There were no effects on survival, hematology, urinalysis, and general observations of behavior and appearance except for smaller body size in the high dose groups. Food consumption was reduced in the 200-ppm males ($p<0.01$ for weeks 1 to 78, not statistically significant for weeks 82 to 104) and females ($p<0.01$ for weeks 1 to 91, not statistically significant for weeks 95 to 104). The overall average food consumption was significantly ($p<0.05$) decreased only for the 200 pm groups (Table 15). The body weights were reduced in the females (100 and 200 ppm; $p<0.05$ for all weeks) and in the males (200 ppm only, $p<0.05$ for all weeks) (Table 15). For organ weights, the most affected were the testes with weights significantly reduced (73% and 41% of control) in the 100 and 200-ppm male groups (Table 16). Absolute and relative kidney weights were elevated at 100 and 200 ppm, as were absolute and/or relative liver weights at the same levels.

Yellow body fat was noted in dose-related manner in 100 and 200-ppm groups (Table 15); however, microscopic evaluation did not show any abnormality. Glomerulonephrosis (total, multifocal and diffuse) was found in kidneys from 25 ppm to 200-ppm males, and in 50 ppm to 200-ppm females with dose-response relationship shown only for the female data (Table 15). If only the diffuse form, a more serious extent of injury, was consider, then the incidences were lower but dose-response relationship was demonstrated for both genders. The incidences for this endpoint were statistically significant at 50 to 200 ppm for males, and only at 200 ppm for females. The severity of the diffuse glomerulonephrosis was moderate at 25 ppm but was generally graded as severe at higher concentrations.

In the males, there were elevate incidences of testes noted as small and soft in the 100 and 200 ppm groups (Table 15). The reduction in size may be due to testicular atrophy, which was evident at 50 ppm and was marked at 100 and 200 ppm. The testes were described as almost completely void of germinal cells. For the females, uterine tissues showed dose-related increase incidences of endometrial polyps, stromal polyps, adenocarcinoma, and hyperplasia (Table 15). The registrant (American Cyanamid Company) made several points regarding these uterine lesions:

(1) These findings were unrelated to treatment since the MTD was reached in the affected groups; the MTD was determined by the >10% reduction in body weight.
(2) The uterine polyps and related lesions should not be considered oncogenic responses. They

were proliferative lesions in aging females, representing an estrogenic hormonal-type response rather than a preneoplastic event. There was no evidence of progression toward malignancy since there was no increased incidence in endometrial sarcomas with treatment.
(3) The endpoint was irrelevant to humans since the hormonal physiology between female rats and humans are different.

After considering the registrant's comments, DPR concluded that there was insufficient evidence to indicate that hydramethylnon caused uterine tumors. The incidences at dosages lower than the MTD were clearly not statistically different from the concurrent control values, and were apparently within the range of historical values. At dosages above the MTD, hydramethylnon might have caused endometrial stromal polyps; however, it was not possible to determine to what extent this response was due to direct effect of the treatment, and to what extent the response was due to altered general physiological condition.

At the 1988 Proposition 65 Scientific Advisory Panel meeting on the listing of hydramethylnon as a carcinogen, DPR presented incidence data for adrenal medullary tumors. The incidences for the males were 2/50, 3/50, 3/50, 5/39, and 2/49 for 0, 25, 50, 100, and 200 ppm, respectively. The incidences for the females were 0/50, 2/50, 1/50, 2/39, and 5/49 for 0, 25, 50, 100, and 200 ppm, respectively. The increase in incidences with the treated female 200 ppm group was considered not to be treatment related since the increase was marginal and at a dose well above the MTD (defined by $ 10% decrease in body weight) (Table 15).

The lowest dose, 25 ppm, was the LOEL for the study based on total incidences of glomerulonephrosis in males at 25 ppm, but the evidence was considered marginal. The NOEL for the same finding in females was 25 ppm with a LOEL at 50 ppm. The DPR Data Reviewer suggested using the more extensive "diffuse" finding (with a NOEL at 25 ppm for both genders) as an appropriate indicator of a treatment effect. There was a good correlation between diffuse glomerulonephrosis and marked enlarged kidneys. This study was considered acceptable to DPR based on FIFRA guidelines. U.S. EPA considered the 50 ppm as the NOAEL with a LOAEL at 100 ppm for effects in the male (small, soft testes; decreased testicular weights, and testicular atrophy) and in the female (decreased body weight gain). While noting that the incidences (total) for glomerulonephrosis were higher in the treated males and females than in the controls, the U.S. EPA stated that the data did not show a dose-response relationship (U.S. EPA, 1998a).

Table 15. Effects of hydramethylnon in rats after dietary exposure for 2 years.[a]

Effects	**Concentration in ppm *(mg/kg/day, male/female)***				
	0	**25** *(1.2/1.5)*	**50** *(2.4/3.0)*	**100** *(4.9/6.2)*	**200** *(10.0/12.1)*
Males					
Food consumption as g/rat/day average for 104-weeks (% of control)	24.3 (100%)	24.5 (101%)	24.4 (100%)	23.9 (98%)	22.2* (91%)
Body weight, average at week 104, g (% of control)	792 (100%)	838 (106%)	808 (102%)	752 (95%)	657* (83%)
Testis weight (absolute, g)	3.66	4.11	3.85	2.68*	1.49**
Yellow body fat	0/30++	0/32	0/32	8/35**	21/31**
Glomerulonephrosis					
Total (multifocal and diffuse) (%)	19/49++ (38%)	33/49** (66%)	35/50** (70%)	38/50** (78%)	31/50** (62%)
Diffuse (%)	0/49++ (0%)	3/49 (6%)	8/50** (16%)	7/50** (14%)	10/50** (20%)
Testes, small and soft	7/50++	4/50	7/50	19/50**	42/50**
Testicular atrophy					
Unilateral	6/49	3/50	2/50	0/47	0/50
Bilateral	2/49++	1/50	7/50	23/47**	46/50**
Arteritis	1/49++	2/50	8/50*	12/47**	11/50**
Mineralization	1/49	2/50	2/50	6/47*	2/50
Females					
Food consumption as g/rat/day average for 104-weeks (% of control)	18.2 (100%)	18.3 (100%)	18.7 (102%)	17.7 (97%)	15.3* (84%)
Body weight, average at week 104, g (% of control)	573 (100%)	538 (94%)	543 (95%)	447* (78%)	333* (58%)
Yellow body fat	0/29++	0/37	1/30	12/29**	12/28**
Glomerulonephrosis					
Total (multifocal and diffuse) (% incidence)	10/50++ (20%)	12/50 (24%)	23/50** (46%)	27/50** (54%)	31/50** (62%)
Diffuse (% incidence)	2/50++ (4%)	2/50 (4%)	2/50 (4%)	7/50 (14%)	12/50** (24%)
Uterine tissues					
Endometrial/ stromal polyp	1/49++	3/50	5/50	8/50*	9/50**
Stromal tumors	1/49	0/50	0/50	0/50	0/50
Combined endometrial/stromal tumors	2/49++	3/50	5/50	8/50*	9/50*
Adenocarcinoma	0/49	0/50	0/50	0/50	1/50
Hyperplasia	0/49	0/50	0/50	2/50	2/50

a/ Data from IRDC, 1982a. . *, **denote significance at $p<0.05$, and $p<0.01$, respectively based on Fisher' Exact test. +,++ denote significance at $p<0.05$ and $p<0.01$, respectively based on Cochran-Armitage trend test. Incidences are number of animals affected/number of animals examined.

III.D.2. Oral - Mouse

CD-1 mice (50/sex/group) were given hydramethylnon (93% purity; 0, 25, 50, 100, or 200 ppm) in the diet for 18 months (78 weeks) (IRDC, 1982b; Squire, 1987; Busey, 1988). The dosages were 0, 3.57, 6.93, 14.2, and 28.6 mg/kg/day for males; 0, 4.45, 6.87, 17.3, and 33.1 mg/kg/day for females. Survival was reduced in a dose-related manner at 100 and 200 ppm in males and females. Survival in 200-ppm males and females at week 52 was 19/50 and 17/50, respectively (Table 16). By the end of the study, only 50% of the 100-ppm groups survived. The treated groups showed staining of the anogenital area or ventral surface, rales and/or labored breathing, tremors and hunched posture; these signs were observed prior to death. Due to high mortality, the investigators terminated the 200-ppm dose groups on week 55. Certain lesions in the lungs (pneumonia) and kidneys (chronic nephritis) were considered contributors to the high mortality in the 200 pm groups. Food consumption was generally reduced in the 100 and 200-ppm groups in a dose-related manner with statistically significant ($p<0.01$) reduction in the 200-ppm group (Table 16). Body weights for the 50-ppm, 100-ppm, and 200-ppm groups were reduced; the reduction for the latter two groups was statistically significant throughout the study.

Necropsy showed effects in three organs: testes, kidneys, and lungs (Tables 16 and 17). Microscopic examination of the testes showed hypospermia, interstitial cell hyperplasia, and germinal cell degeneration. The incidences for these findings were significantly ($p<0.01$) elevated at 50 ppm to 200 ppm. The degeneration was generally focal to multifocal among males of 50 ppm to 100 ppm and involved one or both gonads. In comparison, these lesions were primarily multifocal to diffuse among the 200-ppm males and they were bilateral. The relative severity of the germinal cell degeneration was also significantly increased (moderate to severe) among the 200-ppm males.

In the kidneys, the incidences of renal amyloidosis and chronic nephritis were elevated in a dose-related manner (though not statistically significant) in mice that died on study (Table 16). These were considered the cause of death for these mice. In addition, females had increased incidence and severity of pigment accumulation in cortical renal tubules; the pigment resembled lipofusin or hemosiderin.

In the lungs, alveolar bronchiolar hyperplasia, adenoma and carcinoma were noted in all treated females (Table 17). In Table 17, the incidence data from the original report (IRDC) and two subsequent analyses by Drs. Squire (Squire, 1987) and Busey (Busey, 1988) are included. The statistical analyses performed by U.S. EPA are indicated (Sette, 1991). Hyperplasia showed a dose-related and significant increase only from Busey's evaluation. For adenoma, the incidences for the doses below the MTD (100 ppm) were elevated and were statistically significant in the IRDC report. The incidences for carcinomas did not show any dose-response relationship in all three evaluations. With adenomas and carcinomas combined, the incidences were significantly increased at 50 ppm (IRDC and Squire), and at 100 ppm (IRDC only), but not at 200 ppm. For this study, U.S. EPA determined a NOAEL of 25 ppm (3.57 mg/kg/day) and a LOEL of 50 ppm in males for testicular lesions. The NOAEL for females was <25 ppm (<4.45 mg/kg/day) with a LOEL of 25 ppm for lung adenomas and carcinomas.

After consideration of the original lung tumor data, reevaluation reports, and the U.S.

EPA reviews, DPR concluded that the evidences for lung tumor effects were equivocal, and lung non-neoplasia effects were limited to 100 ppm or above. The NOEL for this study was 25 ppm (3.57 mg/kg/day) based on testicular degeneration and kidney amyloidosis and chronic nephritis at 50 ppm (6.93 mg/kg/day for males and 6.87 mg/kg/day for females). This study was considered acceptable to DPR under FIFRA guidelines.

Table 16. Effects of hydramethylnon in mice after dietary exposure for 18 months.[a]

Effects	**Concentration in ppm *(male/female, mg/kg/day)***				
	0 *(0)*	**25** *(3.57/4.45)*	**50** *(6.93/6.87)*	**100** *(14.2/17.3)*	**200[b]** *(28.6/33.1)*
Males					
Survival (# animals alive)					
Total at 52 weeks	46/50	48/50	45/50	37/50	19/50
Total at 78 weeks	43/50	44/50	36/50	23/50	0/50
Food consumption (% control)	100%	100%	96%	96%	86%**
Body weight (g, % Control)					
Week 52	40 (100%)	39 (98%)	38 (95%)	37 (93%)	33 (83%)
Week 78	41 (100%)	40 (98%)	40 (98%)	37 (90%)	NA
Testis					
Hypospermia	0/50++	0/50	10/50**	24/50**	20/50**
Interstitial cell hyperplasia	3/50++	3/50	19/50**	28/50**	27/50**
Germinal cell degeneration	4/50++	6/50	14/50**	16/50**	48/50**
Kidney[c]					
Amyloidosis (% affected)	1/7 (14%)	2/6 (33%)	1/14 (7%)	7/27 (26%)	9/33 (27%)
Chronic nephritis (% affected)	3/7 (43%)	4/6 (67%)	8/14 (57%)	17/27 (63%)	25/33 (76%)
Females					
Survival (# animals alive)					
Total at 52 weeks	47/50	45/50	42/50	35/50	17/50
Total at 78 weeks	38/50	38/50	33/50	23/50	0/50
Food consumption (% of control)	100%	98%	98%	96%	81%**
Body weight (g, % Control)					
Week 52	35 (100%)	33 (94%)	34 (97%)	33 (94%)	30 (91%)
Week 78	36 (100%)	35 (97%)	35 (97%)	35 (97%)	NA
Kidney[c]					
Amyloidosis (% affected)	4/12++ (33%)	3/11 (27%)	9/17 (53%)	20/27* (74%)	26/35** (74%)
Chronic nephritis (% affected)	8/12 (67%)	8/11 (73%)	12/17 (71%)	15/27 (56%)	27/35 (77%)
Pigments in tubules (% affected)	3/12++ (25%)	4/11 (36%)	5/17 (29%)	10/27 (37%)	23/35* (66%)

a/ Data from IRDC, 1982b. . *, **denote significance at $p<0.05$, and $p<0.01$, respectively based on Fisher' Exact test. +,++ denote significance at $p<0.05$ and $p<0.01$, respectively based on Cochran-Armitage trend test.

b/ Survivors of 200 ppm dose groups were terminated at week 55.

c/ Incidences for those who died on study. Incidences of amyloidosis in survivors were low and not dose-related.

Table 17. Lung lesions in female mice after dietary exposure to hydramethylnon for 18 months[s].

Lung lesions	Dose in ppm				
	0	**25**	**50**	**100**	**200[e]**
Hyperplasia					
IRDC [b] (%)	3/46 (7%)	2/43 (5%)	1/43 (2%)	1/35 (3%)	3/16 (19%)
Squire[c] (%)	3/50 (6%)	4/50 (8%)	6/49 (12%) p=0.15[f]	6/49 (12%)* p=0.022[f]	3/47 (6%)
Busey[d] (%)	13/50 (26%)	14/50 (28%)	15/50 (30%)	17/49 (34%)*	22/48 (46%)**
Adenomas only					
IRDC[b] (%)	6/48 (12%)	11/47 (23%)	12/45 (27%)*	10/37 (27%)*	4/27 (15%)
Squire[c] (%)	7/50 (14%)	11/49 (22%)	13/47 (28%)*	8/46 (17%)	1/42 (2%)
Busey[d] (%)	7/46 (15%)	12/43 (28%)	11/43 (26%)	7/36 (20%)	1/16 (6%)
Carcinomas					
IRDC[b] (%)	2/47 (4%)	4/46 (9%)	6/43 (14%)	3/36 (8%)	1/22 (5%)
Squire[c] (%)	1/47(2%)	2/46 (4%)	1/43 (2%)	2/36 (6%)	0/21 (0%)
Busey[d] (%)	2/47 (4%)	0/46 (0%)	2/43 (5%)	3/36 (8%)	0/21 (0%)
Adenomas and carcinomas					
IRDC[b] (%)	8/48 (17%)	15/47 (32%)*	18/45 (40%)**	13/37 (35%)**	5/27 (19%)
Squire[c] (%)	8/50 (16%)	13/49 (27%)	14/47 (30%)*	10/46 (22%)	1/42 (2%)
Busey[d] (%)	9/47 (19%)	12/46 (26%)	13/43 (30%)	10/36 (28%)	1/21 (5%)

a/ Data and statistical analyses from Sette, 1991. Number of tumor bearing animals/ number of animals at risk (excluding those that died before observation of the first tumor). *,** Significance by Peto's prevalence test accounting for time to tumor and mortality; if not possible, pair-wise comparison at $p<0.05$, and $p<0.01$, respectively.

b/ IRDC data: first hyperplasia, adenoma, and carcinoma were observed on week 42 (200 ppm), 40 (50 ppm), and 42 (200 ppm), respectively.

c/ Squire data: first hyperplasia, adenoma, and carcinoma were observed on week 15 (50 ppm), 24 (100 ppm), and 45 (0 ppm), respectively.

d/ Busey data: first hyperplasia, adenoma, and carcinoma were observed on week 11 (50 ppm), 45 (0 ppm), and 45 (0 ppm), respectively.

e/ Surviving mice were sacrificed at week 55.

f/ The author noted that prevalence test examined data for different time intervals. Different p values might be associated with equal incidents.

III.D.3. Oral - Dog

Purebred beagles (4/sex/group) were given hydramethylnon (92% purity; 0, 0.33 1.0, or 3.0 mg/kg/day) daily in gelatin capsules for 26 weeks (Marshall, 1980). The active ingredient was formulated in lactose premix with lactose only for controls. Body weight gain and food consumption were not significantly affected by treatment, except that one 3 mg/kg/day male began losing weight consistently from week 2 to week 8. At that time, the dog's weight had dropped from an initial 9.1 kg to 6.2 kg. The animal was not treated from day 42 until day 98; his body weight rose to 9.8 kg. His weight was reduced again when he was put back on the treatment. He was put off the test diet on day 140 to the rest of the study. Incidence of soft stools, mucoid stools, and diarrhea were higher in the 3 mg/kg/day dogs than other groups (Table 18). The authors of the report considered the clinical signs (soft stools, mucoid stools, and diarrhea) were due in part to the osmotic laxative properties of lactose. However, it should be noted that the report showed no meaningful difference between the amounts of lactose in control versus the high dose treatments. Since only summary data were provided, it was not possible to determine whether the incidences of clinical signs for this dog were included in the summary data. Most of other data for this animal were not included in the summaries, at the request of the sponsor. Overall, the summary data suggested dose-related increase in combined incidences of clinical signs. However, the Medical Toxicology Branch did not consider the summarized data for clinical signs at 0.33 mg/kg/day and 1.0 mg/kg/day were of sufficient vigor to use as the basis for a LOEL.

There were no treatment-related effects in any organs examined (including the testes) with regard to organ weight, gross pathology, and histopathology. Yellow-tinged body fat was noted for 4 of 8 dogs at the high dose. The NOEL was 1 mg/kg/day due to inappetance and clinical signs in the 3 mg/kg/day group. This study was considered acceptable by DPR to fill the dog chronic study data requirement. The U.S.EPA has determined a NOAEL of 1 mg/kg/day for soft stools, mucoid stools, and diarrhea at 3 mg/kg/day.

Table 18. Effects of hydramethylnon in dogs after oral exposure for 26 weeks.[a]

Effects	Concentration in mg/kg/day			
	0	**0.33**	**1.0**	**3.0**
Soft stools	139	208	234	357
Mucoid Stools	23	33	24	69
Diarrhea	9	18	19	39
Combined findings	171	259	277	465

a/ Data from Marshall, 1980. Total incidence of treatment-related clinical signs by group-number of times specified observation was reported per group for the duration of the study.

Table 19. The No-Observed-Effect Level (NOEL) and Lowest-Observed-Effect Level (LOEL) for chronic toxicity of technical hydramethylnon.[a]

Species/ Exposure duration	NOEL/LOEL (ppm)	NOEL/LOEL (mg/kg/day)	NOEL/LOEL Absorbed mg/kg/day	Effects	Ref.
Rat/diet/ daily/ 2 years	50/100 25/50	2.4/4.9 1.5/ 3.0	0.24/ 0.49 0.15/ 0.3	Testicular effects Glomerulonephrosis (diffuse)	1*
Rat/diet/ daily/ 3-generation	<50/50	<4.7/4.7	<0.47/0.47	Parental-9body weight and fertility (testis not examined at 50 ppm) Pup-9body weight	2
Rat/diet/ daily 2-generation	25/50 75/ >75	2.0/4.0 5.9/ >5.9	0.2 / 0.4 0.59/ >0.59	Diffuse bilateral degeneration of seminiferous tubules in F0 male No pup effects	3
Mouse/diet/ daily/ 18 months	25/50	3.57/ 6.93	0.357/0.693	Testicular degeneration, kidney amyloidosis and chronic nephritis (clinical signs of anogenital stain, rales and/or labored breathing, tremors, and hunched posture at 100 ppm)	4*
Dog/capsule /daily/26 weeks	**NA**	**1/ 3**	**0.1 / 0.3**	**Clinical signs (soft stools, mucoid stools, diarrhea) and weight loss**	**5***

a/ *Study was considered acceptable to DPR according to FIFRA guidelines. References: 1. IRDC, 1982a; 2. Bio/dynamics, Inc., 1982; 3. Schroeder, 1995; 4. IRDC, 1982b; 5. Marshall, 1980. References 2 and 3 are described under **III.F. REPRODUCTIVE TOXICITY**. Bolded study is selected as the critical study for risk characterization.

b/ The absorbed dose was based on a 10% oral absorption factor.

III.E. GENOTOXICITY

Summary: Hydramethylnon was not genotoxic in *in vitro* and *in vivo* assays. A summary of the genotoxicity studies is in Table 21.

III.E.1. Gene Mutation

Salmonella typhimurium strains (TA1535, TA1537, TA98, and TA100) and *E. coli* strain (WP-2 uvrA) were incubated with hydramethylnon (91.64% purity) either with plate incorporation method (0, 10, 100, or 1000 *u*g/plate) or disc method (0, 1000 *u*g/disc) (Allen, 1979). There was no increase in reversion rate in the absence or presence of Aroclor 1254-induced rat liver. This study was considered acceptable to DPR.

Schizosaccharomyces pombe P1, haploid strain for mutation in the adenine biosynthesis pathway, was incubated with hydramethylnon (91.5% purity; 0, 3.13, 6.25, 12.5, 25 or 50 *u*g/ml) for 16 hours in the absence or presence of rat liver preparation (Edwards and Forster, 1986b). There was a decrease in survival in preparations without activation at 5.0 *u*g/ml (43% survival), 15.8 *u*g/ml (4% survival), and 50 *u*g/ml (none survived). No increase in mutation frequency was detected in any of the treated groups. This study was considered acceptable to DPR.

III.E.2. Structural Chromosomal Aberration

Chinese Hamster Ovary (CHO) cells were incubated with hydramethylnon (91.6% purity; 0, 0.5, 0.75, 1.0, 1.25 or 1.5 *u*g/ml) for 7.5 or 17.5 hours in the absence or 2 hours in the presence of Aroclor-induced rat liver preparation (Litton Bionetics, Inc., 1985). There was no increase in aberrations in the treated cells compared to controls. This study was considered acceptable to DPR.

Male Crl:COBS rats (10/group) were given hydramethylnon (91.6% purity; 0, 3, 30, or 90 mg/kg/day) by gavage and dosed daily for 5 days followed by 17 weeks of mating in a dominant lethal study (Harnois, 1979). Reduced body weight gain was noted in the 30 mg/kg/day group and body weight loss in the 90 mg/kg/day group (Table 20). Food consumption was not reported. Rats in these two groups also showed perianal area staining and bloody nasal crusting (Table 20, neither individual nor incidence data were provided). The report did note that two of the 90 mg/kg/day rats were still affected in the week after treatment. Recovery, however, was complete in both animals on day 22. Testes weights were reduced (58% of control) in the 90 mg/kg/day group. The epididymides were reported to appear smaller when testicular weight was below 3 g. Seminal vesicles and prostate were reported to be normal. Male fertility (as measured by pregnancy rate) was markedly decreased beginning in week 6 at 90 mg/kg/day and continued through week 17 for 6 males. Fertility was somewhat decreased at 30 mg/kg/day with apparent recovery by week 12. The authors suggested that the reduction in fertility might be due to hydramethylnon effect on spermatogenesis. During the weeks of low fertility, spermatocytes and/or spermatogonia were the primary cells observed in the ejaculate. There was no evidence of dominant lethal effect and the NOEL was> 90 mg/kg/day. The NOEL for other effects (reduced body weight gain, reduced fertility) was 3 mg/kg/day. This study was considered unacceptable to DPR because there were inadequate numbers of animals used in the mating for a dominant lethal study.

Table 20. Effects of hydramethylnon in rats after gavage exposure for 5 days.[a]

Effects	Concentration in mg/kg/day			
	0	**3**	**30**	**90**
Body weight gain	20.89g	21.34g	12.81g (61% of control)	-1.01g
Clinical signs[b]				
Perianal stains/bloody nose	-	-	+	+
Soft feces, inactivity, bloody crusting	-	-	-	+[c]
Testes weight (g)	3.64±0.27	3.86±0.22	3.70±0.33	2.11±0.93
Pregnancy rate (%)				
Week 6	90	90	70	30
Week 7-10	100	90	70-80	0
Week 11-14	100	80-90	90-100	20-40
Week 15-17	100	90	100	20-50

a/ Data from Harnois, 1979.
b/ Individual data were not provided.
c/ Observed for several days after the end of exposure.

III.E.3. Other Genotoxic Effects

Saccharomyces cerevisiae strain D4, diploid with two defective, non-complementing alleles of ade-2 and trp-5 loci was incubated with hydramethylnon (91.6% purity; 0, 1.56, 3.13, 6.25, 12.5, or 25 *u*g/ml) for 16 hours in the absence or presence of phenobarbitone-induced rat liver preparation (Edwards and Forster, 1986a). Marginal cytotoxicity (10%-12% decrease in survival) was observed only at 25 *u*g/ml without liver preparation. Hydramethylnon had no effect on gene conversion. This study was considered acceptable to DPR.

Table 21. The genotoxicity of hydramethylnon.[a]

Study types	Exposure conditions	Effect	References
Gene mutation			
S. typhimurium TA1535, TA1537, TA 98 and TA100	0 to100 *u*g/plate " rat liver	Negative	Allen, 1979*
S. pombe	0 to 50 *u*g/ml " rat liver	Negative	Edwards and Forster, 1986b*
Structural Chromosomal Aberration			
CHO cells	0 to 1.5 *u*g/ml " rat liver	Negative	Litton Bionetics, Inc., 1985*
Rats- Dominant lethal study	0 to 90 mg/kg/day for 5 days, then 17 weeks of mating	No dominant lethal effect. Other effects: reduced body weight gain, perianal stains and bloody nasal crusting, reduced testis weight and pregnancy rate	Harnois, 1979
Other Studies			
S. cerevisiae	0 to 25 *u*g/ml " rat liver	Negative	Edwards and Forster, 1986a*

a/ * indicate the studies were acceptable to DPR under FIFRA guidelines.

III.F. REPRODUCTIVE TOXICITY

Summary: Multiple-generation reproductive toxicity studies showed that hydramethylnon caused reduced fertility in rats. This effect was apparently not reversible as reduced fertility was observed in treated rats given control diets for several weeks. The primary target organ for hydramethylnon was the testis, which showed degeneration and atrophy, aspermia, and cellular debris in the epididymides.

III.F.1. Oral - Rat

Sprague-Dawley male rats (10/group) were given a single oral dose of hydramethylnon (91.6% purity; 0 or 800 mg/kg) at about 4 weeks of age (Fischer, 1983). They were then placed on a basal diet for 4 weeks, and mated with untreated females. No treatment-related effects on reproductive performance, reproductive organ weights or gross observation were reported. There were no microscopic examinations of the tissues. This study was considered by DPR to be unacceptable and not upgradeable due to deficiencies: single dose, young test animals, small group size, and lack of histopathological examinations.

CD rats (12 males and 24 females/treatment group) were given hydramethylnon (92% purity; 0, 25, 50, 100, and 200 ppm) in the diet in a 3-generation study (status report in Bio/dynamics, Inc., 1980; final report in Bio/dynamics, Inc., 1982). The F0 parents of the higher two groups were discontinued after the first generation and fed a control diet in a recovery experiment. The mean of mean weekly hydramethylnon intakes are listed below:

Groups	**Hydramethylnon intake in mg/kg/day**					
	F0		**F1**		**F2**	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**
25 ppm	2.3	2.5	1.9	2.2	1.9	2.1
50 ppm	4.7	5.0	4.0	4.5	4.0	4.4
100 ppm	9.2	9.8	control diet		control diet	
200 ppm	17.8	18.2	control diet		control diet	

During treatment, no treatment-related effects were found in the adults of the 25 ppm and 50-ppm groups. But at 100 ppm and 200 ppm, the F0 generation showed body weight decrements in both genders during the growth phase (Table 22). At 200 ppm, there was a marked decrease in frequency of mating and no pregnancies (Table 22). In the 100-ppm group, there were no pregnancies in the first mating period (F1a litter=0), and only 6 pregnancies in the second mating period (F1b litter=6). Of the F1b litters, two entire litters were stillborns with the gestation lengths of 23 and 24 days, compared to 21-22 days for the majority of litters in all groups. The mean live litter sizes for F1b on days 0 and 21 were significantly reduced. The body weights of the pups from all treated groups were less than that for the control (77% to 94% of control). Gross examinations showed small testes in the 100 and 200-ppm F0 males (Table 22). Microscopic evaluation showed seminiferous tubule degeneration in these males. Of the affected males, bilateral diffuse degeneration of the tubules was seen in 1 of the 100-ppm group, and in 9 of the 200-ppm group. Epididymides were similarly affected in a dose-related manner. Of the 12 males examined per group, no controls were noted to have decreased number of sperm or absence of sperm in ducts; however, bilateral absence of sperm in ducts were noted for 2 of the

100-ppm group and for 8 of the 200-ppm group. These examinations were not done for the 25 ppm or 50 ppm groups. For the second and third generation, without the 100- and 200-ppm groups, there were no significant reproductive findings.

During the 4 weeks that the 100-ppm and 200-ppm F0 parents were fed a control diet (recovery phase), these animals showed high food consumption and gain weight. In a mating trial, the 100-ppm group showed similar reproductive result as controls. However, the 200-ppm group had slightly fewer confirmed mating and no pregnancies. The parental 200-ppm group was again placed on a control diet for an additional 30 days. Again there was no evidence of parturition. Seminiferous tubular degeneration persisted in the 100-ppm and 200-ppm groups but was observed at a lower incidence (Table 22). The testes of the 25-ppm and 50-ppm groups were not examined.

The parental toxicity and reproductive effect NOEL was #50 ppm (4.7 mg/kg/day for males and 5.0 mg/kg/day for females) based on findings of decreased parental body weight and fertility, decreased pup weight, and testicular effects at 100 ppm and 200 ppm at F0 generation. This study was considered unacceptable to DPR because the protocol did not follow FIFRA guidelines. Among the deficiencies were that the two high dose groups were discontinued after F0 parents were evaluated and no microscopic examination of tissues of F1 or subsequent generation adults. An additional study (Schroeder, 1995) was conducted to establish a valid NOEL for testicular lesions in F1 adults.

Table 22. Effects of hydramethylnon in rats after dietary exposure in a 3-generation reproductive toxicity study.[a]

Effects	**Concentration in ppm *(mg/kg/day, F0 male/females)***				
	0 *(0/0)*	**25** *(2.3/2.5)*	**50** *(4.7/5.0)*	**100** *(9.2/9.8)*	**200** *(17.8/18.2)*
Body weight (treatment week 9)					
F0 Male	478	450	475	422**	389**
F0 Female	271	253	256	235**	236**
F0 generation					
F0 females pregnant/# mated					
F1a litter	17/19	21/22	21/24	0/23**	0/16**
F1b litter	16/20	20/22	21/22	6/17*	0/7**
Mean live litter size (day 0)					
F1a litter	12.5	11.9	12.5	N/A	N/A
F1b litter	14.4	14.5	13.6	5.0**	N/A
Mean live litter size (day 21)					
F1a litter	9.7	9.6	9.8	N/A	N/A
F1b litter	9.9	10.0	10.0	4.8++	N/A
Mean pup weight (day 21, g)					
F1a litter	53.3	49.3*	49.0*	N/A	N/A
F1b litter	57.1	53.7	52.1*	43.7**	N/A
F0 Gross and microscopic examination after treatment					
Small testes	0/12	NA	NA	5/12**	12/12**
Seminiferous tubular degeneration	0/12	NA	NA	4/12*	12/12**
Epididymides, bilateral, absence of sperms	0/12	NA	NA	2/12	8/12**
F0 Recovery sacrifice histopathology					
Seminiferous tubular degeneration-diffuse					
Bilateral	0/12	NA	NA	1/12	9/12
Unilateral	0/12	NA	NA	1/12	1/12
Seminiferous tubular degeneration-multifocal					
Bilateral	0/12	NA	NA	1/12	2/12
Unilateral	0/12	NA	NA	1/12	0/12

a/ Data from Bio/dynamics, Inc., 1982. *, ** Significant by t-test, $p<0.05$ or $p<0.01$, respectively. ++ Significant by t-test with Smith-Satterwaite correction, $p<0.01$ from the report for litter size data. NA=not examined.

Crl:CD® BR rats (30/sex/group) were dosed with hydramethylnon (98.2% purity; 0, 25, 50, or 75 ppm) in the diet continuously for 2 generations, with one mating period per generation (Schroeder, 1995). The mean hydramethylnon intakes (mg/kg/day) are listed below:

Groups	**Hydramethylnon intake in mg/kg/day**			
	F0		**F1**	
	Male	**Female**	**Male**	**Female**
25 ppm	2.0	2.3	1.8	2.1
50 ppm	4.0	4.6	3.8	4.3
75 ppm	5.9	6.6	5.8	6.7

There were no treatment-related deaths or clinical signs. At premating period, the body weights of the F0 parents were reduced significantly ($p<0.05$) for the 75 ppm males for some weekly measurements (Table 23). However, the body weights were increased significantly ($p<0.05$) for the 75 ppm females in the F1 parents. These results reflected the food consumption levels for these groups. Maternal weight during gestation showed consistent reduction in gains (110 g compared to 129 g for control in F0) at the high dose for both F0 and F1 generations. Of the reproductive parameters, the changes at 75 ppm were: (1) a reduction in F1 high dose males with evidence of mating (22 compared to 24 for control), (2) associated reduction in F1 females pregnant (18 compared to 25 in control), and (3) tendency toward low implantation rates in 75 ppm matings. Three 75-ppm pregnancies resulted in one implant (2 cases) or three implants (1 case), neither of which yielded viable pups at birth. Also, live litter sizes were reduced in both generations, although statistical significance was limited to the first generation (9.7 compared to 13.0 for control).

Germinal epithelial degeneration with scattered tubules was common (12/30 animals) at 75 ppm, but diffuse degeneration (unilateral or bilateral) was observed in lower incidences (1/30 of the F0 50 ppm males, 3/30 F0 75 ppm males, and 1/30 F1 75 ppm males) (Table 23). This study did not find any seminiferous tubule degeneration at 25 ppm or in controls. The primary reproduction study (Bio/dynamics, Inc., 1982; Table 22) had identified diffuse bilateral degeneration of seminiferous tubules in 100 ppm and 200 ppm males, supporting the single finding at 50 ppm in the present study as a treatment effect. Since this endpoint was found in two studies, the single incident at the F0 50-ppm male was considered a plausibly treatment-related event. Thus the NOEL was 25 ppm (2.0 mg/kg/day for diffuse bilateral degeneration of seminiferous tubules in 1/30 F0 males at 50 ppm. This was considered a valid supplemental study to complement the primary (non-accepted) reproduction study (Bio/dynamics, Inc., 1982) to fill the reproduction study data requirement for SB 950. U.S. EPA also determined an adult NOAEL of 25 ppm (1.66 mg/kg/day) for testes: degeneration of the germinal epithelium and aspermia; epididymis-increased cellular debris. Offspring NOAEL was 75 ppm for no effects observed at the highest dose. U.S. EPA uses the 25 ppm NOAEL to address all residential dermal and inhalation exposures.

Table 23. Effects of hydramethylnon in rats after dietary exposure in a 2-generation reproductive toxicity study.[a]

Effects	F0 in ppm (*male/female, mg/kg/day*)				F1 in ppm (*male/female, mg/kg/day*)			
	0 *0*	**25** *2.0/2.3*	**50** *4.0/4.6*	**75** *5.9/6.6*	**0** *0*	**25** *1.8/2.1*	**50** *3.8/4.3*	**75** *5.8/6.7*
Body Weights (g) during pre-mating periods								
Males								
Wk 0	188	189	189	186	210	219	209	211
Wk 5	391	386	381	376	413	432	415	427
Wk10	487	486	466	461*	497	525	504	521
Females								
Wk 0	146	146	145	146	156	167*	162	167*
Wk 5	230	231	226	222	243	254	250	260*
Wk10	260	258	254	252	273	285	283	298**
Body Weight gain during gestation (g)- Females								
Days 0-20	129	127	122	110**	121	121	118	106*
Histology- Males								
Testes: Germinal epithelial degeneration (scattered tubules)								
Absent	30/30	30/30	29/30	25/30	30/30	30/30	30/30	17/30
Minimal	0/30	0/30	0/30	0/30	0/30	0/30	0/30	10/30
Mild	0/30	0/30	0/30	2/30	0/30	0/30	0/30	1/30
Moderate	0/30	0/30	0/30	0/30	0/30	0/30	0/30	1/30
Testes: Germinal epithelial degeneration/atrophy (generalized)								
Unilateral- marked	0/30	0/30	0/30	2/30	0/30	0/30	0/30	0/30
Bilateral - marked	0/30	0/30	1/30	1/30	0/30	0/30	0/30	1/30
Aspermia	0/30	0/30	1/30	3/30	0/30	0/30	0/30	1/30
Epididymides: increased cellular debris ducts	0/30	0/30	0/30	5/30	0/30	0/30	0/30	6/30

a/ Data from Schroeder, 1995. . *, **denote significance at $p<0.05$, and $p<0.01$, respectively based on Fisher' Exact test.
+,++ denote significance at $p<0.05$ and $p<0.01$, respectively based on Cochran-Armitage trend test.

III.G. DEVELOPMENTAL TOXICITY

Summary: Hydramethylnon caused reduced body weight gain in pregnant rats and rabbits. Both species showed similar clinical signs (soft stool, anogenital stains) and yellow body fats. Fetal body weights were reduced and may be attributed to the body weight loss of the dams. Increased ossification variation was reported in fetal rats exposed to hydramethylnon *in utero*.

III.G.1. Oral - Rat

Pregnant CD rats (26/group) were gavaged with hydramethylnon (92% purity; 0, 3, 10, or 30 mg/kg/day) during day 6 to15 of gestation (Bio/dynamics Inc., 1979). There was a dose-related decrease in maternal body weight gain but statistically significant from day 12 onward (Table 24). Food consumption was not measured. The 30 mg/kg/day group was most affected and reported to show increased incidences of red nasal mucous, alopecia, soft stool, and anogenital staining (data not provided). Necropsy of 5/26 animals in this group showed decreased thymus size (Table 24). Yellow discoloration of the fat was noted for the 10 and 30 mg/kg/day groups. Developmental toxicity was limited to the 30 mg/kg/day group and included slight reduced fetal weight and slight ossification delays (Table 24). The reduction in fetal weight was statistically significant and was 90% and 93% of the control for males and females, respectively. The ossification delays (incomplete supraoccipital ossification and rudimentary ribs) were elevated. The maternal NOEL was 3 mg/kg/day for decreased body weight gain at 10 and 30 mg/kg/day, and clinical signs at 30 mg/kg/day. The developmental NOEL was 10 mg/kg/day for decreased fetal weight and ossification variations. This study was considered acceptable to DPR according to FIFRA guidelines. These NOELs are the same as those established by the U.S. EPA.

Table 24. The maternal and developmental effects of hydramethylnon in rats after exposure during gestation.[a]

Effects	Concentration in mg/kg/day			
	0	**3**	**10**	**30**
Maternal Effects				
Body weight gain (Day 6-15)	52g	49g	35g**	8g**
Clinical signs (red nasal mucus, alopecia, soft stools, anogenital staining)	-	-	-	+
Thymus - small	0/26	0/26	0/26	5/26
Developmental Effects				
Fetal weight -Male	3.75g	3.74g	3.72g	3.37g** (90%)
Female	3.45g	3.52g	3.53g	3.20g** (93%)
Incomplete Supraoccipital ossification				
Litter	1/ 25 (4%)	8/ 25 (32%)	3/ 24 (13%)	9/ 24 (38%)
Fetus	1/220 (0.4%)	8/206 (4%)	3/188 (2%)	9/211 (4%)
Rudimentary ribs				
Litter	14/ 25 (56%)	16/ 26 (62%)	18/ 24 (75%)	16/ 24 (67%)
Fetus	22/220 (10%)	25/206 (12%)	25/188 (13%)	35/211 (17%)

a/ Data from Bio/dynamics Inc., 1979. Statistical difference from the control group: ** $p<0.01$ from the report. Incidences shown were number of animals (adults, fetuses or litters) affected/total animals (adults, fetuses or litters) examined.

III.G.2. Oral - Rabbit

In a pilot study, pregnant New Zealand rabbits (5/group) were given hydramethylnon (91.6% purity; 0, 5, 15, 30, 60, or 100 mg/kg/day) by gavage on gestation days 6 through 18 (IRDC, 1982c). No effects were observed at 5 mg/kg/day. Discharge from the eyes was noted in doses $ 15 mg/kg/day. At 30 and higher concentrations, body weight loss and yellow body fat were noted. Abortion (one/group) was noted in all groups, except in 5 mg/kg/day. There were 5 deaths; one of 30 mg/kg/day on gestation day 18, one of 60 mg/kg/day on gestation day 12, and three of 100 mg/kg/day on gestation days 10, 16, and 20. Results of this study were used to determine the doses for the definitive study (IRDC, 1982d).

In the definitive study, pregnant New Zealand rabbits (16/group) were given hydramethylnon (91.6% purity; 0, 5, 10, or 20 mg/kg/day) by gavage on gestation days 6 to 18 (IRDC, 1982d). The dams showed decreased body weight gain (statistical significance starting on day 6), and increased incidences of reduced stool amounts or soft stools, yellow body fat, and matting and/or discharge in anogenital region (Table 25). These effects were significant ($p<0.05$) findings at 10 and 20 mg/kg/day (Table 25). Two animals died in the 20 mg/kg/day group (gestation day 21 and 27). Three animals in each 10 and 20 mg/kg/day group aborted (gestation days 25-29). The NOEL for maternal toxicity was 5 mg/kg/day for these effects. The only developmental toxicity reported was decreased fetal weight at 20 mg/kg/day (Table 25) with a developmental NOEL of 10 mg/kg/day. The low fetal body weight was attributed to the body weight loss in the dams. This study was considered acceptable to DPR under FIFRA guidelines. U.S. EPA has determined a maternal NOAEL of 5 mg/kg/day for soft stools and reduced amount of stool. But the U.S. EPA developmental NOAEL was 5 mg/kg/day for decreased fetal body weight (8%, a value outside of the historical range) (U.S. EPA, 1998a).

Table 25. The maternal and developmental effects of hydramethylnon in rabbits after exposure during gestation.[a]

Effects	Concentration in mg/kg/day			
	0	**5**	**10**	**20**
Maternal Effects				
Weight gain (g) d6-18	122±157	50±318	-22±111*	-283±184**
Reduced stool amounts	7/16++	10/16	13/16*	16/16**
Soft stool	0/16++	2/16	5/16*	6/16**
Yellow body fat	0/16	0/16	1/16	8/16**
Matting/anogenital stain	0/16	0/16	few	few
Abortion[b]	0/16	0/16	3/16	3/16
Death[b]	0/16	0/16	0/16	2/16
Developmental Effect				
Mean fetal weight (g) % of control	42±7 (100%)	38±8 (95%)	35±10 (83%)	31±7* (74%)

a/ Data from IRDC, 1982d. Incidences were based on the text of the report. Individual data were not provided. *,** denote significance at $p<0.05$ and $p<0.01$, respectively by Fisher's exact test. ++ denotes significance at $p<0.01$ by Cochran-Armitage Trend test.

b/ Occurred post treatment (after gestation day 18).

III.H. NEUROTOXICITY

A delayed neurotoxicity study under current FIFRA guidelines is not required for hydramethylnon.

III.I. IMMUNOTOXICITY

Weanling castrated Holstein calves (9/group) were fed Amdro (113.5 g/day/calf) for 7 weeks (Evans *et al*., 1984). The results were presented as graphs in the report. After 2-weeks, leukopenia was observed as white blood cell count was significantly lower (about 6,500 cells/mm^3) than that (about 9,000 cells/mm^3) for controls. Differential counts showed significantly ($p<0.05$) reduced lymphocytes (about 4,500/mm^3 compared to about 5,500/mm^3 for control) and eosinophils (about 20/mm^3 compared to about 200/mm^3 for control). Eosinopenia was present from days 21 to day 49 of treatment. There were variable changes to other blood parameters but no clear treatment-related effect. There was also a significant ($p<0.05$) decrease (about 101.5^{o}F to 102°F compared to 102.5^{o}C to 103°C in controls) in rectal temperature after 25, 32, and 39 days of treatment. Serum proteins, serum IgG1 and IgG2 levels, antibody formation (anti-KLH), serum anti-Brucella titers, and cell-mediated immunity response were either different during a few time points or similar to the controls. Microscopic examination of the tissues did not show any effects. The authors suggested that hydramethylnon selectively affected the "production of immuno-competent T and B cells, rather than depress differentiation and functional maturation at a peripheral site." The decrease in body temperature was thought to indicate a central physiological effect, a malfunction in thermoregulatory mechanisms.

IV. RISK ASSESSMENT

IV.A. HAZARD IDENTIFICATION

The most appropriate data for the hazard identification are those from human studies. However, there were few reports of human exposure to hydramethylnon and they did not provide sufficient data for evaluation. In the absence of human data, hydramethylnon pharmacokinetics and toxicity observed in laboratory animals were assumed to occur in humans. Toxicity endpoints and critical NOELs for risk characterization are discussed in this section.

IV.A. Selection of Critical Endpoints

Yellow body fat, decreased food consumption and the associated reduced body weight gain, clinical signs, and testicular lesions were the predominant effects observed in experimental animals exposed to hydramethylnon. The yellow body fat was due to deposition of hydramethylnon and its metabolites in the fat tissue (Hussain,1980; Zdybak and Robinson, 1992) since hydramethylnon is a yellow to tan compound. The biological significance of this observation is unknown since there were no histological changes or altered fat metabolism associated with this finding (IRDC, 1982a). The decreased food consumption was reported in dermal, dietary and gavage administrations and thus apparently was not associated with palatability of hydramethylnon (Table 14). This endpoint was considered of toxicological significance since it was dose-related and resulted in decreased body weight gain.

Clinical signs were reported in hydramethylnon-treated animals in several studies (Harnois, 1979; Moreno *et al*., 1983b; American Cyanamid Company, 1979; Marshall, 1980; IRDC, 1982b). The most common signs were bloody nasal discharges and gastrointestinal effects (perianal area staining, soft stools, mucoid stools, and diarrhea). These signs occurred in the presence of weight loss and decreased survival; they were likely indications of systemic stress induced by the treatment.

Hydramethylnon caused testicular effects in multiple species (rat, dog, and mouse) after oral exposures (Table 7, 14, and 19). After acute exposure at high doses, reduced testicular weight was observed in rats. It was not known if there were any pathological changes since histopathology was not performed in this study. With subchronic and chronic exposures, testicular damage was evident and consisted of tubular degeneration, atrophy, presence of giant cells and debris, and tubular vacuolation. Furthermore, the presence of spermatid giant cells as an indicator of degeneration persisted 4 weeks after cessation of exposure (Table 10, Fischer, 1980f). There appeared to be a progression of testicular damage as tubular atrophy and aspermiogenesis were still observed after the recovery phase (Table 10; Fischer, 1980 f and g).

The mechanism for the testicular effects by hydramethylnon is unknown; it may be related to the inhibition of mitochondrial function noted for its insecticidal activity. The testicular effects might be route-specific because there were no such effects in the dermal toxicity studies with rabbits (Moreno *et al*., 1983b; Thompson, 1982) at doses (absorbed dose of 8.9 mg/kg/day as the highest dose tested) higher than the LOELs (0.45 to 2.03 mg/kg/day as absorbed doses, Table 14) for this endpoint in oral studies. However, difference in absorption

amount might only be one factor influencing the toxicity of hydramethylnon between routes. The effects of hydramethylnon on the testes likely contributed toward the reduced reproductive performance reported in the 2-generation and 3-generation reproductive toxicity studies (Biodynamics, Inc., 1982; Schroeder, 1995) and the dominant lethal study (Harnois, 1979). However, hydramethylnon did not cause any developmental effects in rabbits (IRDC, 1982d) and only ossification variations in the rat (Bio/dynamics, Inc., 1979). The fetal body weights were reduced in rabbits exposed to hydramethylnon *in utero* (IRDC, 1982d); however, the reduction was attributed to body weight loss in the does (Table 25).

IV.B. Selection of Critical NOELs

Critical NOELs were established for acute, subchronic, and chronic toxicity of hydramethylnon from oral and dermal administrations. Route-specific studies were preferred in order to minimize the uncertainties associated with route-to-route extrapolation. When route-specific studies, such as for acute and chronic dermal toxicity of hydramethylnon, were not available or inadequate because of limited study information, then oral studies were used in the hazard identification.

As part of the hazard identification, the NOELs and LOELs from different routes were compared to determine if there were route-specific effects or sensitive routes of exposure. Due to limited information, the only adjustment to these doses was the use of the absorption factor, which was 5% and 10 % for dermal and oral exposures. A comparison of the LOELs for similar effects suggested a difference between oral and dermal exposures that could not be accounted for by correction of absorption amount alone. The LOELs (in terms of absorbed doses) for body weight reduction were lower for oral than for dermal routes of exposures (Table 26). Similarly, the LOELs for testicular effects ranged from 0.45 to 2.03 mg/kg/day (absorbed doses) by the dietary route (Fischer, 1979 c and d; Fischer, 1980 f and g; and Tegeris, 1979), while there was no testicular effect at 8.9 mg/kg/day (absorbed dose) by the dermal route in the only dermal subchronic toxicity study (Thompson, 1982).

The potential for oncogenicity from lifetime exposure was not evaluated because DPR concluded while there was suggestive evidence for oncogenicity, there was insufficient evidence to evaluate the oncogenic potential in humans (see discussion under **IV.B.4. Oncogenicity - Weight of Evidence**).

IV.B.1. Acute Toxicity

For acute exposure, single dose studies (LD_{50} type studies), developmental toxicity studies (with the assumption that developmental effects may be caused by a single exposure), or other short-term studies (Table 7) were considered in the selection of a critical NOEL. The acute oral critical NOEL was 3 mg/kg/day (0.3 mg/kg/day, absorbed) for decreased body weight, clinical signs (perianal area and bloody nasal discharges), and reduced fertility at 30 mg/kg/day in

rats given hydramethylnon for 5 days (Harnois, 1979). Since incidence data were not given in

the report, the signs were assumed to have occurred from an acute exposure (single or few days of exposure). Other short-term studies, such as the developmental toxicity studies, with clinical signs reported also did not provide occurrence information (Bio/dynamics, Inc., 1979; IRDC, 1982d; Tables 24 and 25). This NOEL was supported by decreased body weights and clinical signs observed in pregnant rats and rabbits at similar NOELs, 3 mg/kg/day and 5 mg/kg/day, respectively, during the 12-days of dosing during gestation (Bio/dynamics, Inc., 1979; IRDC, 1982d). The use of the critical NOEL at 3 mg/kg/day addressed effects observed at higher doses such as clinical signs at 400 mg/kg in the single dose study (Fischer, 1979a) and ossification variations at 30 mg/kg/day in the developmental toxicity study with rats (Bio/dynamics, Inc., 1979).

For acute dermal exposure, acute dermal LD_{50} studies and the subchronic dermal toxicity study were considered. The critical acute dermal NOEL was 50 mg/kg/day (1.8 mg/kg/day, absorbed) for decreased food consumption in a FIFRA acceptable dermal subchronic toxicity study. This effect was reported throughout the study with statistically significant reductions at 250 mg/kg after 4 days of treatment (Thompson, 1982; Table 12). There were no treatment-related clinical signs or skin effects. The critical NOEL was not selected from acute dermal toxicity studies because of the high doses used or because no effects were observed (Table 6). For example, clinical observations (diarrhea, few feces, yellow nasal discharges, ptosis, and lethargy) were reported at 2000 mg/kg, the only dose tested. It is unknown what the absorbed dose was for this study since the concentration used was much higher than that used in the dermal absorption studies (range of 7 to 150 mg/kg; Sharp, 1993; Frantz and Beskitt, 1993).

IV.B.2. Subchronic Toxicity

For subchronic oral exposure, the critical NOEL of 1 mg/kg/day (0.1 mg/kg/day, absorbed) was derived from results of two dog studies given hydramethylnon in capsules by gavage (American Cyanamid Company, 1979; Marshall, 1980). In the 13-week study, decreased food consumption and body weights were observed with the lowest dose (3 mg/kg/day) as the LOEL (Table 13; American Cyanamid Company, 1979). These effects were relatively mild because the decrease in food consumption was statistically significant for only a few weeks, and the body weight loss was not statistically significant (Table 13). The result from the 26-week study (Marshall, 1980) showed that the subchronic NOEL was at 1 mg/kg/day as the effects at 3 mg/kg/day was consistent with those from the 13-week study. For all species studied, testicular effects were observed at higher doses (LOELs ranged from 4.5 to 20.3 mg/kg/day) in both dog and rat oral subchronic toxicity studies (Table 14). The use of 1 mg/kg/day (0.1 mg/kg/day as absorbed dose) as the critical NOEL would, therefore, protect the animals from the testicular effects after oral exposure. This critical NOEL was not used in this document because only acute and chronic dietary exposures were considered. This value may be used in future assessments.

For subchronic dermal exposure, there was only one study available. It was an acceptable study conducted under FIFRA guidelines, and a NOEL of 50 mg/kg/day was determined in the study (Thompson, 1982). In this study, rabbits showed increased relative liver weights and decreased body weights at 250 mg/kg with a NOEL at 50 mg/kg (1.8 mg/kg/day, absorbed). This NOEL was considered the critical NOEL. Testicular effects were not observed at the highest dose tested (250 mg/kg or 8.9 mg/kg/day absorbed).

IV.B.3. Chronic Toxicity

For oral exposure, the critical chronic NOEL was 1 mg/kg/day (0.1 mg/kg/day, absorbed) for clinical signs (soft stools, mucoid stools, diarrhea) and weight loss in dogs observed at 3 mg/kg/day (Marshall, 1980). This NOEL was supported by NOELs of 1.5 mg/kg/day to 3.57 mg/kg/day in other studies for kidney and testicular effects in rats and mice (Table 19).

For dermal exposure, two approaches were considered because there were no dermal chronic toxicity studies. One approach was to use the critical oral NOEL. This approach assumed that the toxicity of the oral and dermal routes were the same. As discussed previously, there were differences in the pharmacokinetics and toxicity between these two routes. An alternate approach was to apply a default factor of 10 to extrapolate the chronic NOEL from the dermal subchronic. For hydramethylnon, the acute and subchronic dermal NOELs were the same, 50 mg/kg/day or absorbed dose of 1.8 mg/kg/day. Application of a 10-fold factor would reduce it to 5 mg/kg/day (absorbed dose of 0.18 mg/kg/day), a level only two-fold higher than the NOEL (0.1 mg/kg/day, absorbed) from the chronic oral study. Since there were uncertainties associated with both approaches, the lower value (0.1 mg/kg/day, absorbed) from the oral exposure study was selected as a more health protective level for risk characterization.

IV.B.4. Oncogenicity - Weight of Evidence

The U.S. EPA first evaluated the oncogenicity data for hydramethylnon in 1987 and concluded that there was sufficient evidence for oncogenicity from animal studies and classified hydramethylnon as a B2 (probable human) based on the findings of: elevated incidence of pulmonary adenomas/ carcinomas combined in female and male mice (IRDC, 1982b) and an increase in uterine polyps in female rats (Quest, 1987). In response to the U.S. EPA first review, the registrant conducted a re-evaluation of the histological slides for the lungs by another pathologist (Squire, 1987). The U.S. EPA noted that this second evaluation differed sufficiently from the original evaluation that a third evaluation was needed (Dykstra, 1988). The report from the third evaluation (Busey, 1988) concurred with the original IRDC and Squire (1987) evaluation that overall, hydramethylnon did not cause lung tumors in mice. In 1989, the California Proposition 65 Carcinogenicity Panel determined that there was no clear evidence for oncogenicity (Whatley, 1989).

In 1991, the U.S. EPA analyzed the data from all three pathological reports (IRDC, 1982b; Squire, 1987; Busey, 1988) and the incidences are shown in Table 17 (Sette, 1991). Hyperplasia showed a dose-related and significant increase only from Busey's evaluation. For adenoma, the incidences for the doses below the MTD (100 ppm) were elevated and were statistically significant in the IRDC report. The incidences for carcinomas did not show any dose-response relationship in all three evaluations. With adenomas and carcinomas combined, the incidences were significantly increased at 25 ppm (IRDC only), 50 ppm (IRDC and Squire), and at 100 ppm (IRDC only), but not at 200 ppm. None of the data showed statistical significance in the trend analysis. The historical data for mice were considered either too limited or not comparable in time or personnel; therefore, the concurrent control was considered the most relevant. The U.S. EPA concluded that hydramethylnon oncogenic potential classification

should be changed from B2 to C, a possible human carcinogen because of statistically significant increases in lung tumor in female mice based on IRDC original data (Sette, 1991). Potency factors were not calculated. The classification was downgraded from B2 to C because of several considerations.

(1) The incidences for bronchial hyperplasia, as a precursor, in females were varied among the three evaluations.
(2) Of the three reports, only Busey (1988) showed dose-related increase in incidences of hyperplasia but only at the Maximum Tolerated Dose (100 and 200 ppm).
(3) In terms of tumors, dose-response was observed only for the two lower doses. The U.S. EPA did not conduct quantitative analyses for the derivation of potency factors.
(4) The registrant submitted additional mutagenicity studies, which further showed that hydramethylnon was not genotoxic.
(5) The lung tumors in male mice and uterine polyps in female rats were determined not to be toxicologically significant since the incidences were increased at maximally tolerated doses.

In the RED, chronic toxicity was addressed by reference dose approach using non-oncogenic endpoints (U.S. EPA, 1998a). Chronic worker and residential exposures were evaluated using a reference dose approach based on the NOEL of 1 mg/kg/day for clinical signs (soft stool, mucoid stool, and diarrhea) in dogs (Marshall, 1980) and for reproductive effects in rats (Schroeder, 1995). Chronic dietary exposure was considered negligible.

For this risk characterization document, weight-of-evidence analysis showed "suggestive evidence of carcinogenicity"[6] for hydramethylnon as defined in the U.S. EPA 1999 draft Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999a). There were no data on the potential of hydramethylnon for oncogenicity in humans. Results from experimental animal studies showed treatment-related tumors only in the mouse study (IRDC, 1982b), but not in the rat study (IRDC, 1982a). Furthermore, these tumors were found in only one site (lung tumors) and only in one gender (female mice) (IRDC, 1982b). DPR conducted two statistical analyses on the female lung tumor data with the high dose incidence excluded because there was high mortality in that group (Table 26). The combined incidences of lung adenomas and carcinomas showed significantly different than the control based on pair-wise comparisons using the Peto's prevalence test and the Poly-3 trend test[7], which accounted for early mortality. These tests also showed a statistically significant trend ($p<0.02$), in contrast to the lack of trend in the analysis performed by the U.S. EPA. The slope of the dose-response curve was shallow with a small increase in incidence over the 4-fold increase in the dose (25 ppm to 100 ppm) (Table 17 and 26). While hyperplasia, adenoma, and carcinomas were detected, there was no obvious progression of lesion, i.e. decreased incidences of hyperplasia with increased incidences for

[6] "Suggestive Evidence of Carcinogenicity, but not sufficient to assess human carcinogenicity potential" - This descriptor is appropriate when evidence from human or animal data is suggestive of carcinogenicity, which raises a concern for carcinogenicity effects but is judged not sufficient for a conclusion as to human carcinogenic potential. Examples of such evidence may include: a marginal increase in tumors that may be exposure-related, or evidence is observed only in a single study, or the only evidence is limited to certain high background tumors in one sex of one species. Dose-response assessment is not indicated for these agents. Further studies would be needed to determine human carcinogenic potential.

[7] The Poly-K test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account (NTP, 2002). National Toxicology Program uses this test for oncogenicity data analysis.

carcinomas as the doses were increased. The significance of these tumors for human exposure was unclear since the route of administration in the study was gavage while dermal exposure would have been more relevant for human exposure.

Other studies did not suggest any oncogenic potential for hydramethylnon. Pharmacokinetic studies showed that hydramethylnon was poorly absorbed by the oral or dermal routes of administration. After oral administration, tissue distribution studies showed high levels in the fat, liver, and kidney, but not the lungs. There was no indication of metabolic activation of hydramethylnon as less than 1 % of the administered dose was converted to metabolites after oral exposure. Genotoxicity studies showed that hydramethylnon was not genotoxic in *in vitro* and *in vivo* assays. Mechanism of toxicity studies showed that hydramethylnon was an inhibitor of the mitochondrial respiratory transport system (Hollingshaus, 1987). A structure-activity relationship analysis could not be conducted since hydramethylnon, an amidinohydrazone, is the only compound with a toxicology database for this class of compounds.

Therefore, the weight of the evidence showed only suggestive evidence for hydramethylnon oncogenicity. In concurrence with the U.S.EPA, a quantitative analysis (calculation of potency factors) was considered not necessary due to level of the evidence and the marginal increase in incidences of lung tumors in the female mice from the IRDC (1982b) study.

Table 26. Lung tumors in female mice after chronic dietary exposure to hydramethylnon.

Lung lesions	**Dose in ppm**			
	0	**25**	**50**	**100**
Adenomas and carcinomas based on IRDC incidence data				
Incidence	8/48 (17%)+	15/47 (32%)*	18/45 (40%)**	13/37 (35%)**
Peto's test	p=0.0262	p=0.037	p=0.007	p=0.006
Poly-3 trend test	p=0.0240	p=0.0302	p=0.0056	p=0.0178

a/ Statistical analyses for trend were performed using Peto's prevalence test and Poly-3 trend test. Number of tumor bearing animals/ number of animals at risk (excluding those that died before observation of the first tumor). *,** Significance by Peto's prevalence test accounting for time to tumor and mortality; if not possible, pair-wise comparison at $p<0.05$, and $p<0.01$, respectively.

b/ IRDC data: first hyperplasia, adenoma, and carcinoma were observed on week 42 (200 ppm), 40 (50 ppm), and 42 (200 ppm), respectively.

c/ Squire data: first hyperplasia, adenoma, and carcinoma were observed on week 15 (50 ppm), 24 (100 ppm), and 45 (0 ppm), respectively.

d/ Busey data: first hyperplasia, adenoma, and carcinoma were observed on week 11 (50 ppm), 45 (0 ppm), and 45 (0 ppm), respectively.

e/ Surviving mice were sacrificed at week 55.

IV.B.5. Aggregate Exposure

For potential aggregate exposure, the critical NOELs should be based on common endpoints observed in the individual routes of exposure (U.S. EPA, 2001). For acute exposure, the common endpoint was decreased food consumption and body weight observed in both oral and dermal exposures. The critical NOELs (as absorbed doses) were 0.3 and 1.8 mg/kg/day, for oral and dermal exposures, respectively. For chronic exposure, only the critical oral NOEL (absorbed dose of 0.1 mg/kg/day) was available to address aggregate exposure.

IV.B.6. Summary

The critical NOELs and the endpoints for risk characterization of hydramethylnon in this document are listed in Table 27. For dietary exposure, the NOELs were used as exposure dosages. For dermal exposure of workers and residents, the NOELs as absorbed dosages were used since the exposure estimates are expressed in such terms. For aggregate exposure, the NOEL expressed as absorbed dose for each component (dietary or residential/occupational) was used. In addition, Table 27 showed the NOELs and endpoints that the U.S. EPA used in the establishment of the tolerance for pineapple (U.S. EPA, 2003). The current values used by U.S. EPA were different than those in the RED and in the time-limited tolerance assessment for pineapples (U.S. EPA, 1998a and 1998c). The comparison showed several differences between DPR and U.S. EPA:

1. Acute dietary exposure: DPR selected a NOEL of 3 mg/kg/day for clinical signs in rats given hydramethylnon for 5 days (Harnois, 1979) to address the exposure by the general population. Since incidence data were not given in the report, the signs were assumed to have occurred from an acute exposure. The U.S. EPA did not address the general population dietary exposure because there was no single dose endpoint in the database. Instead, the U.S. EPA addressed only the acute exposure of women of child-bearing age by selecting a reproductive toxicity endpoint (abortion) in rabbits with a NOEL of 5 mg/kg/day (IRDC, 1982d). Since the DPR NOEL value was lower than that for abortion, its use would address the abortion concerns raised by the U.S. EPA.

2. Chronic dietary exposure: DPR selected a NOEL of 1 mg/kg/day for clinical signs observed in a dog study (Marshall, 1980). In comparison, the U.S. EPA selected a NOEL of 1.66 mg/kg/day for testicular effects in rats from a 2-generation reproductive toxicity study (Schroeder, 1975). DPR had considered both studies, which were both acceptable under FIFRA guidelines, and decided on the dog study because of the lower NOEL and relevance of the endpoints. The use of 1 mg/kg/day as the critical NOEL by DPR would address concerns regarding testicular effects at a higher NOEL.

3. Residential dermal exposure: DPR selected NOELs from a FIFRA acceptable dermal toxicity study (Thompson, 1982) for acute and subchronic exposures. The use of studies conducted via the same route as human exposure was preferred since there were differences in the pharmacokinetics and toxicity of hydramethylnon between dermal and oral routes (see **IV.B. Selection of Critical NOELs**). For chronic exposure, an oral study was used because there was no dermal chronic toxicity study. In comparison, the U.S.

EPA used the same critical NOEL of 1.66 mg/kg/day (Schroeder, 1975) for all dermal residential exposure duration. This difference was mainly due to how DPR and U.S. EPA defined the exposure durations as footnoted in Table 27. The U.S. EPA durations were more broadly defined with some overlaps between duration. An additional difference was the dermal absorption factors, which were 5% and 1% for DPR and U.S. EPA, respectively.

4. Residential inhalation exposure: DPR considered inhalation exposure to hydramethylnon as negligible and did not estimate exposures. U.S. EPA designated the 1.66 mg/kg/day (Schroeder, 1975) as the NOEL also for inhalation exposure.

5. Lifetime exposure: Both DPR and U.S. EPA concurred that the data showed suggestive evidence for oncogenicity and did not calculate oncogenic risk.

Table 27. Critical NOELs and endpoints for the risk characterization of hydramethylnon by DPR and U.S. EPA.[a]

Route of Exposure	DPR		U.S. EPA[b]	
	Duration[c]/ population	**NOEL[d]/ endpoint**	**Duration[c]/ population**	**NOAEL[d]/ endpoint**
Dietary	Acute - general population	3 mg/kg/day (0.3 mg/kg/day) Decreased body weight, clinical signs, reduced fertility in a rat oral study (Harnois, 1979)	Acute - women of child bearing age only	5 mg/kg/day Abortions in a rabbit oral study (IRDC, 1982d*)
	Chronic - general population	1 mg/kg/day (0.1 mg/kg/day) Clinical signs in a dog oral study (Marshall, 1980)	Chronic - general population	1.66 mg/kg/day Testicular effects in a rat oral study (Schroeder, 1975)
Dermal	Acute - residents and workers	50 mg/kg/day (1.8 mg/kg/day) Decreased food consumption in a rabbit dermal study (Thompson, 1982*)	All residential dermal exposures	1.66 mg/kg/day (0.017 mg/kg/day) Testicular effects in a rat oral study (Schroeder, 1975)
	Subchronic- residents and workers	50 mg/kg/day (1.8 mg/kg/day) Decreased food consumption in a rabbit dermal study (Thompson, 1982*)		
	Chronic- residents and workers	1 mg/kg/day (0.1 mg/kg/day) Clinical signs in a dog oral study (Marshall, 1980)		
Inhalation	All durations	not assessed	All residential inhalation exposures	1.66 mg/kg/day (1.66 mg/kg/day) Testicular effects in a rat oral study (Schroeder, 1975)

a/ *Study was considered acceptable to DPR according to FIFRA guidelines. Schroeder, 1975 supplemented an unacceptable reproductive toxicity study (Bio/dynamics, Inc., 1982) to fill the SB 950 data requirement.

b/ NOELs/endpoints were from U.S. EPA (2003). While U.S. EPA developed reference concentration for inhalation exposure, this route was not assessed in their risk assessments.

c/ DPR defined acute, subchronic, and chronic duration for workers and residents as single to few days, 60 days per season, and 60 days in a year. U.S. EPA defined these durations: short-term (1 to 30 days), intermediate-term (1 to 6 months), and long-term (several months to lifetime).

d/ For the DPR NOELs, the absorbed doses in parentheses were based on 10% and 5% for oral and dermal absorption factors, respectively, and amortized for daily exposure. For the U.S. EPA NOAELs, the absorbed doses in parentheses were based on 1% and 100% for dermal and inhalation absorption factors, respectively.

IV.B. EXPOSURE ASSESSMENT

Humans are potentially exposed to hydramethylnon via occupational, residential, and dietary activities. For occupational/residential exposures, three exposure groups are identified: (1) workers involved in agricultural uses, (2) workers involved in non-agricultural uses, and (3) non-user residents or passers-by on treated grounds (Appendix A). The exposure values are expressed as absorbed dosages using a 5% dermal absorption factor. The upper bound, average, and amortized exposure values are estimates for acute, subchronic, and chronic exposures, respectively (Table 28). The amortized values were the average values reduced by a factor of 6 to account for 60 days of use in a year (Appendix F). Inhalation exposure is considered insignificant since hydramethylnon has low vapor pressure and it is used in the form of granules. U.S. EPA also did not assess the inhalation exposure of hydramethylnon based on the same considerations.

For dietary exposure, the only food-related uses for hydramethylnon are on rangeland and pineapples. No tolerances are established for possible residues in the meat, milk, or meat byproducts from animals grazed on treated land because hydramethylnon is metabolized in these animals (U.S. EPA, 1998a). Secondary residues were also not expected from the use of hydramethylnon on pineapples (U.S. EPA, 1998c and 2003). Acute and chronic dietary exposures to potential hydramethylnon residues are conducted. Since pineapples are available in California throughout the year, seasonal exposure assessment is considered unnecessary.

IV.B.1. Occupational Exposure

For agricultural aerial and ground applications, there were no chemical-specific exposure data for any scenarios. The U.S. EPA Pesticide Handlers Exposure Database (PHED) was used to derive the exposure values. The workers were assumed to be exposed 60 days per season or per year. The upper bound exposures were 0.01 *u*g/kg/day for most workers and 0.05 *u*g/kg/day for loaders of aerial application (Table 28A. Handlers). The average exposures ranged from 0.004 *u*g/kg/day (flaggers of aerial application) to 0.023 *u*g/kg/day (loaders of aerial application). The amortized exposures ranged from 0.001 *u*g/kg/day (flaggers and applicators of aerial application, applicators of ground application) to 0.004 *u*g/kg/day (loader of aerial application).

Harvesters and other fieldworkers could be exposed to hydramethylnon via contact with dislodgeable residues on treated foliage (Table 28A. Fieldworkers). Since there were no chemical-specific data on reentry exposure or dislodgeable foliar residues, the exposures estimated were based on results of foliar residue studies for other pesticides, and on default dermal transfer rates used for three levels of contact activities. The exposure activities for these fieldworkers were categorized into low, medium, and high reflecting the extent of the contact. Low exposure crops/activities included row crops, low-growing ornamentals, turf, and cotton. Medium exposure crops/activities included some row crops, field crops, and fruit trees. High exposure crops/activities included mostly labor- and contact-intensive activities, such as grape girdling and greenhouse plant harvesting. The exposure estimates were intended as an initial estimate of the range of acute and long-term reentry exposures involved and were all based on reentries at day 0 post-application. For low to high exposures, the range of the upper bound

values was 0.4 *u*g/kg/day to 2.0 *u*g/kg/day. These same values were assumed for subchronic exposures. The chronic exposure was 1/6 (60 days/365 days) of the upper bound values.

Table 28. Upper-bound and average daily hydramethylnon exposures estimated for workers and residents.[a]

Work Task	Absorbed Dosage (*u*g/kg/day)		
	Upper bound	**Average**	**Amortized Exposure[b]**
A. Agricultural Workers			
Handlers			
1. Aerial application			
Loader	0.05	0.023	0.004
Applicator	0.01	0.006	0.001
Flagger	0.01	0.004	0.001
2. Ground application			
Applicator	0.01	0.005	0.001
Fieldworkers[c]			
Low exposure	0.4	0.4	0.07
Medium exposure	1.0	1.0	0.17
High exposure	2.0	2.0	0.33
B. Non-agricultural Workers			
1. Aerial application			
Loader	0.05	0.023	0.004
Applicator	0.01	0.006	0.001
Flagger	0.01	0.004	0.001
2. Ground application			
Applicator	0.01	0.005	0.001
3. Via spreader			
Resident	0.003	NA	NA
PCO	0.01	0.01	0.002
4. By bare hand			
Resident	0.05	NA	NA
PCO	0.24	0.24	0.04
C. Residents[d]			
Low exposure	0.4		
Medium exposure	1.0	NA	NA
High exposure	2.0		

a/ Exposure estimates were from Tables 2 to 4 of the Hydramethylnon Human Exposure Assessment (Appendix A). NA=not applicable.

b/ Amortized exposure to account for 60 days per season (60 days/365 days =6) exposure as per memorandum (Appendix F).

c/ The exposure levels were categorized into low, medium, and high reflecting the extent of the contact. Low exposure crops/activities included low growing plants, medium exposure crops/activities included some row crops and fruit trees. High exposure crops/activities included mostly labor- and contact-intensive activities. The exposure estimates for upper bound were intended as an initial estimate of the range of acute and long-term reentry exposures involved and assumed exposures on day 0 post-application.

d/ Exposure estimates for field workers were used for residents to determine the maximum possible exposure levels.

For non-agricultural uses of hydramethylnon granules in homes or commercial buildings, the exposure estimates for aerial and ground applications were the same as those for agricultural uses (Table 28.B.1. and 2.). For use in spreaders (hand-held rotary or push-type), the exposure estimates were based on data for diazinon granules (Table 28.B.3.). For application by hand, the PHED was used (Table 28.B.4.). In each case, the pest control operators (PCO) were assumed to apply the granules approximately 5 times more often (*i.e.*, working longer hours per day) than that for residents. For use of hydramethylnon via spreaders or bare hands, the residents were assumed to have only acute exposures and the exposures were 0.003 *u*g/kg/day and 0.05 *u*g/kg/day, respectively. For the PCOs, the average exposures were assumed to be the same as the acute (for lack of data on the former): 0.01 *u*g/kg/day (via spreader) and 0.24 *u*g/kg/day (by hand). Their amortized exposures were 0.002 *u*g/kg/day and 0.04 *u*g/kg/day, respectively. No handling exposures were expected from the application of Ready-to-use roach or ant killer bait products since these products are in child-resistant packages with minimal direct contact.

IV.B.2. Residential Exposure

For outdoor exposures of non-user residents and passers-by (including children), the highest possible exposures were those for fieldworkers who come in direct contact with treated foliages. Depending on the use and extent of contact, the exposures ranged from 0.4 to 2.0 *u*g/kg/day (Table 28.C.). The actual exposures were likely to be lower since people would unlikely be present on treated areas infested with ants and hydramethylnon is not used as a prophylaxis. Exposure of children to hydramethylnon from indoor use was considered insignificant since the bait stations are in child-resistant packages. There were no ambient air data for hydramethylnon and inhalation exposure was not expected.

IV.B.3. Dietary Exposure

The DEEM™ (Dietary Exposure Evaluation Model) computer program, version 7.76, was used to estimate the dietary exposures. The program contained individual food consumption from the USDA 1994-1996 and 1998 nationwide Continuing Survey of Food Intake by Individuals (CSFII). The CSFII is conducted by USDA's Agricultural Research Service that provides information on 2-day food and nutrient intakes by 20,607 individuals of all ages. The 1998 supplemental survey included additional consumption data for infants and children (newborn through age nine). For acute exposure, only the users (consumers) were considered in the estimates. For chronic exposure, the mean consumption rates for all surveyed were used.

As a first-tier approach, the tolerance (0.05 ppm) and one-half of the tolerance for hydramethylnon in pineapples were used as the residue values for acute and chronic exposure, respectively. Also, 100% of crop treatment was assumed. Potential exposure to hydramethylnon in the drinking water was not estimated since environmental fate studies (Appendix B) showed hydramethylnon unlikely to leach from the soil to the ground water. There are no water health advisory levels. U.S. EPA recently estimated the levels in the water using simulation or modeling based on data for use pattern, physical characteristics, and environmental fate of hydramethylnon (U.S. EPA, 2003). For acute exposure, the levels were 76.09 ppb for surface water, and 0.035 ppb for ground water. For chronic exposure, the levels were 1.45 ppb for surface water, and 0.035 ppb for ground water. When these estimated levels were used to

determine the drinking water level of concern (DWLOC), the aggregate exposure (dietary and drinking water exposures) did not exceed the acute or chronic population adjusted dose (aPAD or cPAD).

The acute dietary exposures ranged from 0.299 *u*g/kg/day (females 13-19 years, not pregnant or nursing) to 1.262 *u*g/kg/day (nursing infants, <1 years old) (Table 29). For chronic dietary exposures, the range was 0.001 *u*g/kg/day for several adult groups to 0.010 *u*g/kg/day (females 13+ years, nursing).

Table 29. Acute and chronic dietary exposures to hydramethylnon from use on pineapples.[a]

Population Subgroups	**Acute Exposure 97.5 percentile *u*g/kg/day**	**Chronic Exposure Average *u*g/kg/day**
U.S. Population	0.643	0.002
Western Region	0.985	0.003
Hispanics	1.050	0.003
Non-Hispanic Whites	0.551	0.002
Non-Hispanic Blacks	0.524	0.003
Non-Hispanic/Non-White/Non-Black	0.974	0.003
All Infants	1.062	0.006
Nursing Infants (<1 year old)	1.262	0.003
Non-nursing Infants (<1 year old)	1.035	0.008
Children 1-6 years	1.125	0.009
Children 7-12 years	0.526	0.004
Females 13+ years (pregnant/not nursing)	0.487	0.003
Females 13+ years (nursing)	1.046	0.010
Females 13-19 years (not pregnant or nursing)	0.299	0.001
Females 20+ years (not pregnant or nursing)	0.447	0.001
Females 13-50 years	0.599	0.002
Females 16-65 years	1.041	NA
Males 13-19 years	0.419	0.001
Males 20+ years	0.335	0.001
Males 16-65 years	0.929	NA
Seniors 55+ years	0.309	0.001

a/ Dietary exposures were based on the use of tolerance (0.05 ppm) and 1/2 of tolerance as residue levels for acute and chronic dietary exposures, respectively. The consumption rates were based on the CSFII consumption surveys for 1994 to 1998. NA=not available from the DEEM software.

IV.B.4. Aggregate Exposure

Aggregate exposure is the combined exposure of multiple pathways such as air, food, and drinking water. As stated in the U.S. EPA guidelines, aggregate exposure should link spatial (*i.e.*, all pathways agree in place/location), temporal (*i.e.*, all pathways agree in time), and demographic (*i.e.*, all pathways agree in age/gender/ethnicity and other demographic characteristics) characteristics of each route in effort to derive a consistent and reasonable assessment of total exposure (U.S. EPA, 2001). The estimation of exposure and risk should focus on the individual with each of the individual sub-assessments "linked back to the same person and the aggregate intake should reflect the food, drinking water, and residential intakes that are for the same individual at the same time, in the same place, and under the same demographic conditions" (U.S. EPA, 2001). The collective exposures and risks for individuals are then used to develop those values for population subgroups and the entire population.

For hydramethylnon, the underlying assumption was that there is potential for aggregate exposure from occupational/residential and dietary exposures. Due to insufficient exposure data, it was not possible to estimate the aggregate exposure at an individual level. Instead, this assessment divided the population broadly into workers (who work with hydramethylnon) and residents (those who come into contact with hydramethylnon treated areas). The dietary component of the workers was based on the exposure of adults (16+ years old) and adults (20+ years old) from individual consumption surveys for acute and chronic exposures, respectively. The adult (16+ years old) group was selected because 16 years old is the minimum age requirement for workers. Since the dietary exposure software could not calculate chronic exposure for the same age group, the 20+ years old group with the highest exposure was used instead. The dietary exposure for residents was based on the highest exposed children group, 1-6 years (Table 29). The infant subgroups were not considered since it is unlikely that they would come into contact with treated ground due to their limited mobility. Their dietary exposures (1.035 to 1.262 *u*g/kg/day for acute and 0.003 to 0.008 *u*g/kg/day for chronic exposures) were similar to those for children 1-6 years old. A summary of the components for aggregate exposure is shown below:

Exposed Groups	Aggregate Exposure	Selected exposure values	
		Dermal Exposure (Table 28)	Dietary Exposure (Table 29)
Workers	Acute	Upper bound values	97.5th percentile exposure for 16+ years females (1.041 *u*g/kg/day)
	Chronic	Amortized values	Mean exposure for 20+ years old females (0.001 *u*g/kg/day)
Residents	Acute	Upper bound values	97.5th percentile exposure for 1-6 years old children (1.125 *u*g/kg/day)
	Chronic	Amortized values	Mean exposure for children 1-6 years old (0.009 *u*g/kg/day)

IV.C. RISK CHARACTERIZATION

The potential health hazard associated with the use of hydramethylnon was considered for occupational and residential as well as dietary exposures. For single routes of exposure, non-oncogenic effects were characterized in terms of a margin of exposure (MOE), defined as the ratio of the critical NOEL to the estimated human exposure levels. For aggregate exposure, the risk was determined by a total MOE approach[8] (U.S. EPA, 2001). This approach is used when there is a common effect with different NOELs for the different routes of exposure but with the same uncertainty factor applied for both routes. The magnitude of the total MOE expresses only the risks for the specific endpoints.

The critical NOELs were listed in Table 27 and the exposure levels for the various exposure scenarios were presented in Tables 28 and 29. The NOELs as absorbed doses were used to calculate the MOE from occupational and residential exposures, which were expressed in absorbed terms. The uncorrected NOELs were used for dietary exposures, which were based on the residues on the treated commodities and consumption rate, not absorbed doses.

IV.C.1. Occupational Exposure

The acute and subchronic margins of exposure for occupational exposures ranged from 900 (high activity field workers) to >100,000 (most of other workers) (Table 30 A. and B.). The chronic margins of exposure ranged from 303 (high activity field workers) to >100,000 (most of other workers).

IV.C.2. Residential Exposure

The acute margins of exposure for residential exposures ranged from 900 (high activities) to 4,500 (low activities) (Table 30 C.). These MOEs were based on exposures for field workers on day 0 post-application. There were no subchronic or chronic exposures.

IV.C.3. Dietary Exposure

The margins of exposure for acute dietary exposure to pineapple ranged from 2,377 (nursing infants, <1 year old) to 10,042 (females 13-19 years, not pregnant or nursing) (Table 31). For chronic dietary exposure, the margins of exposure were all greater than 100,000.

IV.C.4. Aggregate Exposure

The margins of exposure for aggregate acute exposure ranged from 686 (high activity residents) to >2,000 (most worker scenarios). They were essentially those for dietary exposure

8 $\text{Total MOE} = \dfrac{1}{\dfrac{1}{\text{MOE oral}} + \dfrac{1}{\text{MOE dermal}}}$

alone because dietary was the major component of the exposure and the critical NOEL was lower than that for dermal exposure. On the other hand, the aggregate chronic exposure was largely contributed by occupational or residential dermal component, as the chronic dietary exposure was relatively low. The MOEs for aggregate chronic exposure ranged from 303 (high activity residents) to 87,608 (aerial application applicators and flaggers).

Table 30. Margins of Exposure for hydramethylnon exposures estimated for workers and residents.[a]

Work Task	Margins of Exposure		
	Acute	Subchronic	Chronic
A. Agricultural Workers			
Handlers			
1. Aerial application			
Loader	36,000	78,260	25,000
Applicator	>100,000	>100,000	100,000
Flagger	>100,000	>100,000	100,000
2. Ground application			
Applicator	>100,000	>100,000	100,000
Fieldworkers			
Low	4,500	4,500	1,429
Medium	1,800	1,800	588
High	900	900	303
B. Non-agricultural Workers			
1. Aerial application			
Loader	36,000	78,260	25,000
Applicator	>100,000	>100,000	100,000
Flagger	>100,000	>100,000	100,000
2. Ground application			
Applicator	>100,000	>100,000	100,000
3. Via spreader			
Resident	>100,000	NA	NA
PCO	>100,000	>100,000	50,000
4. By bare hand			
Resident	36,000	NA	NA
PCO	7,500	7,500	2,500
C. Residents[b]			
Low	4,500	NA	NA
Medium	1,800	NA	NA
High	900	NA	NA

a/ The MOEs were based on exposure estimates in Table 28 and the NOELs for dermal exposure in Table 27. The upper bound, average, and amortized exposure estimates were used to address acute, subchronic, and chronic exposures, respectively. The absorbed NOELs were 1.8 mg/kg/day (decreased food consumption in rabbits after dermal exposure, Thompson, 1982), 1.8 mg/kg/day (decreased body weight and increased relative liver weights in rabbits after dermal exposure; Thompson, 1982), and 0.1 mg/kg/day (clinical signs in dogs after oral exposure; Marshall, 1980) for acute, subchronic, and chronic exposures, respectively. NA=no exposures estimated.

b/ Exposures were based on those for field workers and day 0 post-application.

Table 31. Margins of exposure for acute and chronic dietary exposures to hydramethylnon.[a]

Population Subgroups	Acute Exposure	Chronic Exposure
U.S. Population	4,663	435,944
Western Region	3,047	367,701
Hispanics	2,855	289,074
Non-Hispanic Whites	5,442	496,463
Non-Hispanic Blacks	5,727	355,306
Non-Hispanic/Non-White/Non-Black	3,079	382,936
All Infants	2,824	155,740
Nursing Infants (<1 year old)	2,377	358,561
Non-nursing Infants (<1 year old)	2,899	128,207
Children 1-6 years	2,667	116,348
Children 7-12 years	5,703	260,266
Females 13+ years (pregnant/not nursing)	6,164	393,465
Females 13+ years (nursing)	2,869	104,782
Females 13-19 years (not pregnant or nursing)	10,042	800,192
Females 20+ years (not pregnant or nursing)	6,708	706,964
Females 13-50 years	5,006	571,290
Females 16-65 years	2,881	NA
Males 13-19 years	7,152	951,746
Males 20+ years	8,964	897,183
Males 16-65 years	3,228	NA
Seniors 55+ years	9,712	952,835

a/ Exposures are presented in Table 29 and the NOELs for oral exposure in Table 27. The exposures were not corrected for absorption. The NOELs were 3 mg/kg/day (decreased body weights, clinical signs, and reduced fertility in rats after oral exposure, Harnois, 1979) and 1 mg/kg/day (clinical signs in dogs after oral exposure, Marshall, 1980) for acute and chronic exposures, respectively.

Table 32. Margins of Exposure for aggregate exposure to hydramethylnon.[a]

Work Task	Margins of Exposure	
	Acute	Chronic
A. Agricultural Workers		
Handlers		
1. Aerial application		
Loader	2,668	24,146
Applicator	2,836	87,608
Flagger	2,836	87,608
2. Ground application		
Applicator	2,836	87,608
Fieldworkers		
Low	1,756	1,426
Medium	1,108	588
High	686	303
B. Non-agricultural Workers		
1. Aerial application		
Loader	2,668	24,146
Applicator	2,836	87,608
Flagger	2,836	87,608
2. Ground application		
Applicator	2,836	87,608
3. Via spreader		
Resident	2,867	NA
PCO	2,836	46,697
4. By bare hand		
Resident	2,668	NA
PCO	2,081	2,491
C. Residents		
Low	1,675	NA
Medium	1,075	NA
High	673	NA

a/ The aggregate MOEs for workers (A. and B.) were based on the MOEs for worker exposures (Table 30) and the MOEs for dietary exposures of females 16+ years for acute exposure and 20+ years for chronic exposure (Table 31). The aggregate MOEs for residents (C.) were based on the MOEs for residents (Table 30) and MOEs for dietary exposures of children 1-6 years (Table 31). The equation for the calculation was:

$$\text{Total MOE} = \frac{1}{\frac{1}{MOE_{occupational\,/\,residential}} + \frac{1}{MOE_{dietary}}}$$

V. RISK APPRAISAL

V.A. INTRODUCTION

Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that adverse effects of a substance will occur in humans under specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization, which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed.

V.B. HAZARD IDENTIFICATION

The uncertainties in hazard identification were associated with the paucity of acute toxicity studies to define the NOEL for a single day exposure. For both acute dermal and oral exposures, the critical NOELs were based on effects observed after several days of dosing. The critical acute dermal NOEL of 50 mg/kg/day (absorbed dose of 2.5 mg/kg/day) was based on decreased food consumption observed after 6 days (Thompson, 1982). The actual acute NOEL for a single day exposure was likely to be higher than the 5-day NOEL, resulting in higher MOEs than those calculated using a 5-day NOEL. Similarly, the critical acute oral NOEL was based on clinical signs observed in rats during the 5-day experiment (Harnois, 1979). Since incidence data were not given in the report, the signs were assumed to have occurred from a single (acute) exposure. Other short-term studies, such as the developmental toxicity studies, with clinical signs reported also did not provide occurrence information (Bio/dynamics, Inc., 1979; IRDC, 1982d; Tables 24 and 25). The acute single day oral NOEL could be higher than the 3 mg/kg/day value if the effects reported were a result of several days of repeated exposures.

Another uncertainty was the use of an oral study to address chronic dermal exposure due to a lack of such a study. In the extrapolation, the assumption was that the pharmacokinetics for the two routes and different species were the same and that correction for absorption was sufficient to determine the dose. The actual chronic dermal NOEL may be higher or lower than those for the oral route. This assumption could also add uncertainty to determination of oncogenic potential for human exposure to hydramethylnon. The weight of evidence analysis showed suggestive evidence of oncogenicity for hydramethylnon based on results from a lifetime feeding study in mice (IRDC, 1982b; **IV.B.4.Oncogenicity - Weight of Evidence**). The uncertainty was associated with the assumption that similar results would be observed with dermal exposure, a more relevant route for human exposure.

V.C. EXPOSURE ASSESSMENT

There were uncertainties associated with the occupational and residential exposure estimates and they are briefly discussed in this section (full discussion in Appendix A). The dermal exposures of the applicator, flagger, and loader might be underestimated by 2-fold due to the use of exposure rates from small sample size in the PHED for these workers. The exposures could be overestimated by 15 to 20% due to the default body weight and surface areas values used. On the other hand, other sources of overestimation were: unlikelihood that the same worker or same work crew would handle hydramethylnon for 60 days out of a 90 day season, actual exposure was less than a full day, and actual dermal absorption factor in humans was less than for rats (5%). The use of day 0 after application for reentry likely resulted in overestimation of harvester/field worker exposures.

The dietary exposures were likely overestimates of actual exposure since the tolerance was the basis for the residues and 100% of the pineapple crop was treated with hydramethylnon. Since the margins of exposure were greater than the benchmark level of 100 for the protection of human health, there was no need to refine the residues for more realistic estimation of the dietary exposure. The aggregate exposures were a combination of occupational/residential exposure and dietary exposures. These values were also likely to be overestimates due to the conservative assumptions used to estimate the exposures for each of the components. While potential exposure to hydramethylnon in the drinking water was not included in the dietary or aggregate exposure in this document, MOEs were expected to remain acceptable if the drinking water component was added since the estimated residues were relatively low (U.S. EPA, 2003). The U.S. EPA assessment showed that the aggregate exposures (dietary and drinking water exposures) for acute and chronic exposures were less than their respective population adjusted doses.

V.D. RISK CHARACTERIZATION

The assessment showed that the MOEs for hydramethylnon exposures under all scenarios and routes were greater than 100 (Tables 30-32). When the NOEL for non-oncogenic effects is based on animal data, a MOE of 100 is generally considered adequate for human health protection against potential acute or chronic toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for intraspecies variability, as well as an uncertainty factor of 10 for interspecies variability. These uncertainty factors assume that humans may be up to 10 times more sensitive to the effects of a chemical than the most sensitive experimental animal; and that there may be up to a 10-fold variation in response between humans. For oncogenicity, the risk from lifetime exposure was not calculated since the weight of evidence analysis showed suggestive evidence and the increase in lung tumor incidences was marginal (see discussion under **IV.B.4. Oncogenicity – Weight of Evidence**).

V.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

The Food Quality Protection Act of 1996 mandated U.S. EPA to "upgrade its risk assessment process as part of the tolerance setting procedures" (U.S. EPA, 1997a and b). The improvements to risk assessment were based on the recommendations from the 1993 National Academy of Sciences report, "Pesticides in the Diets of Infants and Children" (NRC, 1993). The Act required an explicit finding that tolerances are safe for children. U.S. EPA was required to use an extra 10-fold safety factor to account for potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S. EPA determined, based on reliable data, that a different margin would be safe. In addition, U.S. EPA must consider: (1) aggregate exposure from all non-occupational sources; (2) effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity; (3) the effects of *in utero* exposure; and (4) the potential for endocrine disrupting effects. In recent documents, U.S. EPA used 3 criteria for the determination of the factor: (1) completeness and reliability of the toxicology database, (2) completeness and reliability of the exposure database, and (3) potential pre- and post-natal toxicity (U.S. EPA, 1999 b, c, and d). The latter criterion requires the consideration of evidence for developmental and reproductive toxicity, and developmental neurotoxicity.

V.E.1. Pre- and Post-natal Sensitivity

In recent years, issues have been raised on the adequacy of the risk assessment process to address the potential increased sensitivity of infants and children to pesticides. The basis of this concern was discussed in detail in the 1993 National Research Council report: *Pesticides in the Diets of Infants and Children* (NRC, 1993). In the 1994 DPR report: *A Joint Review of Existing Federal and State Pesticide Registration and Food Safety Programs* (also known as the PECC report), the PECC recommendation was to address the susceptibility issue on a case-by-case basis when specific data become available (DPR, 1994). A review of recent time-limited tolerances for pesticides showed that U.S. EPA generally applied an additional uncertainty factor of 10 for an incomplete database where one or more FIFRA required reproductive or developmental toxicity studies were not available. An additional uncertainty factor of 3 (MOE of 300) was used when the NOEL for developmental or reproductive effects was lower than that for maternal toxicity, or when there was no developmental neurotoxicity study. The criteria for the developmental toxicity testing included findings of teratogenicity to the central nervous system, neuropathology and neurotoxicity, hormone-like activity, and developmental toxicity (for effects other than structural abnormalities of the CNS) (Levine and Butcher, 1990). U.S. EPA has proposed that a development neurotoxicity study be included in the core toxicology data set (U.S. EPA, 1998d).

There was no evidence for increased sensitivity to the prenatal and post-natal toxicity of hydramethylnon when NOELs for developmental or reproductive toxicity were compared with those for maternal toxicity. In both the rat and rabbit developmental toxicity studies, the fetal NOELs were higher than the maternal NOELs (Table 7; Bio/dynamics, Inc., 1979; IRDC, 1982d). The only significant effects in the fetuses were reduced fetal body weight (rats and

rabbits) and ossification variations (rats only). In the 3-generation reproductive toxicity study, there was a reduction of pup weight at the same LOEL (50 ppm) as that for maternal body weight decrease and fertility reduction (Bio/dynamics, Inc., 1982). However, in the 2-generation reproductive toxicity study with a more complete protocol, there were no effects the pups at the highest dose tested (75 ppm) (Schroeder, 1995). While testicular effects were observed in several studies and might have contributed toward reduced fertility in the 2-generation reproductive toxicity study (Bio/dynamics, Inc., 1982), the NOELs for these effects were at or lower than those for fetal or pup effects. Overall, the critical NOELs selected for risk characterization addressed both testicular and fetal effect concerns.

With respect to neurotoxicity, hydramethylnon is not considered as a neurotoxicant. There were non-specific clinical signs observed which may have involved the nervous system or general stress due to treatment. For example, in the acute dermal study, the rabbits were reported to have diarrhea and lethargy during the 24 hours but at a high dose (2000 mg/kg) (Moreno *et al*., 1983b). In the 26-week dog study, soft stools, mucoid stools, and diarrhea were observed in dogs treated with 3 mg/kg/day (Marshall, 1980). The NOEL for these latter effects was selected as the critical NOEL for chronic exposure (Table 19).

Therefore, the current database did not show that infants and children may be more sensitive to the hydramethylnon effects. U.S. EPA did not use an additional uncertainty factor in the evaluation of the emergency exemption and tolerance for pineapple use (U.S. EPA, 1998c and 2003) and in the reregistration eligibility assessment (U.S. EPA, 1998a).

V.E.2. Aggregate Exposure

The potential for aggregate exposure was addressed in this document.

V.E.3. Cumulative Toxicity

Hydramethylnon is the only amidinohydrazone compounds with pesticidal activity (U.S. EPA, 1998c and 2003). U.S. EPA has concluded that hydramethylnon does not have a common mechanism of toxicity with other compounds.

V.E.4. Endocrine Effects

There is no evidence of hydramethylnon-induced endocrine disruption in the database.

VI. TOLERANCE ASSESSMENT

No tolerance assessment was performed since the only established tolerance for food use was on pineapple and the tolerance (0.05 ppm) was used as the residue value for dietary exposure assessment.

VII. CONCLUSIONS

The human health risk from potential exposure to hydramethylnon was evaluated in this Risk Characterization Document. The exposure scenarios included occupational and residential dermal exposures due to the handling of hydramethylnon during application, residential dermal exposure from direct contact to treated areas, dietary exposure from consuming treated pineapples, and the aggregate exposure from non-dietary and dietary sources. The risks associated with these exposures were assessed using toxicity endpoints from experimental animals and were calculated as margins of exposure. The critical acute oral endpoints were decreased body weight gain, clinical signs, and reduced fertility in rats. The critical acute and subchronic dermal endpoint was mainly decreased body weight gain in rabbits. The critical chronic oral and dermal endpoint was clinical signs in dogs. The database showed only suggestive evidence for oncogenicity and was insufficient to assess the human oncogenicity potential for hydramethylnon.

Overall, this assessment showed that human exposure to hydramethylnon was relatively low due to the physical and chemical properties and few uses. Worker exposures included workers involved in aerial, ground, and hand applications as well as harvesters and fieldworkers who may be in contact with treated foliage. The general public may be exposed to treated foliages. For these exposure scenarios, the margins of exposures were all greater than the benchmark of 100 for occupational, residential, dietary, or aggregate exposures to hydramethylnon. The risks associated with all current use scenarios should be considered acceptable.

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Appendix A

Occupational and Residential Exposure Assessment

HUMAN PESTICIDE EXPOSURE ASSESSMENT

HYDRAMETHYLNON

(An Insecticide for the Control of Ants and Cockroaches Primarily in Nonfood Areas in Domestic Dwellings and Commercial Establishments)

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HS-1804 February 26, 2004

ABSTRACT

Hydramethylnon (CAS name: tetrahydro-5,5-dimethyl-2(1*H*)-pyrimidinone [3-[4-(trifluoromethyl)phenyl]-1-[2-[4-(trifluoromethyl)phenyl]ethenyl]-2-propenylidene]hydrazone) is a trifluoromethyl aminohydrazone insecticide of low acute mammalian toxicity. It is a slow activating stomach toxicant registered for the control of a variety of ants (including fire ants) and cockroaches, primarily in noncrop and nonfood areas. From 1982 through 1998, a total of 2 illnesses/injuries occurring in California were reported to have been associated with exposure to hydramethylnon used alone, or used in combination with other pesticides. As of September 2001, 47 hydramethylnon products were actively registered in California, including the 4 allowed for use on container or field-grown ornamentals, non-bearing fruit, berries, and the like. Of the hydramethylnon active ingredient used in California today, more than 97% is for structural pest control. Despite this current use pattern, the present exposure assessment was performed to calculate the absorbed daily dosages (ADD) for (potential or actual) users and residents or bystanders of all groups, to the extent necessary. It is written to be an integral part (Volume 2) of the risk characterization document prepared by the Department of Pesticide Regulation for all legal uses of hydramethylnon. The toxicological endpoints for the risk assessment include developmental and male reproductive adverse effects. The best conservative estimate of (acute) ADD calculated for aerial or ground loaders working with hydramethylnon granules was 0.05 μg/kg BW/day. This was the highest calculated among the agricultural handlers. The highest ADD (from the dose range finder list) calculated for reentry exposure of fieldworkers, and for that of non-user residents as well, was 2.0 μg/kg BW/day; this was for individuals assumed to be involved in very high crop-contact or high exposure (post-application) activities. For homeowner users and non-agricultural handlers working in the industrial, institutional, or residential setting, the highest ADD observed was 0.24 μg/kg BW/day, that for pest control operators applying granules by (bare) hand. The results of two rat studies indicated that dermal absorption of hydramethylnon is likely to be less than 5% over a 10- or 24-hour exposure period. A review of the available animal metabolism studies revealed that once absorbed, hydramethylnon is excreted rapidly as unchanged parent compound (>70% of applied dose in 36 hours) primarily via the (rat) feces.

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HUMAN PESTICIDE EXPOSURE ASSESSMENT

HYDRAMETHYLNON

(An Insecticide for the Control of Ants and Cockroaches Primarily in Nonfood Areas in Domestic Dwellings and Commercial Establishments)

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Cal/EPA Department of Pesticide Regulation

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I. INTRODUCTION

Hydramethylnon is a tri-fluoromethyl aminohydrazone insecticide of low acute mammalian toxicity. It is a slow activating stomach toxicant registered for the control of a variety of ants and cockroaches, primarily in noncrop and nonfood areas. Over the years, 62 products have been registered in California that contain hydramethylnon as the active ingredient (AI). As of September 2001, 47 hydramethylnon products were actively registered, including the 4 allowed for use on field-grown ornamentals, non-bearing fruit, berries, and the like. Of the hydramethylnon AI used in California today, more than 97% is for structural pest control. Despite this current use pattern showing little or no use in agricultural fields, all potential exposures from all legal uses were considered in this exposure assessment as common practice. This practice is meant to address potential use pattern changes. For example, red imported fire ants are known to inhabit agricultural fields. These pests, which have been observed in the southern part of California, may migrate to the agricultural regions.

Introduced as an insecticide by American Cyanamid Company, hydramethylnon was first registered with the U.S. Environmental Protection Agency (U.S. EPA, 1999) in August 1980. In April 1991, U.S. EPA issued a Phase 3 Data Call-In (DCI) to require further registration data on product chemistry, on environmental fate, on toxicology, and on worker exposure. In 1995, U.S. EPA issued additional DCIs to require the submission of data on foliar residue dissipation, on dermal passive dosimetry exposure, and on inhalation passive dosimetry exposure. American Cyanamid subsequently also committed to amend their product labels to comply with state restrictions dealing primarily with labeling requirements (as outlined in Section V of the RED mentioned below). Upon reviewing some of the DCI data and the new labels, U.S. EPA (1999) prepared a Reregistration Eligibility Decision (RED) document for hydramethylnon. Although U.S. EPA has not yet made a determination regarding the common mode or mechanism of toxicity of hydramethylnon, they have concluded that the residential and occupational exposures involved are minimal.

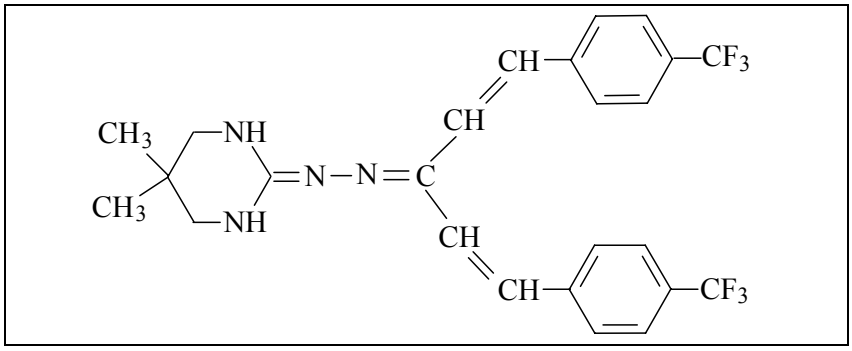
In spite of its relatively low acute toxicity observed in animals, hydramethylnon is currently among the Proposition 65 list of chemicals known to the state of California to cause cancer or reproductive toxicity. Hydramethylnon was first listed in California both as a developmental toxicant and as a male reproductive toxicant on March 5, 1999. According to the summary of toxicology data prepared by the Medical Toxicology Branch (MedTox) for hydramethylnon (Aldous, 1993), possible adverse effects were identified in chronic, oncogenicity, and reproduction studies. In part due to its low volatility, currently hydramethylnon is not included in the list of chemicals to be regulated by the Department of Pesticide Regulation (DPR) as toxic air contaminants.

A risk characterization document (RCD) is currently being prepared by DPR for all uses of hydramethylnon, partly in response to the insecticide's adverse developmental and male reproductive effects. The present human exposure assessment by the Worker Health and Safety Branch (WH&S) is written to be an integral part of this RCD.

II. EXPOSURE-RELATED FACTORS

1. Physical and Chemical Properties

Hydramethylnon (CAS name: tetrahydro-5,5-dimethyl-2(1*H*)-pyrimidinone [3-[4-(trifluoro-methyl)phenyl]-1-[2-[4-(trifluoromethyl)phenyl]ethenyl]-2-propenylidene]hydrazone); CAS Registry No. 67485-29-4; molecular formula $C_{25}H_{24}F_6N_4$; molecular weight 494.50) is a non-systemic insecticide. According to U.S. EPA (1999) and the open literature (e.g., Tomlin, 1994), technical grade hydramethylnon is a yellow to orange crystalline solid with a characteristic vegetable oil odor and a melting point of 189 – 191°C. It is insoluble in water (0.005 – 0.007 mg/L at 25°C), slightly to moderately soluble in alcohols, and soluble in acetone, chlorobenzene, and 1,2-dichloroethane. The vapor pressure is 2 x 10^{-8} mm of Hg at 25°C. The average partition coefficient (K_{ow}) of hydramethylnon between η-octanol and water was determined to be 27,965 (log K_{ow} = 4.45). It undergoes photolysis in sunlight. The following is the chemical structure of hydramethylnon:



2. Formulations and Label Uses

Technical hydramethylnon currently available in the United States is manufactured by American Cyanamid Company, under the trade name Amdro Technical Insecticide (EPA Reg.

No. 241-270). This product contains 95% AI and is intended only for use in the formulation of other end-use hydramethylnon insecticide products. As of September 2001, 47 hydramethylnon end-use products registered in California. These 47 end-use products were available in 4 formulations, as summarized in Table 1. The granular formulation may be applied via broadcast or to individual mounds for control of a variety of ants, including fire ants. Both the impregnated gel formulation and the tablet/cake/pellet type are ready-to-use (RTU) products intended to be indoor bait stations for the control of (primarily household) ants and cockroaches. Hydramethylnon is also used for the control of subterranean termites in a bait package that is sold to and only for use by certified Pest Control Operators (PCOs).

Table 1. Uses/Formulations of Hydramethylnon Products Registered in California

Uses	Formulations[a]	Crop Types/Sites
Greenhouse	granular (0.73%)	mushroom house, ornamentals, non-bearing fruit/nuts, etc.
Nursery (including non-commercial)	granular (1.0%, 0.73%); bait cartridge (0.3%); RTU bait (0.9%, 1.0%, 1.65%, 2.0%)	ornamentals, field crops, hobby greenhouse, refuge sites, etc.
Forests/NonCrop	granular (0.73%)	trees, tree plantations, etc.
Rights-of-Way	bait cartridge (0.3%) granular (0.73%)	windbreaks, utility poles, fences, retaining walls, etc.
Conservation Lands	granular (0.73%)	protected grasslands/forests, etc.
Parks/Paths	gel (2.0%); bait cartridge (0.3%) granular (0.73%, 1.0%)	recreation areas, camps, golf courses, landscape plants, etc.
Animal Premises/ Cemeteries	gel (2.0%, 2.15%); bait cartridge (0.3%); granular (0.73%, 1.0%)	dairy barns, poultry houses, grassy areas, refuge sites, etc.
Waterways	granular (0.73%)	ant mounds
Abatement	granular (0.73%)	ant mounds
Structural (residential or industrial)	bait cartridge (0.3%); RTU bait (1%, 1.65%); gel (2.0%, 2.15%); granular (1.0%, 0.73%)	porches, driveways, sidewalks, garbage, buildings, homes, crawl spaces, attics, windowsills, etc.

[a] RTU = ready-to-use (in child-resistant disc); in parentheses are percent of active ingredient.

Use of hydramethylnon on pasture and rangeland grasses is permitted in some other states but not in California. For nonfood uses, the indoor and outdoor sites are rather broad. These areas include in and around homes, on lawns, in and around outside buildings/barns, rights-

of-way/uncultivated lands, agricultural soils/crops, golf courses, animal sleeping quarters, non-critical premises in hospitals or clinics, indoor and outdoor commercial/industrial equipment or establishment, and much more. In essence, the nonfood use sites cover just about all noncrop or nonfood areas where ants and roaches (of any type) frequent or colonize.

3. Label Precautions

The hydramethylnon products registered in California are all classified as having Category III toxicity (with the signal word CAUTION). The hazards from ingestion and dermal contact are indicated on the labels for all formulations other than the RTU type; and a statement of practical treatment or at least a contact number is included on all the 47 labels.

The labels for the four broader-use, 0.73% granular products (EPA Reg. Nos. 241-322-AA; 241-322-ZA; 241-322-ZB; and 241-322-ZC) specify that applicators wear waterproof gloves, long pants, a long-sleeved shirt, and shoes plus socks when working with the granules. These personal protective equipment (PPE) and clothing requirements are consistent with the Worker Protection Standard (WPS) set forth for agricultural pesticides [40 CFR 170.240(d)(4-6)]; the four products are allowed to be used on container or field-grown ornamentals, non-bearing fruit, berries, and the like. The restricted entry interval (REI) for use of these four products on agricultural commodities is 12 hours.

There are 6 other granular formulations among the 47 end-use products. These 6 other granule products are intended to be sprinkled or spread to small noncrop or nonfood areas. Of these 6, 4 (EPA Reg. Nos. 64240-1-ZA, 64240-25-AA, 64248-6-ZA, and 64248-19-AA) require the use of gloves when handling the granules.

No PPE or (specific) clothing requirements are indicated on the labels for the other two granule products, or for the rest of the non-granular formations (i.e., those used as bait stations). None of the 47 product labels contains any statement about dermal sensitization.

4. California Requirements

California Code of Regulations (2001) requires that employees wear protective eyewear when engaged in certain handling tasks, including many of those considered in this exposure assessment. Other special requirements are already covered on the product labels.

5. Usage in California

The use of hydramethylnon in California was not included in the 1994 or the 1995 Pesticide Use Report (PUR). The PUR for 1996 (DPR, 1999a), 1997 (DPR, 1999b), and 1998 (DPR, 2000) indicated that over 97% of the hydramethylnon AI used in each of these three years was for structural pest control. The remaining 1 to 3% was primarily for public health or regulatory pest control, landscape maintenance, rights-of-way, and research commodity. The annual usages of hydramethylnon in 1996, 1997, and 1998 were 1,741, 5,456, and 3,183 lbs, respectively.

6. Sales in California

The PURs do not cover pesticide uses in all residential areas, such as those by homeowners or non-licensed persons. To some extent, the annual usage for these unreported sites can be

approximated from the mill assessment data, which are confidential information where fewer than 4 registrants are involved. Nonetheless, at the time of this documentation, these sales data cannot be made available for internal review (due to some sales reporting errors to be corrected by the registrants).

7. Reported Illnesses in California

The Pesticide Illness Surveillance Program database maintained in WH&S indicated that from the first available year 1982 through 1998, a total of 2 cases occurring in California were reported to have been probably associated with exposure to hydramethylnon used alone (Mehler, 2000). Both cases, one (a bystander office worker) occurring in 1996 and the other (a bystander convalescent hospital employee) in 1998, were classified as having a probable association with hydramethylnon used for structural pest control treatment. The 1996 case was reported as having respiratory symptoms only, whereas the 1998 case involved skin and systemic effects. Neither case resulted in hospitalization or in any days lost from work.

8. Significant Exposure Scenarios

According to the RED (U.S. EPA, 1999), hydramethylnon has established tolerances from use on grasses in pastures and rangeland. However, the use of the insecticide on these two commodities is not permitted in California. U.S. EPA has also concluded that exposure of hydramethylnon to drinking water is not likely, given that this insecticide hydrolyzes rapidly, especially under sunlight. Consumer use in residential settings thus appears to be the greatest source of potential exposure to children or non-user adult residents.

Based on current registered uses and in accordance with the RED, 6 major exposure scenarios were identified for hydramethylnon users or handlers. These exposure scenarios are: (1) loading granular for aerial or ground application; (2) flagging for granular aerial application; (3) application of granular by aerial equipment; (4) application of granular by ground equipment (e.g., tractor-drawn, gandy type spreader); (5) loading and application of granular by hand-held equipment; and (6) hand broadcast (distribution) of granular.

The potential for post-application (reentry) occupational and residential exposures also exists. As pointed out in the RED, there could be some exposure to hydramethylnon for golf-course maintenance workers, for mowers on sod farms, and for persons in buildings following indoor applications. Four granular product labels (EPA Reg. Nos. 241-322-AA; 241-322-ZA; 241-322-ZB; and 241-322-ZC) permit the use of hydramethylnon in and around field-grown or container ornamentals in California. Therefore, flower cutters and the like could be exposed to hydramethylnon in greenhouses or open fields where ornamentals were treated.

The exposure scenario that involves occupational or residential handling of the RTU type, child-resistant bait stations was not included in this exposure assessment. Such exposure was expected to be biologically insignificant, or to be much less than that from hand broadcasting the granular products under scenario 6 above. Also excluded from consideration was the use scenario involving applications of gel bait to cracks and crevices by syringe dispenser. Although inadvertent exposure to the dispenser or treated surface may result in some gel on the hand surface, it is expected that either this gel layer should soon be wiped off by the applicator, or the gel would get on to only a small part of the hand.

III. ACUTE TOXICITY AND PHARMACOKINETICS

1. Acute Toxicity and Dermal Sensitization

Acute toxicity has been investigated in animals for technical (≥ 95% AI) hydramethylnon. According to U.S. EPA (1999), the acute dermal LD_{50} for this technical grade was >2,000 mg/kg in rabbits (Toxicity Category III). The acute inhalation LC_{50} for 4 hours of whole-body exposure to this technical grade was 2.9 mg/L in male and female rats combined (Toxicity Category IV). The acute oral LD_{50} for this technical grade was 1,146 mg/kg in male and female rats combined (Toxicity Category III). U.S. EPA considered the eye and the dermal irritation observed from exposure to this technical grade in rabbits to be, respectively, moderate (Toxicity Category IV) and none (Toxicity Category IV). For other formulations, especially those of 2% gel, the acute toxicities were concluded by MedTox (Rubin, 1993), by U.S. EPA (Dykstra, 1988), and by WH&S (Knaak, 1983) to be generally less severe than those observed for this technical grade. Based upon the findings of a study using both a technical formulation of slightly lower grade (92%) and a 3.2% concentrate (Siglin and Becci, 1982), U.S. EPA also determined that hydramethylnon is not a dermal sensitizer.

2. Dermal and Inhalation Absorption

There are no human data for dermal absorption of hydramethylnon. Nor is there any human or animal dermal absorption study available for the technical grade. Two animal dermal absorption studies are available, however, with the gel formulations.

In one study (Frantz and Beskitt, 1993), young adult (approximately 8 weeks old) male Sprague-Dawley rats were dosed topically with a 2.15% (by weight) gel preparation of ^{14}C-hydramethylnon. A preliminary review of the data indicated that as much as 2.0% of the radioactivity might have been absorbed from a 10- or 24-hour exposure, if the residues bound to the skin at the application site were included.

The skin of young male Sprague-Dawley rats was also used in another absorption study (Sharp, 1993). The test material used was from a slightly different gel preparation containing 2.16% AI (by weight) of ^{14}C-hydramethylnon. In this second study, the amount of radioactivity absorbed appeared to be slightly higher than that observed in the first study; it might have been as much as 3% for a 10-hour exposure, again if the amount of radioactivity in the skin of the test site were included.

Based on the results of these two animal studies, and on the fact that no dermal absorption data were available for the technical or the granular formulations, a dermal absorption of 5% was used in this exposure assessment. This determination was based on the concern that gel inert ingredients might *retard* the percutaneous absorption of hydramethylnon to a greater extent than the granular inerts would. There is indication (Dugard, 1977) that percutaneous absorption of chemicals varies with the substance (vehicle) in which the active chemical is suspended or contained. Another more important reason for doubling the observed dermal absorption is that the applied doses in the above two studies were over 100 $\mu g/cm^2$, a level typically many times above the range of human doses encountered in pesticide exposure assessment. There is some indication (Wester and Maibach, 1976; Thongsinthusak *et al.*, 1999) that as the amount of test material on the skin increases (10- to 100-fold), the efficiency

of absorption decreases (2- to 5-fold) although the total amount absorbed always increases. U.S. EPA used 1% in their RED for hydramethylnon (1999). Their value was derived from the same two studies but without accounting for the residues bound to the skin.

No inhalation absorption studies were available for hydramethylnon. Because inhalation exposures from the various label uses of hydramethylnon were considered to be insignificant compared to dermal exposure, no attempts were made to determine inhalation absorption in this exposure assessment. U.S. EPA (1999) also reached the same conclusion regarding inhalation exposure to hydramethylnon. Otherwise, the default values used by WH&S for inhalation uptake and intake for most (especially for non-volatile) chemicals, including hydramethylnon, would be 50% and 100%, respectively (Thongsinthusak *et al*., 1993).

3. Animal and Human Metabolism

Human Studies. No metabolism or pharmacokinetic studies were available or submitted by the registrants for evaluation of hydramethylnon's biotransformation directly in humans, as such human studies apparently had never been conducted or reported.

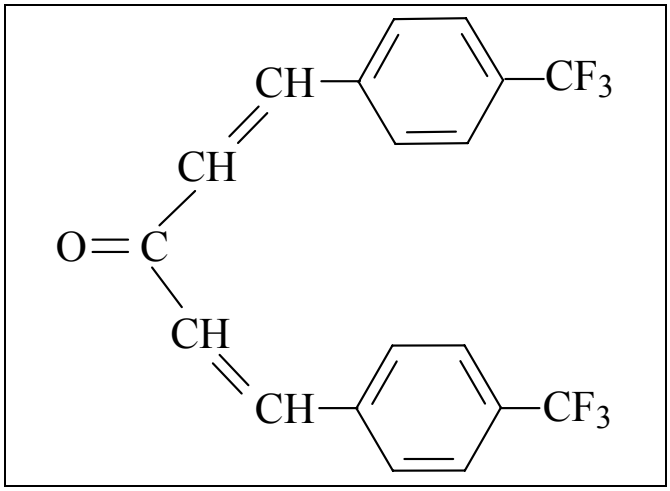
Animal Studies. In a metabolism study by Zdybak and Robinson (1992), five young male and five young female Sprague-Dawley rats were dosed by gavage with ^{14}C-labeled hydramethylnon in either the phenyl or the pyrimidinyl ring. These rats received a single low dose of approximately 3 mg/kg rat body weight, a single high dose of approximately 100 mg/kg, or an *un*labeled low dose (i.e., ~ 3 mg/kg) once daily for 14 consecutive days followed by a single *labeled* low dose on day 15. Urine and feces were collected over 7 days. The collection of expired carbon dioxide and volatile organic compounds was not attempted on grounds that a 3-day preliminary study had shown no exhalation of such materials. More than 89% (after adjustment to 100% recovery) of the applied dose was recovered in feces over the 7-day period, with most of the radioactivity (≥95%) being the unchanged parent compound. In contrast, the urine contained only a small amount (<5%) of parent compound and a variety of minor polar (e.g., benzoate and cinnamate) metabolites combined. Most of the elimination occurred within the first 24 to 36 hours after dosing. There was no significant sex or dose-related variation observed in these urine and fecal eliminations.

In another radiobalance study (Hussain *et al*., 1979), five groups of 3 Sprague-Dawley male rats each were given a single oral dose equivalent to 10 ppm of the benzylic, ^{14}C-labeled hydramethylnon in their daily diet, plus an additional group serving as controls. These animals were sacrificed in groups at 24, 48, 96, 144, or 216 hours following dosing. Approximately 90% of the radioactivity was found to have been excreted within 9 days. Of this amount, 88.4% was in feces and 1.7% in urine. The radioactivity eliminated in the feces during the first 24 hours, which amounted to 71.5% of the oral dose, contained 92.7% of the unchanged parent compound. The urine contained mostly polar metabolites but no parent compound.

In order to elucidate the metabolic pathways beyond the excretion pattern, in the second study additional male Sprague-Dawley rats were treated with a higher oral dose of hydramethylnon labeled ^{14}C in either the benzylic (equivalent to 74 ppm in diet) or the pyrimidinyl (equivalent to 79 ppm in diet) ring, plus a control group. These rats were

sacrificed in groups at 24, 48, and 96 hours. Analysis of tissue extracts from rats treated with these high doses showed that in the fat and kidney, most of the radioactivity was again associated with the unchanged parent compound.

There were 18 or more hydramethylnon metabolites identified in the liver from the tissue extraction analysis. Of these, the most significant other than the parent compound was 1,5-bis(α,α,α-trifluoro-*p*-tolyl)-1,4-pentadien-3-one. The following is the chemical structure of this significant metabolite.



IV. ENVIRONMENTAL CONCENTRATIONS

1. Ambient Air

No data on ambient air concentration of hydramethylnon were submitted to WH&S. Ambient air data for this chemical are not anticipated to be available any time soon, especially when the insecticide is not on the list of toxic air contaminants and is not considered a volatile or a semi-volatile compound.

2. Dislodgeable Foliar Residues

Despite the DCI (Data Call-In) issued in 1995 by U.S. EPA (1999) requiring the submission of foliar residue data, there were no chemical-specific dislodgeable foliar residues (DFR) studies available for hydramethylnon. Surrogate residue data and assumptions were hence used to estimate post-application exposure from dermal contact with foliar residues.

3. Turf and Other Surface Residues

There were also no chemical-specific data on other surface residues such as those on sod-farm or golf course turfgrass, which may not be considered as the same type of foliar residues as those present on foliage of more common agricultural commodities. Surrogate residue data and assumptions were hence also used to estimate post-application exposure from dermal contact with surface residues.

V. EXPOSURE ASSESSMENT

To facilitate discussion, the exposure scenarios identified in Section II-8, which were based on formulations and use patterns summarized in Table 1, were subsumed into three groups: (1) working with hydramethylnon for agricultural use; (2) working with hydramethylnon for non-agricultural use; and (3) children and adult non-user residents or passers-by. These three user groups are not necessarily mutually exclusive in terms of the types of exposure potential involved. For example, hydramethylnon may also be applied to airports, corrals, forests, or uncultivated areas in a relatively large operation via ground or even aerial equipment. Another point noteworthy is that those working with hydramethylnon for non-agricultural use may include both PCOs and resident users. Both residents and PCOs may apply granular bait by hand or via a hand-held spreader. In accordance with U.S. EPA (1999), inhalation exposures to hydramethylnon in all cases were estimated to be insignificant (compared to dermal exposure) partly due to its low vapor pressure and the size of the granules involved (which are oily in nature and larger than 140 microns, and hence less inhalable). No chemical-specific data on worker exposure were available for any of the use scenarios.

1. Agricultural Use

Handlers. The exposures to granular hydramethylnon for applicators, loaders, and flaggers are summarized in Table 2. The basic assumptions used in the calculations are footnoted in the table. The baseline dermal exposure rates used for these workers were based on the arithmetic means derived from the Pesticide Handlers Exposure Database (PHED, 1995) surrogate subsets appended to this document. The subsets were not limited to A or B grade quality data (as common practice), but in a couple of cases here extended to lower grades due to scarcity of data. Several worker exposure studies were evaluated by WH&S (Formoli and Fong, 1995), in which exposures were monitored for pilots, aerial flaggers, and aerial loaders handling the 10G formulation of molinate. The dermal exposure rates derived from these formulation-specific studies (as well as from their evaluations by WH&S) were not used as surrogate here because molinate is a much more volatile chemical and available in 50- and up to 1,500-lb bulk bags. In contrast, the 0.75% hydramethylnon granules are available in 4.5-lb bags. In addition to the differences in loading and application equipment involved, the exposure rates reported for molinate were all per hour, not per pound of AI handled (thus further making it not a good surrogate to use). The basic assumption is that more work and time will be required to fill up, say, a 500-lb hopper if much smaller bags are used.

As reflected in Section II-5, to this date hydramethylnon has not been truly used on agricultural crops. However, the exposures to hydramethylnon were considered here for agricultural workers because agricultural uses are allowed by four product labels registered in California (EPA Reg. Nos. 241-322-AA; 241-322-ZA; 241-322-ZB; and 241-322-ZC). It is important to note that certain fire ants species such as red imported fire ants are known to inhabit fields where their large above-ground mounds can become a pest problem in planting and harvesting crops. For example, this species will feed on wheat, corn and sorghum seed, and the like. These ants are exothermic (i.e., cold-blood) creatures. Their body temperatures and physiological functions thus necessarily depend on the outside temperature, meaning that they are unlikely a year-long pest in (the same) agricultural fields. In short, because outdoor fire ants and the kind are seasonal pest problems typically lasting no more than 3 months per

year, and for lack of specific use data, the seasonal exposure frequencies for these agricultural handlers were assumed to be roughly 60 days (less weekends and reapplication intervals). *As footnoted in Table 2, the upper-bound and the average absorbed dosages were estimated for acute and subchronic or chronic exposures, respectively.*

Table 2. Upper-bound and Average Daily Exposures Estimated for Agricultural Handlers Working with Hydramethylnon Granules[a].

Work Task	Exposure[b] (µg/lb AI)	Maximum Label Rate[c] (lb AI/acre)	Acres/Day[d] upper	Acres/Day[d] ave.	Daily Exposure (µg/person)[e] upper	Daily Exposure (µg/person)[e] average	Absorbed Dosage (µg/kg/day)[f] upper	Absorbed Dosage (µg/kg/day)[f] average
1. aerial								
loader	7.2	0.015	600	300	64.8	32.4	0.05	0.023
applicator	2.0	0.015	600	300	18.0	9.0	0.01	0.006
flagger	1.3	0.015	600	300	11.7	5.9	0.01	0.004
2. ground								
applicator[g]	10.5	0.015	100	50	15.8	7.9	0.01	0.005

[a] upper-bound and average are for acute and subchronic or chronic exposures, respectively; workers were assumed to wear long pants, a long-sleeved shirt, shoes plus socks, and waterproof gloves, as per label requirements; exposure frequencies for these work groups were all assumed to be 60 days per season as well as per year (*see* text for justification).

[b] dermal exposure rate from PHED (*see* Appendix for subsets attached and the Exposure Appraisal subsection for further discussion).

[c] maximum label rate, as based on the four 0.73% granular products discussed in Section II-3.

[d] the upper (bound) is the default maximum assumed for lack of specific use data; this default maximum is not unreasonable, in that 15 of the 97 aerial applicators (replicates) in PHED treated more than 600 acres per monitoring duration, with the highest total daily usage observed being 1,061 acres (*see* Dong, 1999; Dong and Haskell, 1999 for further discussion); the average (ave.) value is assumed to be half of the maximum used here, and is the maximum used by U.S. EPA (1999) in their RED for hydramethylnon (based on information submitted to them by registrants).

[e] daily exposure (µg/person) = (dermal exposure rate) x (maximum label rate) x (daily acreage).

[f] absorbed dosage (µg/kg/day) = (daily exposure) x (5% dermal absorption) x (70 kg body weight)$^{-1}$; *see* Section III-2 for dermal absorption, and the 70 kg body weight is the average for male and female adults combined (U.S. EPA, 1997), as for a hypothetical person.

[g] including loading (i.e., exposure rate = 10.5 µg/lb AI handled = [7.2 µg/lb AI handled from mixing/loading] + [3.3 µg/lb AI handled from using a drop-type tractor-drawn spreader]).

Fieldworkers. Harvesters and other fieldworkers are subject to exposure from contact with dislodgeable hydramethylnon residues present on treated foliage. Data on reentry exposure to hydramethylnon for these workers were not available to WH&S. For these fieldworkers, it is

thus necessary to extrapolate the dermal exposure from a dermal transfer rate or factor, which is defined here simply as the ratio (or sometimes some other relation, such as linear regression) of hourly dermal exposure typically in μg/hr to DFR in μg/cm^2. Both of these variables should be measured more or less at the same time. The term DFR is defined as the amount of residues that can be removed from both sides of treated foliage surfaces using aqueous surfactant. When multiplied with a proper dermal transfer rate, the DFR under study may be readily converted to hourly dermal exposure of workers entering a treated area. This conversion is based on the common assumption that *(dermal exposure) = (dermal contact or transfer rate)* x *(surface concentration)*.

Table 3. Upper-bound Range Finder Daily Reentry Exposure to Hydramethylnon for Fieldworkers (and Residents) Engaged in Low, Medium, and High Crop Contact/High Exposure Activities[a].

Exposure[b] Activities	DFR (μg/cm^2)[c] (at 0.015 lb AI/acre)	Dermal Transfer[d] (μg/hr per μg/cm^2)	Daily Exposure[e] (μg/person)	Absorbed Dosage[f] (μg/kg/day)
low	0.035	2,000	560	0.4
medium	0.035	5,000	1,400	1.0
high	0.035	10,000	2,800	2.0

[a] workers were assumed to wear long pants, a short-sleeved shirt without gloves; ***these range finder post-application exposures were also intended for residents reentering treated sites*** (*see* discussion in text).

[b] as examples, low exposure crops/activities include mostly row crops, low-growing ornamentals, established turf, and (cotton) scouting; medium exposure crops/activities include some row crops, mostly field crops, and mostly fruit trees, such as ornamental trees, shrubs, and sod farm turf; high exposure crops/activities include mostly labor- and contact-intensive activities, such as grape girdling and harvesting of greenhouse roses (*see*, e.g., Dong, 1994, 1995, 1999; Dong and Haskell, 1999 for more specific examples).

[c] estimates for DFR (dislodgeable foliar residues) were based on an upper confidence limit (UCL) for the generic *mean* initial deposition generalized from 21 foliar residue studies on 14 pesticides (Dong, 1993; *see* also the section on Exposure Appraisal). This UCL value (2.36 μg/cm^2 per lb AI sprayed before adjustment for the maximum label rate of 0.015 lb hydramethylnon AI/acre) was calculated from the algorithm for upper confidence limit for the mean, as outlined in Appendix 6 (*see* text for further discussion).

[d] these upper-bound dermal transfer rates (μg/hr per μg/cm^2) were based primarily on those observed or used in earlier pesticide exposure assessments (*see* Dong, 1994, 1995, 1999; Dong and Haskell, 1999; Haskell, 1995); they are consistent with those used in the RED by U.S. EPA (1999).

[e] daily exposure (μg/person) = (DFR) x (dermal transfer rate) x (8 hours/day).

[f] absorbed dosage (μg/kg/day) = (daily exposure) x (5% dermal absorption) x (70 kg body weight)$^{-1}$; *see* Section III-2 for dermal absorption, and the 70 kg body weight is the average for male and female adults combined (U.S. EPA, 1997), as for a hypothetical person.

There were no chemical-specific DFR data available to WH&S. A conservative or *first-tier* range finder approach was thus used to assess the reentry exposures in question. This approach involved the use of dermal transfer rates at three exposure activity levels and an

upper confidence limit for the generic *mean* initial deposition of DFR. The three dermal transfer rates (factors) used were 2,000, 5,000, and 10,000 μg/hr per μg/cm^2, representing typically as the maximum for low, medium, and high crop contact or high exposure activities, respectively, as reflected in earlier pesticide exposure assessments (e.g., Dong, 1994, 1995, 1999; Dong and Haskell, 1999; Haskell, 1995). This range of dermal transfer rates is also consistent with that used by U.S. EPA (1999) in their RED for hydramethylnon.

The upper-bound *mean* initial deposition (2.36 μg/cm^2 per lb AI sprayed) was generalized from 21 foliar residue studies on 14 liquid pesticides (Dong, 1993), following the algorithm presented in Appendix 6 (*see* also the section on Exposure Appraisal for use of liquid formulations as surrogate). It was calculated from the arithmetic mean of 2.0 μg/cm^2/lb AI sprayed + [(2 standard deviations) ÷ (sample size of 21)$^{-1/2}$] in an attempt to represent a 95% upper confidence limit for the mean initial deposition. This upper-bound mean initial deposition rate (which later applied to hydramethylnon's maximum label rate) again is comparable to that used by U.S. EPA, after taking into account the potential for residue build-up due to carry-over from reapplication. U.S. EPA assumed a rate estimate of 20% of the AI applied as their agency's default, yielding 2.2 μg/cm^2 per lb AI sprayed. The reentry exposures estimated from using the surrogate rates and DFR are summarized in Table 3 above. For reasons given earlier for handlers, the exposure frequencies for all fieldworkers were also assumed to be 60 days.

It is important to note that the estimations presented in Table 3 are solely for the purpose of finding the range of acute and long-term reentry exposures involved. The intention was to determine if upon a preliminary assessment based on an array of conservative assumptions, there is still a concern with reentry exposure and hence a need for the provision of use- and chemical-specific data on the dissipation of hydramethylnon DFR. Since there were no chemical-specific data on DFR dissipation, the dose range as estimated was deemed sufficient and necessary for both the acute and the subchronic or chronic reentry exposures. Otherwise, the DFR used for estimation of subchronic or chronic reentry exposures typically should be based on those specific to the *average* reentry days, not to day 0 post-application (*see* the Exposure Appraisal section for further discussion).

2. Non-Agricultural Use

Potential handler exposures from the use of granular hydramethylnon in *large* non-agricultural operations (if any in future) were assumed to be similar to those presented in Table 2. (That is, the exposures estimated for Scenarios 1 and 2 in Table 4 below were actually reproduced from those presented in Table 2.) For application of the granular bait in small operations, such as when applying the granules in or around homes or commercial establishments, two surrogate exposure rates were used. The dermal exposure rate calculated for granular diazinon (Dong, 1999), after adjustment for maximum label rate, was used for loading and applying hydramethylnon with a hand-held rotary or push-type granular spreader

For dispersion by hand, the PHED exposure rate (taking into account the small contribution from inhalation) based on arithmetic mean was used (as used in Dong, 2001). The exposures calculated with these two surrogate exposure rates are summarized in Table 4. As footnoted in this table, the commercial operators (i.e., the PCOs) were assumed to apply the granules

Table 4. Upper-bound and Average Daily Exposures Estimated for Non-Agricultural Handlers Working with Hydramethylnon Granules[a].

Work Task	Exposure[b] (mg/lb AI)	Maximum Label Rate[c] (lb AI/acre)	Acres/Day[d] upper	Acres/Day[d] ave.	Daily Exposure[e] (µg/person) upper	Daily Exposure[e] (µg/person) average	Absorbed Dosage[f] (µg/kg/day) upper	Absorbed Dosage[f] (µg/kg/day) average
1. aerial								
loader	0.0072	0.015	600	300	64.8	32.4	0.05	0.023
applicator	0.002	0.015	600	300	18.0	9.0	0.01	0.006
flagger	0.0013	0.015	600	300	11.7	5.9	0.01	0.004
2. ground								
applicator[g]	0.0105	0.015	100	50	15.8	7.9	0.01	0.005
3. via spreader[h]								
residents					3.8	NA	0.003	NA
PCOs					18.8	18.8	0.01	0.01
4. by bare hand[i]								
residents	200.0	0.015	0.02	0.02	66.0	NA	0.05	NA
PCOs	200.0	0.015	0.11	0.11	330.0	330.0	0.24	0.24

[a] upper-bound and average are for acute and subchronic or chronic exposures, respectively; for scenarios 1 and 2 dealing with large non-agricultural operations, workers were assumed to wear long pants, a long-sleeved shirt, shoes plus socks, and waterproof gloves (as would agricultural workers); users in scenarios 3 and 4 are not required to wear additional clothing or personal protective equipment; and exposure frequencies for these worker groups (excluding residents) were all assumed to be 60 days per season as well as per year (*see* text for justification).

[b] dermal exposure rates were from PHED and, for scenarios 1 and 2, identical to those listed in Table 2 (*see* Appendix for subsets attached and the Exposure Appraisal subsection for further discussion).

[c] maximum label rate, as was based on the four 0.73% hydramethylnon granular products discussed in Section II-3; for some uses, the 1.0% granular is also available but for smaller operations leading to lower daily usage.

[d] except otherwise noted, the upper (bound) is the default maximum assumed for lack of specific use data; this default maximum is not unreasonable, in that 15 of the 97 aerial applicators (replicates) in PHED treated more than 600 acres per monitoring duration, with the highest total daily usage observed being 1,061 acres (*see* Dong, 1999; Dong and Haskell, 1999 for further discussion); the average (ave.) value is assumed to be half of the maximum used here and is the maximum used by U.S. EPA (1999) in their RED for hydramethylnon.

[e] except otherwise noted, daily exposure (µg/person) = (dermal exposure rate) x (maximum label rate) x (daily acreage/usage).

[f] absorbed dosage (µg/kg/day) = (daily exposure) x (5% dermal absorption) x (70 kg body weight)$^{-1}$; *see* Section III-2 for dermal absorption, and the 70 kg body weight is the average for male and female adults combined (U.S. EPA, 1997), as for a hypothetical person.

[g] including mixing/loading (i.e., exposure rate = 10.5 µg per lb AI handled = [7.2 µg/lb AI handled from mixing/loading] + [3.3 µg/lb AI handled from ground application using a drop-type tractor-drawn spreader]).

[h] based on the diazinon dermal exposure rate (Dong, 1999) used as surrogate (*see* text for discussion); exposure for residents is assumed to be 5 times less than that for PCOs (*see* text for justification), NA = not applicable; exposure for PCOs was calculated as follows: 18.8 µg/person/day = (7.0 mg/day per 5.6 lb diazinon AI/acre) x (0.015 lb/acre for hydramethylnon); *no data could be used to yield a lower, average daily exposure*.

[i] exposure for residents is assumed to be 5 times less than that for PCOs (*see* text for justification); NA = not applicable; note that 0.11 acre ≈ 5,000 ft^2, as used in the RED (U.S. EPA, 1999*); no data could be used to yield a lower, average daily exposure*.

five times more often than residents would during each workday, under the assumption that the treatment for each site amounts to 1 to 2 hours of work and that PCOs work 8 hours a day. This five-fold assumption is largely consistent with that made by U.S. EPA (1999) in their RED for hydramethylnon.

As footnoted in Table 4, the upper-bound and the average absorbed dosages were estimated for acute and subchronic or chronic exposures, respectively. (Note that for Scenarios 3 and 4 involving small operations, no data could be used to yield a lower, average daily dosage for subchronic or chronic exposures.) It was expected that, like agricultural workers, PCOs would handle hydramethylnon granules no more than 60 days per *severe* ant season (and hence per year as well). Although roaches and non-fire ants can be a pest problem that in some places occurs all year long, the short- or long-term exposure to the bait placed indoors is expected to be insignificant for PCOs or resident users. There should be no direct hand or dermal contact with the hydramethylnon AI when applying the RTU roach or ant killer bait products which are child-resistant.

3. Non-User Residents and Passers-by

As first-tier range finder estimates (*see* Section V-1 under Fieldworkers for specific intention discussed), the reentry exposures presented in Table 3 for fieldworkers were also used for residential post-application exposure to hydramethylnon. These range finders were primarily for exposures from outdoor uses of hydramethylnon, from which children's exposure may be considered insignificant. Rarely are ant killers used for prophylactic purposes, especially in a relatively large area such as lawns or recreational areas. If hydramethylnon is applied to an outdoor place where ants actually exist, children normally are reluctant to play there for fear of ants. Children are not expected to have dermal contact with outdoor surface residues for 8 hours long per day. In accordance with more recent practice within WH&S (*see*, e.g., Dong, 1999; Formoli, 1996), one hour per day was assumed to be a reasonable estimate of the time that a child's full body would exert some type of aerobic contact with a treated surface. Although their body weight can be 7 times less than that of adults, children's body surface will also be 3 times smaller (thus resulting in a smaller dermal transfer rate). Also, as pointed out in Section II-8, this aminohydrazone insecticide hydrolyzes rapidly, especially in sunlight. The post-application exposures presented in Table 3 are thus more than enough as estimates for children. Children's exposure to the indoor bait is expected to be insignificant, given that the bait stations are child-resistant. *In short, as indicated in Table 3, the acute or long-term dosage for residents, including children, at most would range from 0.4 to 2.0 μg/kg/day*.

As stated in Section IV-1, no data on ambient air concentration of hydramethylnon were available. Ambient air data for this chemical are not anticipated to be available any time soon, however, especially when the insecticide is not on the list of toxic air contaminants. It was also justified earlier in this exposure assessment section that inhalation exposure to hydramethylnon was considered to be insignificant (especially when compared to the dermal exposure involved).

4. Exposure Appraisal

In using the absorbed dosages estimated in this exposure assessment, it is important to note that there were uncertainties built into the process that might not be immediately apparent to

the risk assessor or the risk manager. Many of these uncertainties tend to overestimate the exposure involved, but are typically hidden and therefore seldom acknowledged. Below is a brief account of the uncertainties associated with the factors used here that tend to have a critical impact on the exposures estimated.

Exposure Rates from PHED. The Pesticide Handlers Exposure Database (PHED) is a generic database for pesticide applicator, flagger, and mixer/loader exposures that contains measured values of inhalation and dermal exposure rates (e.g., μg per lb AI handled or per hour worked). Built into this database is the well-received, but not fully validated, concept that worker exposure is proportional to the amount of AI handled or the work time spent. WH&S has been using the exposure rates in terms of the amount of AI handled, primarily because the total work time spent within each handling task is not as well defined.

It is important to note that due to small sample size and for the statistical reasons given in Appendix 6 of this document, the PHED exposure rates (and hence the dosages as well) listed in Table 2 (and Table 4) might have been underestimated by approximately two-fold. Another alternative may be to increase the usual margin of exposure benchmark from 100 to 200 for this group of workers, for which the exposures were estimated using the PHED data. As explained in Appendix 6, the more correct approach may be to adjust the PHED mean exposure rates using the associated sample standard deviation and the sample size. However, the calculation of these sample statistics is difficult and complex, if not impossible.

In calculating the absorbed dosage in this exposure assessment, the average body weight assumed for workers and adults was 70 kg. The use of this default value might have overestimated slightly the dosage of hydramethylnon for those work groups whose exposure rates were calculated from PHED. The exposure rates calculated from PHED were based on exposure monitoring studies in which the volunteers were primarily male workers. The average body weight for the male volunteers is approximately 10% higher than the average of 70 kg assumed here for male/female adults (U.S. EPA, 1997; Thongsinthusak *et al.*, 1993), as for a hypothetical person. In addition, the total body surface area used for the PHED rate estimates was 21,760 cm^2, which is about 15% higher than that later re-calculated by U.S. EPA (1997) for an average male adult of 78 kg. In short, the dermal exposures calculated for these work groups were likely based on a somewhat higher ratio of body surface to body weight than should be, thus on this ratio alone possibly overestimating the exposures by 15 to 20%.

Other factors related to the use of PHED were discussed in a paper by Ross *et al.* (2000) and in the exposure assessment document for naled (Dong and Haskell, 1999). Included in the discussions in these two documents were the concerns or uncertainties with the use of non-detects, passive patch dosimetry data, data from partial vs. full workday exposure monitoring, and the arithmetic mean.

Exposure Frequencies (Seasonal Exposure). The annual or seasonal exposure frequencies (60 days) that were assumed for all commercial (agricultural and PCO) workers were likely to have been overestimated. It is unlikely for the same worker or same work crew to deal with severe (fire) ant problems every day in a season that typically lasts no more than 90 days. Yet

due to the lack of more specific data, such a conservative default was assumed. Such uncertainty might lead to an overestimation of the subchronic or long-term risks estimated in the risk characterization document for these workers.

Other Surrogate Data. The diazinon exposure rate used as surrogate in Section V-2 was actually based on a worker exposure study (Weisskopf *et al.*, 1988) conducted a decade ago. In that study, 15 workers were monitored for exposure to diazinon during application of a 14% granular formulation to planters, pastures, lawns, and shrub areas at the rate of 5.6 lb AI per acre. The various types of application equipment used by these workers included a hand-held 5-lb coffee can (for planters and shrub areas), a gandy spreader (for most lawn areas), a Lesco broadcast type spreader (for high grass areas), and a belly grinder (for pastures or areas of weeds). As explained in the exposure assessment document for diazinon (Dong, 1999), the average total body dermal exposure extrapolated from head patches (for upper body), leg patches (for lower body), and hand rinses was approximately 3.5 mg per shift for all work crews. This estimate was then doubled to account for the total daily exposure potential from both the morning and the afternoon shift. Daily exposure can easily be overestimated from less than a full day of exposure monitoring, since saturation or overloading is not an uncommon effect or phenomenon with dermal contact (i.e., skin loading). Ross *et al.* (2000) recently have gathered some empirical evidence supporting such a possibility.

Dermal vs. Oral Plasma Levels. Dosage is expressed as a single static value both in worker exposure and animal toxicology studies. The rates of dermal absorption and of dermal acquisition are often seen or expected to be lower than the rates of oral absorption and oral acquisition in animals used for toxicology testing. In short, the dose via the nonbolus dermal route is likely to be less potent than the same amount administered orally. This factor was also discussed in Dong and Haskell (1999) and in Ross *et al.* (2000).

Dermal Absorption. The dermal absorption of 5% estimated (see Section III-2) and used in this exposure assessment might still be underestimated somewhat, considering the small human doses involved compared to the experimental doses used. There is also no concrete information on the actual impact of the vehicle (gel inerts) used. However, as pointed out in Ross *et al.* (2000), a review on a handful of compounds tested and available indicated that the rat overestimated human dermal absorption by two- to ten-fold.

Dislodgeable Foliar Residues (DFR). The upper confidence limit (UCL) for the mean DFR initial deposition, that of 2.36 $\mu g/cm^2$ presented in Section V-1, was calculated using the algorithm presented in Appendix 6. It was based on the assumption that the individual DFR initial depositions from the 21 studies were randomly selected. This is by no means the case, however, since the 21 studies represented only non-random data available opportunistically at the moment. At one point, it was thought that the UCL should be calculated as the sample mean plus 2 sample standard deviations in order to obtain a more confident UCL for the mean. The final decision was to treat the 21 initial depositions in the sample as randomly selected. Although the calculated UCL of 2.36 $\mu g/cm^2$ was with a confidence much lower than 95%, it is comparable to the default value of 20% of the AI applied (i.e., 2.2 $\mu g/cm^2$ per lb AI applied) that U.S. EPA (1999) used in their RED for hydramethylnon.

Initial deposition of DFR is not chemical-specific. It is primarily a function of the amount of chemical applied and the equipment used. For lack of chemical- and use-specific data on DFR, the UCL of 2.36 $\mu g/cm^2$ calculated in this exposure assessment was intended for use to estimate both the acute and the subchronic or chronic reentry exposures. Ideally, the mean DFR at average reentry days should be used to calculate the estimate for a subchronic or chronic reentry exposure where dermal transfer rate is used (in place of actual exposure monitoring data). In this exposure assessment, the use of an UCL for the mean initial deposition rate (i.e., the mean DFR immediately following application) was considered to be sufficient and necessary. It was considered necessary because data on mean DFR at average reentry days were not available.

The use of an UCL for the mean DFR initial deposition was also considered to be sufficient for the acute reentry exposures. According to the product labels, the restricted entry interval (REI) is 12 hours. In practice, the earliest reentry time for a full 8-hour work is likely close to 24 hours post-application. By that time, the DFR is likely to have dissipated substantially, especially since hydramethylnon hydrolyzes rapidly in sunlight. Another safeguard factor is that the hydramethylnon granules, though oily in nature, are not as adhesive to the foliage as the sprays that were used in the 21 studies, from which the mean DFR was derived. The use of an upper-bound initial deposition was thus considered not necessary for estimating the acute reentry exposure. The estimation of such an upper-bound DFR (for the population, not the sample) is also difficult, if not impossible, in that the sample distribution so derived from the 21 studies on hand could not be proven to represent closely the population distribution.

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VII. APPENDICES

Appendix 1: Subset from PHED for Dermal Exposure of (Agricultural) Mixer/Loaders Working with Granules under Open-Pour Loading.

Appendix 2: Subset from PHED for Dermal Exposure of (Agricultural) Flaggers from Aerial Application of Granules.

Appendix 3: Subset from PHED for Dermal Exposure of (Agricultural) Aerial Applicators (Pilots) Working with Granules.

Appendix 4: Subset from PHED for Dermal Exposure of (Agricultural) Applicators Using a Drop-Type Tractor-Drawn Spreader to Distribute Granules.

Appendix 5: Subset from PHED for Dermal Exposure of Applicators Dispersing Granular Bait by Hand.

(These PHED attachments are neither photocopies nor, due to system incompatibility, from imported files; they were reproduced using a not-so-perfect scanner and hence necessarily with some typing for touch-up. Nonetheless, the accuracy of their contents had been checked to the extent possible.)

Appendix 6: Statistical Justification for Doubling the Mean Exposure Values When the Sample Size Is Small.

APPENDIX 1
(Aerial and Ground Mixer/Loaders)

Name: HYDRAMN1.MLOD Subset Specifications for HYDRAMN1.MLOD

With Solid Type Equal to 4 (Granules) and
With Mixing Procedures Equal to 1 (Open) and
With Outdoor Equal to "X" and
With Dermal Grade Uncovered Equal to "A" "B" and
With Hand Grade Equal to "A" "B"
Subset originated from MLOD.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS PER LB AI MIXED Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	.39	1.43	142.007	.5761	3
NECK.FRONT	Lognormal	.87	1.27	114.3228	.5317	3
NECK.BACK	Lognormal	.011	.1063	155.3151	.033	3
UPPER ARMS	Lognormal	.4365	.582	63.2474	.4942	6
CHEST	Lognormal	.71	.71	50	.6451	3
BACK	Lognormal	.71	.71	50	.6451	3
FOREARMS	Lognormal	.242	.5647	151.3193	.2991	6
THIGHS	Lognormal	.382	.5093	43.2947	.4813	3
LOWER LEGS	Lognormal	.238	.6347	135.5444	.3921	6
FEET						0
HANDS	Lognormal	.17	.6464	288.0105	.126	18
TOTAL DERM:		4.2237	4.1595	**7.1634**	4.2237	

95% C.I. on Mean: Dermal: [-90.3058, 104.6326]

Number of Records: 18
Data File: MIXER/LOADER Subset Name: HYDRAMN1.MLOD

APPENDIX 2
(Aerial Flaggers)

Name: HYDRAMN1.FLAG Subset Specifications for HYDRAMN1.FLAG

With Solid Type Equal to 4 (Granules) and
Subset originated from FLAG.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS PER LB AI MIXED Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	.455	.4875	72.3282	.3785	20
NECK-FRONT	Lognormal	.0375	.042	73.8095	.0328	20
NECK.BACK	Lognormal	.033	.0396	97.9798	.0286	20
UPPER ARMS						0
CHEST	Other	.355	.355	0	.355	4
BACK	Other	.355	.355	0	.355	4
FOREARMS						0
THIGHS						0
LOWER LEGS						0
FEET						0
HANDS						0
TOTAL DERM:	1.1499	1.2355	**1.2791**		1.1499	

95% C.I. on Mean: Dermal: [-4.4386, 6.9968]

Number of Records: 20
Data File: FLAGGER Subset Name: HYDRAMN1.FLAG

APPENDIX 3
(Aerial Applicators)

Name: HYDRAMN1.APPL Subset Specifications for HYDRAMN1.APPL

With Solid Type Equal to 4 (Granules) and
With Application Method Equal to 5 (Fixed Wing) or Equal to 6 (Rotary Wing)
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS PER LB AI MIXED Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	.26	.38	77.0789	.2981	13
NECK.FRONT	Lognormal	.03	.0381	74.8031	.0312	13
NECK.BACK	Lognormal	.022	.0322	77.0186	.0252	13
UPPER ARMS	Other	.291	.291	0	.291	9
CHEST	Other	.355	.355	0	.355	13
BACK	Other	.355	.355	0	.355	13
FOREARMS	Other	.121	.121	0	.121	9
THIGHS						0
LOWER LEGS						0
FEET	Other	.131	.2911	164.9948	.1727	9
HANDS	Lognormal	.1015	.0906	55.5188	.0756	9
TOTAL DERM:	1.6831	1.6665	**1.954**		1.7248	

95% C.I. on Mean: Dermal: [-9.2094, 13.1174]
Number of Records: 13
Data File: APPLICATOR Subset Name: HYDRAMN1.APPL

APPENDIX 4
(Ground Applicators)

Name: HYDRAMN2.APPL Subset Specifications for HYDRAMN2.APPL

With Solid Type Equal to 4 (Granules) and
With Application Method Equal to 17 (Solid Broadcast Spreader, Tractor/Truck/ Agricultural Uses) and
With Cab Type Equal to 3 (Closed Cab/Window Closed)
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, gloves

PATCH LOCATION	DISTRIB. TYPE	MICROGRAMS PER LB AI MIXED Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	.52	1.872	150.5983	.6409	5
NECK.FRONT	Lognormal	.105	.168	108.3333	.0774	5
NECK.BACK	Lognormal	.044	.066	100	.0387	5
UPPER ARMS	Other	.291	.291	0	.291	2
CHEST						0
BACK						0
FOREARMS	Other	.484	.484	0	.484	1
THIGHS						0
LOWER LEGS	Other	.238	.238	0	.238	2
FEET						0
HANDS	Lognormal	.1994	.1994	10.1304	.1989	2
TOTAL DERM:	1.9689	1.8814	**3.3184**		1.9689	

95% C.I. on Mean: Dermal: [-74.9963, 81.6331]
Number of Records: 5
Data File: APPLICATOR Subset Name: HYDRAMN2.APPL

APPENDIX 5
(Applicators Dispersing Granular Bait by Hand)

Name: HYDRAMN3.APPL Subset Specifications for HYDRAMN3.APPL

With Solid Type Equal to 4 (Granules) and
With Application Method Equal to 22 (Others) and
With Study ID Equal to 520 (on Dispersion of Granular Bait by Hand)
Subset originated from APPL.FILE

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, no gloves (*to be back-calculated from gloved hands using a 90% protection factor for gloves*)

PATCH LOCATION	DISTRIB. TYPE	Median	MICROGRAMS PER LB AI MIXED Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	5796.25	5911.864	65.7229	4628.645	16
NECK.FRONT	Lognormal	699.225	788.2688	56.8973	652.2670	16
NECK.BACK	Lognormal	490.452	500.2346	65.7229	391.6546	16
UPPER ARMS	Lognormal	12974.7	13233.48	65.7229	10361.05	16
CHEST	Lognormal	15828.2	16143.94	65.7229	12639.76	16
BACK	Lognormal	15828.2	16143.94	65.7229	12639.76	16
FOREARMS	Lognormal	5394.97	5502.581	65.7229	4308.201	16
THIGHS	Lognormal	17032.0	17371.78	65.7229	13601.10	16
LOWER LEGS	Lognormal	10611.6	10823.26	65.7229	8473.982	16
FEET						
TOTAL DERM:	67696.42	84655.6	**86419.34**		67696.4	

95% C.I. on Mean: Dermal: [-263592.6399, 436431.3225]

HANDS(**gloves**)	Lognormal	4555.6	**4660.951**	65.6070	3613.986	15
Inhalation	Lognormal	288.89	293.0964	68.6837	225.8441	16

Inhalation rate: 14 Liters/Minute
Number of Records: 16
Data File: APPLICATOR Subset Name: HYDRAMN3.APPL

APPENDIX 6

Statistical Justification for Doubling or Adjusting the Mean
Exposure Values When the Sample Size Is Small

This statistical argument is to justify that *whenever the sample standard deviation* is not available, the practice should be to double the *mean* exposure-related value derived from a set of data containing observations fewer than 5 or 6. The same approach is warranted for a sample size n between 6 and 15, if the associated coefficient of variation (CV) is expected to be greater than 100%.

When using the arithmetic mean of an exposure-related parameter in our exposure assessment, technically we should use the population mean μ, not the sample mean $\bar{u}$. In most cases, especially when both n is very large and CV is very small, $\bar{u}$ is close enough to μ with 95% or higher confidence that we can simply use the sample mean, and not the upper confidence limit (UCL) which otherwise would ensure that we are likely to have captured the *true* mean μ.

The UCL for μ, at α = 5%, is approximately equal to $\bar{u} + 1.96[s/(\sqrt{n})]$, where the sample standard deviation s is equal to $CV \cdot \bar{u}$. Note that when n is small (< 25 or so), the above z-value of 1.96 (at α = 5%, for a normal distribution) should be replaced with a slightly higher value from the Student t-distribution. The 95% UCL values calculated from assuming various values for CV and n are listed in Table A1 below.

In most cases, the CV on exposure and exposure-related variables are large, often in the range of 50 to 150%. This is the case with the exposure rates in U.S. EPA's Pesticide Handlers Exposure Database (PHED, 1995) calculated for the various body regions and for inhalation. The PHED subsets attached to the exposure assessment document for naled (Dong and Haskell, 1999), and to this exposure assessment document (as Appendices 1 through 4), readily demonstrate this range of CV. The exposure and field studies that WH&S staff have reviewed over the years also support such findings, as human factors are involved and many sample distributions that WH&S staff have encountered are closer to lognormal than normal. Based on the above CV range and when n is less than 5 or so, the 95% UCL listed in Table A1 are > $1.5\bar{u}$.

It is important to note that in using or interpreting the values (factors) listed in Table A1 below, we assume that the subjects (observations) in the sample were randomly selected. Otherwise, for the same confidence level, the UCL in question would be larger than that derived from Table A1, although its exact value cannot be determined statistically.

Table A1. 95% Upper Confidence Limit (UCL) for the Population Mean Based on the Various Assumed Sample Size *n* and Coefficient of Variation (CV), Calculated as a Factor of the Sample Mean $\bar{u}$ [a]

Sample Size	CV = 10% factor of sample mean	CV = 20% factor of sample mean	CV = 50% factor of sample mean	CV = 75% factor of sample mean	CV = 100% factor of sample mean	CV = 150% factor of sample mean	CV = 200% factor of sample mean
3	1.12	1.29	**1.72**	**2.08**	**2.44**	**3.17**	**3.89**
4	1.10	1.25	**1.63**	**1.94**	**2.25**	**2.88**	**3.50**
5	1.09	1.22	**1.56**	**1.84**	**2.12**	**2.68**	**3.24**
6	1.08	1.20	**1.51**	**1.77**	**2.02**	**2.53**	**3.04**
7	1.08	1.19	1.47	**1.71**	**1.94**	**2.42**	**2.89**
8	1.07	1.18	1.44	**1.66**	**1.88**	**2.33**	**2.77**
9	1.07	1.17	1.42	**1.63**	**1.83**	**2.25**	**2.67**
10	1.06	1.16	1.40	**1.59**	**1.79**	**2.19**	**2.58**
11	1.06	1.15	1.38	**1.57**	**1.75**	**2.13**	**2.51**
12	1.06	1.14	1.36	**1.54**	**1.72**	**2.08**	**2.44**
13	1.06	1.14	1.35	**1.52**	**1.69**	**2.04**	**2.39**
14	1.05	1.13	1.33	1.50	**1.67**	**2.00**	**2.34**
15	1.05	1.13	1.32	1.48	**1.65**	**1.97**	**2.29**
16	1.05	1.13	1.31	1.47	**1.63**	**1.94**	**2.25**
17	1.05	1.12	1.30	1.45	**1.61**	**1.91**	**2.21**
18	1.05	1.12	1.29	1.44	**1.59**	**1.88**	**2.18**
19	1.05	1.11	1.29	1.43	**1.57**	**1.86**	**2.15**
20	1.04	1.11	1.28	1.42	**1.56**	**1.84**	**2.12**
21	1.04	1.11	1.27	1.41	**1.55**	**1.82**	**2.09**
22	1.04	1.11	1.27	1.40	**1.53**	**1.80**	**2.07**
23	1.04	1.10	1.26	1.39	**1.52**	**1.78**	**2.04**
24	1.04	1.10	1.26	1.38	**1.51**	**1.77**	**2.02**
25	1.04	1.10	1.25	1.38	1.50	**1.75**	**2.00**
26	1.04	1.10	1.25	1.37	1.49	**1.74**	**1.98**
27	1.04	1.10	1.24	1.36	1.48	**1.72**	**1.96**
28	1.04	1.09	1.24	1.35	1.47	**1.71**	**1.94**
29	1.04	1.09	1.23	1.35	1.46	**1.70**	**1.93**
30	1.04	1.09	1.23	1.34	1.46	**1.68**	**1.91**

[a] 95% UCL $\approx \bar{u} + (2.5 \cdot \mathrm{CV} \cdot \bar{u})/\sqrt{n}) = \bar{u}\,[1 + (2.5 \cdot \mathrm{CV})/(\sqrt{n})] = \bar{u}$ [factor], where 2.5 is an approximate global Student *t*-value; those estimated factors exceeding 1.50 are listed in bold.

Appendix B

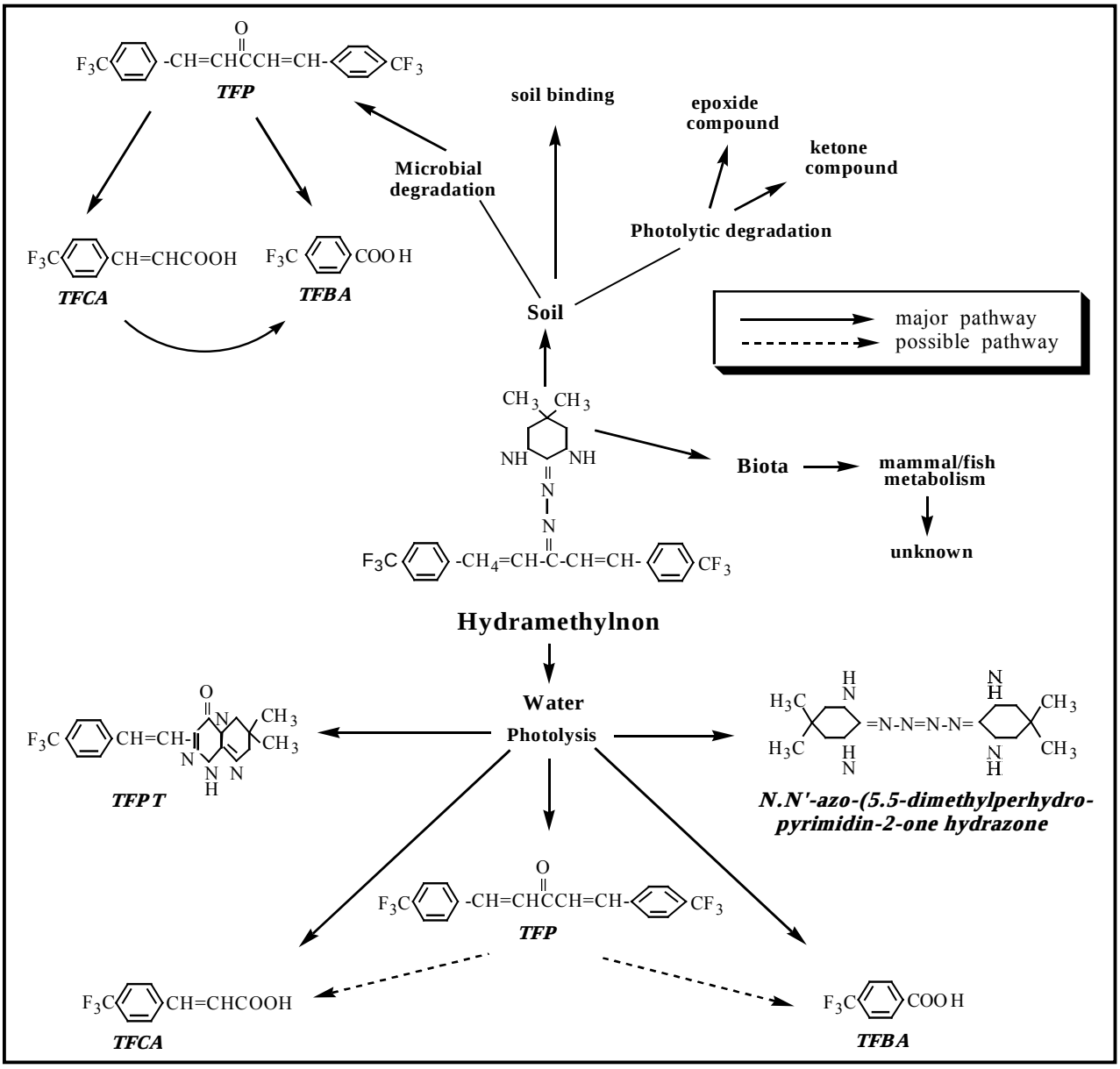
Environmental Fate of Hydramethylnon

Environmental Fate of Hydramethylnon

Juanita Bacey
Environmental Monitoring & Pest Management Branch
Department of Pesticide Regulation
830 K Street
Sacramento, CA 95814-3510

This document reviews all routes of environmental fate for hydramethylnon (HMN) with an emphasis on its use in controlling red imported fire ants. HMN is an amidinohydrazone insecticide. Chemical name: 5,5-dimethylperhydropyrimidin-2-one 4-trifluromethyl-alpha-(4-trifluoromethylstyryl)-cinnamylidenehydrazone

Hydramethylnon Degradation



Physical Properties

Molecular weight *	494.5 g
Water solubility *	0.005 - 0.007 ppm (at 20° C, pH 7.45)
Hydrolysis half-life	30 days (at 25° C)
Vapor pressure	6 x 10^{-8} mmHg (at 25° C)
Henry's Law constant	1.95 x 10^{-7} atm m^3/g mole
Soil photolysis half-life	5 days (at 27° C)
Aqueous photolysis half-life	< 1 hour (at 25 ^{o} C, pH 7.9)
Soil adsorption coefficient: Kd Koc	Varied soil types, pH of 6.5 to 7.1 1.04 x 10^3 – 1.72 x 10^3 cm^3/g 9.5 x 10^4 – 3.6 x 10^5 cm^3/g
Octanol-water coefficient log (Kow)	203 - 212
Aerobic half-life	383 days (at 25° C)
Anaerobic aquatic half-life **	455 - 552 days

* Data from the Agrochemicals Handbook, 1993.
** Data from EPA RED, 1998.
All other data from DPR PestChem Database (Kollman and Segawa, 1995)

Toxicity

Rat	Acute oral LD_{50}	1131 - 1300 mg/kg
Rabbit	Dermal LD_{50}	> 5,000 mg/kg
Mallard Duck	Acute oral LD_{50}	>2,510 mg/kg
Bobwhite quail	Acute oral LD_{50}	1,828 mg/kg
Rainbow trout	LC_{50}	0.16 mg/L (96h)
Channel catfish	LC_{50}	0.10 mg/L (96h)
Bluegill sunfish	LC_{50}	1.70 mg/L (96h)

Farm Chemicals Handbook 1997; The Pesticide Manual, 10th edition 1994

General Information and Mode of Action

Common trade names of hydramethylnon (HMN) are Amdro®, Combat®, and Maxforce®. It is also known as CL 217,300 and AC 217, 300. HMN is used for the control of fire ants, cockroaches, and termites. It is used in residential and commercial buildings, and on landscape areas, lawns, pastures, rangelands, golf courses and commercial grounds. It is produced in ready-to-use bait as a yellow-orange, odorless, granular/powder form and a gelatin form. HMN is normally formulated in a soybean oil attractant and placed on corn-grit carrier. The bait is spread with a granular spreader at a rate of 1 to 2 pounds of bait per acre.

HMN is an amidinohydrazone insecticide. It is selectively toxic to insects with chewing or sponging mouthparts and functions as a slow acting stomach toxicant (Lovell 1979). It is relatively nontoxic to insects that use other modes of feeding and to insects where

exposure is limited to cuticular contact. In insects, HMN has been found to inhibit mitochondrial electron transport, which causes a decrease in physical activity, as well as a decrease in respiration (Hollingshause 1987).

HMN is a slow acting toxicant allowing time for foraging ants to distribute the bait to other members of the colony before they are killed. The bait is carried by the ant to the mound, and then into the nest as food for the colony and queen. Within 24 hours of treatment lethargy sets in, and morbundity within 72-96 hours.

Physical and Chemical Properties

HMN is a yellowish, odorless solid. It is stable to a temperature of 185°C to 190°C. It has a low water solubility of 0.005 to 0.007 ppm at 20°C. Combined with the high soil adsorption coefficient (Koc) of $9.5 \times 10^{4} – 3.6 \times 10^{5}$ cm^{3}/g there is a low potential for leaching in soil. Also, HMN has a high tendency to photodegrade in water and on soil, which suggests that it has a low potential for bioacculmulation in the environment, despite a high Kow of $2.03 \times 10^{2} – 2.12 \times 10^{2}$.

Environmental Fate and Toxicity

Air: The low vapor pressure of 6×10^{-8} mmHg (DPR PestChem Database) indicates that this insecticide is non-volatile; therefore, it is unlikely to be dispersed in air over a large area. The low Henry's Law constant (1.95×10^{-7} atm m^{3}/mole) also indicates that it will not volatize from water to air. In a one-year study of breakdown products in air less than 3% of the initial measured dose was detected (American Cyanamid, 1992). HMN is not applied by spraying; therefore, there is low risk of contamination from drift.

Water - HMN may enter ponds and streams by direct application, erosion of soils, or runoff. Runoff can be influenced by factors such as bait formulation, which is generally on a corn grit carrier, timing of application and rainfall intensity. The low water solubility and high soil adsorption coefficient indicate a low potential to leach in soil and reach ground water. It is fairly stable to abiotic hydrolysis with a half-life of 30 days at 25°C in deionized water (American Cyanamid Company, 1992).

HMN degrades rapidly in surface water when exposed to light. The aqueous photolysis half-life is less than 1 hour (American Cyanamid Company, 1992). pH levels of 4.8 to 8.0 affected the rate of phototransformation only slightly. In the absence of light, no significant degradation was found to take place in water at any pH level, at temperatures of 10-25°C (Chakraborty et al. 1993).

HMN was found to degrade to five photoproducts in water and possibly two unidentifiables (Chakraborty et al. 1993, Mallipudi et al. 1986).

- 1,5-bis(α,α,α-trifluoro-p-tolyl)-1,4-pentadien-3-one (TFP)
- 6,7,8,9-tetrahyrdro-7,7-dimethyl-3[p(trifluromethyl)styryl] – 4H-pyrimido[2,1-c]-triazin-4-one (TFPT)
- P-(trifluoromethyl) benzoic acid (TFBA)

- N, N'-azo-(5,5-dimethylperhydropyrimidin-2-one hydrazone
- P-(trifluoromethyl) cinnamic Acid (TFCA)

Soil – HMN is generally applied as a formulation in bait using a granular spreader. Breakdown via photolysis is the major route for degradation. The soil photolysis half-life of HMN is 5 days. Two photoproducts have been identified as an epoxide compound and a ketone compound (American Cyanamid Company, 1992). Under field conditions HMN is very unstable when exposed to sunlight. Vander Meer et al. (1982) found that in daylight HMN has a half-life of 12 hours; and when exposed to heat (52°C), in the absence of light, decomposition is relatively nonexistent.

The high soil adsorption coefficient causes HMN to bind to soil particles, making it unavailable for microbial degradation. Microbial degradation is very dependent on a number of soil characteristics: moisture, temperature, pH, and soil type. Also, the organic carbon content of the soil may increase adsorption and may increase or decrease microbial degradation.

In field applications some microbial degradation may occur. When ants carry the bait down to the nest, if not eaten immediately, microbial degradation can occur. *Phanerochaete chrysosporium*, a common white rot fungus, has been found to breakdown HMN with a half-life of 14-25 days. This is with no exposure to light. The microbial degradation products are TFP, FTCA and TFBA (Abernethy et al., 1993). Without microbial degradation or photodegradation HMN is persistent in soil with an aerobic half-life of 383 days (American Cyanamid Company, 1992).

Biota – For agriculture purposes HMN is formulated on a bait substance such as corn grits. It is then evenly applied over the treatment area. Based on the application procedure and formulation as a bait, high soil adsorption value, and its high photodegradation tendency, HMN has a low potential for bioaccumulation in the environment.

Insects: HMN is relatively nontoxic to insects that are incapable of ingesting the compound and when exposure is limited to cuticular contact. HMN is not able to penetrate the epicuticular waxes. It is highly toxic when ingested. It functions as a slow acting stomach toxicant (Lovell 1979). Hollingshaus et al. (1983) determined that the LD50 value of the tobacco budworm was 7 μg/g. Forty to fifty percent of the ingested dose was excreted in the feces, but the remaining residues were found throughout the insect. The breakdown products in the insect's system were found to be TFP and 2-hydrazino-1,4,5,6-tetrahydra-5,5-dimethyl pyrimidine hydroiodide. These also broke down further to TFBA and TFCA, and tetrahydro-5,5-dimethyl-2(1*H*)-pyrimidione respectively. HMN has also been found to inhibit mitochondrial electron transport, which causes a decrease in physical activity, as well as a decrease in respiration (Hollingshause 1987).

Plants: Plants do not uptake the pesticide through the root system. Residues detected in crops were from direct foliage contact with the HMN application. The morphology of the foliage determines the available contact area where the bait can be lodged. Narrow

blades such as that of wheat foliage greatly diminished the potential for lodging (American Cyanamid Co., 1982).

Mammals: HMN can be slightly toxic when ingested, with oral LD50 of 1121 to 1300 mg/kg in rats (Farm Chemicals Handbook, 1997).

HMN metabolizes within the body of foraging ruminants (EPA Fact Sheet). Radioactive labeled HMN was given to lactating goats in doses 4 to 10 times the normal application amount. Ninety to ninety-five percent of the cumulative dose (given for a period of 8 days) was excreted in the feces (American Cyanamid Co., 1982). Because of this, the EPA has found that there are no concerns of HMN residues in milk, meat, or meat byproducts of ruminants as a result of pesticide use on pasture or rangeland grasses (EPA, RED, 1998). No HMN breakdown products in mammals were identified.

Fish: HMN can be highly toxic to fish. The LC50 are 0.16 ppm and 0.10 ppm in rainbow trout and channel catfish, respectively (Farm Chemicals Handbook, 1997). Under normal use conditions, because of HMN's low solubility and very short half-life via photodegradation in water, exposure to the chemical is not expected (EPA, RED, 1998).

Characteristics of HMN, such as, its low solubility, large KOW and large KOC, mean it will tend to accumulate in fatty tissues, such as in fish. HMN has been found to accumulate in fish tissues with a bioconcentration factor (BCF) of 1,300X in whole fish, 780X in fillet, and 1,900X in viscera (EPA, RED, 1998). However, due to these same physical properties and rapid photodegradation, aquatic organisms are unlikely to come into contact with HMN. No studies have been done to determine or identify any breakdown products in fish.

Conclusion

HMN is an amidinohydrazone insecticide. It is selectively toxic to insects with chewing or sponging mouthparts and functions as a slow acting stomach toxicant. It is relatively nontoxic to insects that use other modes of feeding and to insects where exposure is limited to cuticular contact. In insects, HMN has also been found to inhibit mitochondrial electron transport, which causes a decrease in physical activity and a decrease in respiration.

The low vapor pressure indicates that this insecticide is relatively non-volatile. The low Henry's Law constant indicates that it has low volatility from water to air. Since HMN is commonly formulated as bait and is spread with a granular spreader, it is unlikely to be volatilized in air over a large area.

The low water solubility and high soil adsorption coefficient indicate a low potential to leach in soil to ground water. It is stable to abiotic hydrolysis and degrades rapidly in water when exposed to light. The aqueous photolysis half-life is less than 1 hour.

In soil, photolysis is the major route for degradation with a half-life of 5 days. Without light HMN is very stable with an aerobic half-life of 383 days. *Phanerochaete*

chrysosporium, a white rot fungus, has been found to breakdown HMN with a half-life of 14-25 days.

Plants do not uptake the pesticide through the root system. Residues detected in crops were from direct foliage contact with the HMN application.

HMN can be slightly toxic to mammals and mostly excreted in the feces. It is highly toxic to fish. The low water solubility, large Kow and large Koc indicate a tendency for HMN to accumulate in fatty tissues. However, under normal use conditions aquatic exposure is low because photodegradation in water is rapid.

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Appendix C

Toxicology Summary for Hydramethylnon

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
HYDRAMETHYLNON (also known as AC 217,300, CL 217,300, or "Amdro")

Chemical Code # 2203 Tolerance # 00395
SB 950 # 326
Original date: 01/03/89
Revised 8/1/89, 12/22/93, 10/31/00, 5/28/02, and 6/14/02

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effects (chronic, not oncogenicity)
Chronic toxicity, dog:	No data gap, no adverse effects
Oncogenicity, rat:	No data gap, no adverse effects
Oncogenicity, mouse:	No data gap, possible adverse effect (chronic, not oncogenicity)
Reproduction, rat:	No data gap, possible adverse effect
Teratology, rat:	No data gap, no adverse effects
Teratology, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, no adverse effects
Chromosome effects:	No data gap, no adverse effects
DNA damage:	No data gap, no adverse effects
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached. In the one-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

All record numbers through 145825 were examined (Document No. 395-072). This includes all records indexed by DPR as of 6/14/02. Some record numbers for older submissions have Record Nos. > 900,000.

File name: t20020614
Revised by Aldous, 6/14/02.

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

****021-028 993353 to 993360** "24-month feeding study of AC 217,300 to rats". IRDC Study No. 141-014, dated 5/12/82 (original report); 1/6/83 (addendum report). Original report consisted of 024:993356 plus appendices (Vols. 25-28). Amended report (Vols. 21-23) added microscopic evaluation of intermediate groups. (Design: CD rats; 0, 25, 50, 100, and 200 ppm; 50/sex/dose; 2-year dietary administration). Original CDFA review (9/4/85) classified study as **acceptable**, **with possible adverse effects** (endometrial polyps, testicular atrophy). The 10/27/88 review agreed on essential points with the original review. The 8/01/89 review removed uterine endometrial stromal polyps and related tumors as "possible adverse effects" in response to the 3/21/89 rebuttal. Females had decreased body weight at 100 and 200 ppm; male weights were reduced at 200 ppm only. In 100 and 200 ppm females, and possibly also 200 ppm males, the "MTD" appears to have been exceeded, based on the magnitude of body weight decrements. Food consumption was significantly reduced in 200 ppm males and females. Yellow body fat was noted in dose-related fashion in 100 and 200 ppm males and females. Glomerulonephrosis was dose-related in females at 50 ppm and above, and in males at 25 ppm and above. Testicular atrophy was evident at 50 ppm and was marked at 100 and 200 ppm: this is the basis for a "possible adverse effect". A NOEL for females is 25 ppm based on kidney effects. There is no NOEL for males, however evidence of a glomerulonephrosis effect at 25 ppm was very marginal. J. Christopher, 9/4/85, and C. Aldous, 10/27/88, 8/01/89.

011 033575 An interim report for 024:993356, above. Semi-monthly hand-written reports, protocol, feed analysis during first year of study. (No separate review needed). C. Aldous, 11/10/88.

044 (no record number: Exhibit 1, this volume). Rebuttal document presenting reasons why study 024:993356 should not be considered to indicate a neoplastic effect on the uteri of rats. Considered in 7/20/89 review.

CHRONIC TOXICITY, DOG

010 993362 "Twenty-six week toxicity study in dogs: AC 217,300". Hazleton Laboratories America, Inc., 6/10/80. Purebred beagles, 22-25 weeks old, 4/sex/group, were administered AC 217,300 (92% purity) in gelatin capsules at 0, 0.33, 1.0, or 3.0 mg/kg/day. The a.i. was formulated in lactose premix (2.5% AC 217,300 w/w for all treated groups, 120 mg/kg/day lactose for controls). **No adverse effect indicated. NOEL = 1 mg/kg/day (primary sign was marked inappetence in one 3 mg/kg/day male, which was consistent with observations of 91-day oral dosing study 009:993327). **Acceptable** to fill dog chronic study data requirement. C. Aldous, 11/21/88.

042 069457, 069458 Nearly exact duplicate of 010:003362. Major difference is that this version lacks a one-page addendum following p. 272 and preceding the feed analysis appendix, which discusses investigators' evaluation of the NOEL. Retain both record numbers (one submission supports an end product and one was sent for SB950 requirements). (C. Aldous, 11/21/88)

ONCOGENICITY, MOUSE

****002-006 993350, 028449-028451, 993361** "Eighteen-month feeding study of AC 217,300 to mice". (Primary report in 002:993350). IRDC, 5/06/82 (Two additional re-evaluations of lung data followed at later dates, in Vols. 039 and 043). AC 217,300 (92%) administered in diet to CD®-1 mice at 0, 25, 50, 100, and 200 ppm. **Possible adverse effects indicated**: testicular degeneration and kidney amyloidosis and chronic nephritis, with NOEL's of 25 ppm (the latter NOEL in both sexes). Mortality was increased in dose-related fashion in both sexes at 100 and 200 ppm. Males and females at 200 ppm had marked weight gain decrements and decreased food consumption. A lesser weight gain decrement was observed in 100 ppm males, which was possibly treatment-related. Major treatment-associated lung findings were bronchopneumonia and pigment-laden macrophages in the alveoli, which were observed in 100 and 200 ppm males and in 200 ppm females: these effects may have been influenced by endemic disease. These lung and kidney effects contributed to increased mortality of 100-200 ppm animals. Study was originally found **unacceptable** in 9/5/85 CDFA review due to overly high dose levels and because the data were not presented in a manner which was convenient to evaluate. The 11/10/88 review still found the study unacceptable, on the basis that viral and/or bacterial disease may have confounded the data. Study was re-classified as **Acceptable** in the 11/18/93 review (see 395-049 114578, below) based on evidence that the Sendai infection had little or no influence on the outcome of the study. J. Christopher, 9/5/85; and C. Aldous, 11/10/88, 7/19/89, and 11/18/93.

039 067113 "A histopathological evaluation of mouse lungs: Chronic feeding study of AC 217,300" (Submitted to American Cyanamid Co. by Robert A. Squire Associates, Inc., May 1987). Re-evaluation of lung slides of male and female mice in study 002:993350. Conclusion: data do not support the supposition that there is a treatment effect on lung tumors. Lung pathology was confounded by disease, possibly Sendai virus plus secondary infection. Considered in C. Aldous review of 002:993350, 11/10/88.

046 087825 Virtual duplicate of 039:067113 (additional header pages in this re-submission). No review needed. Aldous, 1/25/90.

043 067725 "Chronic dietary toxicity and oncogenicity study with AC 217,300 in mice. Amended pathology report." (W. M. Busey, Experimental Pathology Laboratories, Inc., Sept. 15, 1988). Male and female lung slides re-examined; initially blind, then re-examined again in all cases in which Busey's diagnosis was different from Squire's. Some conclusions were changed on re-examination; hence this review was not entirely "blind" nor entirely independent. Conclusion: confirms evaluation of Squire (039:067113, above). Considered in C. Aldous review of 002:993350, 11/10/88.

395-049 114578 (addendum to Record No. 993350). "Second peer review of Amdro", U.S. EPA peer review dated 17 Apr. 1991. Primary reason for non-acceptability of the study was possible confounding effect of Sendai virus infection in the study. This peer review noted very few cases of "atypical bronchial hyperplasia", which pathologists Squire and Busey agreed represented Sendai virus-associated changes. Only 1 or 2 mice dosed below the MTD had such signs of Sendai virus hyperplasia, hence the disease does not appear to have confounded study results. The "Second Peer Review" classified Hydramethylnon as "Group C" (Possible human

carcinogen), based on lung adenomas or adenomas plus carcinomas in females. Examination of the "Second Peer Review" in light of the other data available supports upgrading the study to **Acceptable** status. Aldous, 11/18/93.

046 087826 Virtual duplicate of 039:067725 (additional header pages in this re-submission). No review needed. Aldous, 1/25/90.

039 067112 3-page "Weight of evidence" statement by J. E. Harris regarding rat and mouse oncogenicity. (Considered in 11/10/88 review of mouse study).

011 033574 6-month interim report for 002:993350, above.

044 (no record Number, Tab "Exhibit 1"). Rebuttal ref study 002:993350, above. (Considered in 7/19/89 review of mouse study).

044 072614 Partial duplicate of 039:067113.

REPRODUCTION, RAT

029 993344 "A three-generation reproduction study with AC 217,300 in rats". Bio/dynamics Inc., May 14, 1982. AC 217,300 (92%) administered in diet to CD® rats, 12 males and 24 females/treatment group. Controls plus 4 treatment groups (25, 50, 100, and 200 ppm) were initiated. The higher two groups were discontinued after F0 generation parents had been evaluated in a recovery experiment. **Possible adverse effects indicated:** parental toxicity and reproductive effects: findings at 100 ppm and above were body weight decrements in males and females during the growth phase; markedly reduced pregnancy rate; increased gestation length; increased total litter losses; small mean litter size; diminished pup weight gain during lactation; seminiferous tubular degeneration with diminished or absent sperm in tubular lumen or in epididymal ducts. **Unacceptable**: **an additional study is needed** to establish a valid NOEL for testicular lesions in F1 adults. [J. Christopher had placed apparent NOEL values for parental toxicity and reproductive effects lower than 50 ppm, based on data from one or more individual generations or mating periods, whereas the 1/3/89 review determined that available information is insufficient to establish a NOEL. The latter review indicated that the NOEL is at or below 50 ppm]. J. Christopher (9/3/85), C. Aldous (1/3/89, 7/20/89: see Aug. 1989 CDFA Rebuttal Response for the latter re-examination).

030 993345 Individual data for 029:993344, considered in reviews above.

011 993349 Status report for 029:993344 (no new data), C. Aldous 11/10/88.

****395-068 139742** Schroeder, R. E., “A two-generation reproduction study with AC 217,300 in rats,” Pharmaco LSR, Inc., 7/19/95. Report No. 92-4046. Crl:CD® BR rats, 30/sex/group, were dosed with 0, 25, 50, or 75 ppm hydramethylnon (98.2%) in diet continuously for 2 generations, with one mating period per generation. This supplemental study design covered all elements of a primary reproduction study. NOEL = 25 ppm (2.0 mg/kg/day, a “possible adverse effect”: based on diffuse bilateral degeneration of seminiferous tubules in 1/30 F0 males at 50 ppm). Germinal epithelial degeneration of scattered tubules was common at 75 ppm, but diffuse degeneration of

seminiferous tubules (unilateral or bilateral) was observed only in 3/30 F0 75 ppm males, and in 1/30 F1 75 ppm males. This study did not find any seminiferous tubule degeneration at 25 ppm nor in controls. This study did not identify general somatic toxicity at any dose level. The primary reproduction study (Record No. 993344) had identified diffuse bilateral degeneration of seminiferous tubules in 9/12 males at 200 ppm and 1/12 males at 100 ppm, supporting the single finding in the present study as a treatment effect. Functional reproductive changes at 75 ppm were: (1) a reduction in F1 high dose males with evidence of mating, (2) associated reduction in F1 females pregnant, and (3) tendency toward low implantation rates in 75 ppm matings. Also, live litter sizes were reduced in both generations, although statistical significance was limited to the first generation. Valid supplemental study, which complements the primary (non-accepted) reproduction study to fill the reproduction study data requirement. Aldous, 10/31/00.

011 993331 "CL 217,300: An 8-week feeding and recovery study in maturing rats". American Cyanamid Co., Agricultural Research Division, 6/23/80. 5 groups of 12 males, ca. 100 g body weight at onset. Treatment groups: unrestricted controls, 200 and 400 ppm AC 317,300, and restricted diet groups with feed limited to that taken by 200, and 400 ppm groups, respectively. Six of each group were killed after 4-week treatment period, balance killed after a 4-week recovery period. Marked, dose-related decreases in food consumption accounted for substantially reduced body weight gains in treatment groups. Paired-feeding controls had comparable weight gain decrements. Lesions observed at the end of the treatment period included spermatid giant cells in testes and cellular debris within epididymal tubules in 200 and 400 ppm groups, and focal hepatic cell cytoplasmic degeneration in 400 ppm males. After the recovery period, there was no residual hepatic effect, but gonadal toxicity progressed to dose-related testicular tubular atrophy and altered or damaged germ cells. At this time one 400 ppm male was noted with aspermiogenesis, and in 4 of the 400 ppm males, no spermatozoa could be found within the epididymis. There was no corresponding pathology in restricted feeding groups. C. Aldous, 11/15/88.

011 993332 "CL 217,300: An 8-week feeding and recovery study in mature rats". American Cyanamid Co., Agricultural Research Division, report issued approx. 6/23/80. Five groups of 12 males, weighing 351-368 g at onset. Treatment groups: unrestricted controls, 200 and 400 ppm AC 317,300, and restricted diet groups with feed limited to that taken by 200 and 400 ppm groups respectively. Six of each group were killed after a 4-week treatment period, balance killed after a 4-week recovery period. Dose-related decreases in food consumption accounted for reduced body weight gains in treatment groups. Paired-feeding controls had weight gain decrements comparable to treated groups. Lesions observed at the end of the treatment period included spermatid giant cells in testes, prostate atrophy, and (germ cell) cellular debris within epididymal tubules in the 400 ppm group, and focal hepatic cell cytoplasmic degeneration and hepatic cell atrophy in 400 ppm males. After the recovery period there was no residual liver effect, however gonadal toxicity progressed to testicular tubular atrophy in 400 ppm rats, and debris of damaged germ cells in epididymides of 200 and 400 ppm rats. There was no corresponding pathology in restricted feeding groups. C. Aldous, 12/30/88.

395-019 993346 "Reproductive performance of male albino rats after receiving a single oral dose with AC 217,300 (Amdro)". American Cyanamid, 6/1/83. Ten males per treatment received 0 or 800 mg/kg in a single oral dose at about 4 weeks of age. Males were then placed on basal diet for 4 weeks, and mated with untreated females. Male and female reproductive performance was examined, and there were no treatment effects. Male reproductive organs were

weighed and examined grossly, again without treatment effects. No microscopic examinations of tissues were made. Study is **unacceptable, not upgradeable, with no adverse effects indicated**. Study was faulted for single dose mode of treatment, use of inappropriately young test animals, small group sizes, and especially for failure to do histopathology exams in males, despite the fact that testicular lesions might have been expected, based on chronic and subchronic studies. J. Christopher, 9/4/85.

395-072 145825 Duplicate of 395-019 993346, above.

TERATOLOGY, RAT

007 993338 "Teratogenesis study in rats with AC 217,300". Bio/dynamics, 9/14/79. 26 CD® rats/group gavaged 0, 3, 10, or 30 mg/kg/day AC 217,300 (92% a.i.) days 6-15 of gestation. **No adverse effects. Maternal toxicity NOEL = 3 mg/kg/day (dose-related decrease in maternal body weight, marked at 30 mg/kg/day). Other maternal toxicity signs: decreased thymus size and signs of general weakness or toxicity (30 mg/kg/day) and yellow body fat (10 and 30 mg/kg/day). Developmental toxicity limited to 30 mg/kg/day (slight decrease fetal weight, slight ossification delays such as incomplete supraoccipital ossification, and increased incidence of rudimentary ribs. **Acceptable**, J. Christopher, 8/25/85. (One-liner by C. Aldous, 11/16/88).

TERATOLOGY, RABBIT

001 993342 "Teratology study with AC 217,300 in rabbits". IRDC, 4/7/82. 16 New Zealand White rabbits per group gavaged on gestation days 6-18 with 0, 5, 10, and 20 mg/kg/day AC 217,300 in 0.5 ml/kg corn oil vehicle. **No adverse effects: Maternal NOEL = 5 mg/kg/day (reduced dam body weight, reduced stool amounts or soft stools: all dose-related in 10-20 mg/kg/day dams. Matting and/or discharge in anogenital region in 10 and 20 mg/kg/day dams. Also, 10 and 20 mg/kg/day dams had 1 and 8 cases of yellow body fat at necropsy, respectively). Developmental toxicity NOEL = 10 mg/kg/day (decreased fetal weights at 20 mg/kg/day). **Acceptable**. Reviewed by J. Christopher, 8/30/85. Supplementary review by C. Aldous, no change in status, 12/30/88.

001 993341 Pilot for 001:993342. Examined, no written review. Aldous, 11/17/88.

GENE MUTATION

** 039 067116 "Forward Mutation in Schizosaccharomyces pombe P1 - Test Substance: AC 217,300." (Life Science Research, Roma Toxicology Centre, Italy, 1/14/86, LSR-ETC report no. 129005-M-07585) AC 217,300, 91.5%, lot AC 3196-99B, tested with Schizosaccharomyces pombe P1 haploid strain for mutation in the adenine biosynthesis pathway; without rat liver activation at 0 (DMSO and untreated), 0.781, 1.56, 3.13, 6.25 or 12.5 : g/ml; with activation, at 0, 3.13, 6.25, 12.5, 25 or 50 : g/ml; 16 hours in liquid culture with compound, 5 days after plating for colony formation; number of white (mutant) and sectored colonies counted, 10 plates per concentration, 2 trials; positive controls functioned as expected; high

concentration with activation not cytotoxic but precipitation formed at 100 : g/ml; some decreased survival without activation; **no adverse effect; Acceptable.** Gee, 12/6/88.

** 011 993368 "Mutagenicity Testing of CL 217,300; 1,4-pentadien-3-one, 1,5-bis(a,a,a-trifluoro-p-tolyl)-(1,4,5,6-tetrahydro-5,5-dimethyl-2-pyrimidinyl)-hydrazone in the Ames Bacterial Test." (American Cyanamid, 5/14/79) CL 217,300, 91.64%, batch AC 3196-99-B; tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 and E. coli strain WP-2 uvrA$^-$; with and without Aroclor 1254-induced rat liver activation; plate incorporation method and disc method; disc at 1000 : g/disc and at 0 (DMSO), 10, 100 or 1000 : g/plate, duplicate plates, 2 trials; precipitation at 1000 : g; toxic to bacterial lawn at 100 and 1000 : g for TA100 and TA1537 without activation; no consistent increase in reversion rate; **no adverse effect; Acceptable.** Christopher, 8/28/85 and Gee, 12/7/88.

CHROMOSOME EFFECTS

** 039 067114 "Clastogenic Evaluation of AC 217,300 Insecticide, Lot AC3196-99B in an in vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells: Final Report." (Litton Bionetics, MD, 10/85, LBI Project No. 20990) AC 217,300, hydramethylnon, lot AC3196-99B, purity of 91.6% from record #'s 993368 and 993370 in 011 for same lot; tested with Chinese hamster ovary cells (CHO) with and without Aroclor-induced male rat liver activation at 0 (DMSO), 0.5, 0.75, 1.0, 1.25 or 1.5 : g/ml without activation with cells harvested at 10 and 20 hours (equivalent to 7.5 and 17.5 hours actual exposure); with activation, tested at 0 (DMSO), 1.0, 2.5, 5.0 or 10.0 : g/ml, 2 hours actual exposure followed by additional incubation in complete medium and harvests at 10 and 20 hours; concentrations selected based on preliminary toxicity and cell cycle study; scored 200 cells, 100 from each duplicate treated culture; two trials for 10 hours with the first showing a high incidence of dicentrics in control and treated culture; not confirmed in repeat trial or in 20-hour trial; no increase in aberration due to treatment; positive controls of mitomycin C and cyclophosphamide functioned as expected; **Acceptable, no adverse effect**. Gee, 12/6/88.

044 073353 "A dominant lethal test in male rats treated with CL 217,300 by gavage for 5 days." (American Cyanamid, 6/24/80) CL 217,300, batch AC 3196-99-B, 91.6% purity; given by oral gavage in corn oil at 0, 3, 30 or 90 mg/kg/day, 10 males/group; dosed daily for 5 days, mated with one female per week for 8 consecutive weeks with males in control and high dose groups mated in week 10; all males in control and treatment groups mated in weeks 11 - 17. Male fertility was markedly decreased beginning in week 6 at 90 mg/kg/day and continued through week 17 for 6 males. Fertility was somewhat decreased at 30 mg/kg/day with apparent recovery by week 12. Report states mating behavior was not affected; testes weights were low in high dose group. Report was initially reviewed as indicating a "possible adverse effect" on testes and spermatocytes/spermatogonia and as unacceptable (report missing every other page - see 011:993370, no justification of dose - notation of a possible adverse effect from table III). See Christopher, 8/28/85 and Gee, 12/7/88. Complete report was submitted in 395-044. Report is still **unacceptable** (inadequate numbers of animals for a dominant lethal assay). Changed to no adverse affect with no evidence of a dominant lethal affect. Gee, 8/1/89.

011 993370 (Incomplete report of 044:073353, above).

DNA DAMAGE

** 039 067115 "Mitotic Gene Conversion in Saccharomyces cerevisiae D4 - Test Substance: AC 217,300." (Life Science Research, Roma Toxicology Centre, Italy, 1/14/86, LSR-RTC No 129006-M-07685) AC 217,300, lot AC 3196-99B, 91.6%; concentrations not corrected for purity of a.i.; tested with Saccharomyces cerevisiae strain D4, diploid with two defective, non-complementing alleles of adenoma-2 and trp-5 loci; tested with and without phenobarbitone- induced male rat liver; 0 (DMSO and untreated), 1.56, 3.13, 6.25, 12.5 or 25 : g/ml, 16 hours incubation followed by plating for viability, tryptophan and adenine prototrophy, 3 plates each, two trials; colonies counted and survival and mutation frequency calculated; 25 : g/ml in 0.1 M phosphate buffer, pH 7.4, was considered close to the limit of solubility when diluted from DMSO stock solution; marginal cytotoxicity (10% and 12% decrease) in survival at high concentration without activation only; **no adverse effect, Acceptable**. Gee, 12/6/88.

NEUROTOXICITY

(Not required at this time)

METABOLISM STUDIES

395-050 116894 Fung, C.H., "CD 217,300: Rat metabolism study", American Cyanamid Co., Princeton, NJ, 5/21/92. Sprague-Dawley rats were dosed with Hydramethylnon (designated as CL 217,300) by gavage in corn oil at low (3 mg/kg) or high (100 mg/kg) single doses. Also, multiple-dosing was done with 14 consecutive daily treatments of 3 mg/kg, followed by 3 mg/kg of labeled Hydramethylnon. In all cases, both phenyl and pyrimidinyl ring-labeled treatments were evaluated. There were no substantial differences associated with sex, dose level, or duration of treatment. Elimination was relatively rapid. Most of the label was excreted within 36 hr. Label was excreted principally in feces (about 90%). Parent compound was the major labeled fecal component (70-85% of administered doses, see p. 59). Urinary elimination was about 1-4% of total administered compound (p. 54). The two main identified urinary metabolites were a substituted cinnamic acid and a substituted p-toluic acid. Residues remaining in tissues after 7 days ranged from 3 to 10% of administered dose. The major labeled component of tissues was parent compound, with appreciable amounts of "moderately polar" material as the second-most abundant fraction. Data suggest inefficient absorption and a modest rate of metabolism of absorbed hydramethylnon. Aldous, 12/22/93.

395-062 126488 This is the same study as 395-050 116894, above. This version credits Zdybak, J. M. L. and R. A. Robinson as authors and Xeno Biotic Laboratories, Inc. as test facility. Record 116894 listed C. H. Fung as the author and American Cyanamid Co. as test facility (using similar title page formats, with the same study date listed). The present volume gives a laboratory report number of XBL 90043. Robinson was Study Director, Zdybak was one of the Research Scientists, and Fung signed as Sponsor to the study (pp. 3 and 7 of this volume). The present citation listing Zdybak and Robinson as authors should be used in the future for this report. Aldous, 10/24/00.

395-037 060118 Hussain, M. "The absorption, excretion pattern, tissue residues and metabolism of Carbon-14 labeled CL 217,300 [Tetrahydro-5,5-dimethyl-2-(1H)-pyrimidinone[3-[4-(trifluoromethyl)phenyl]-1-[2-[4-(trifluoromethyl)phenyl]ethenyl]-2-propenylidene] hydrazone in the rat." No worksheet has been made by Medical Toxicology Branch, however the study has been examined by Worker Health and Safety Branch because of its relevance to human exposure. This rat study found that 71.5% of oral dose was eliminated in feces unchanged. The lesser amounts of label found in urine yielded no parent compound, but rather a number of polar metabolites. In tissues sampled (including liver), parent compound was generally the most abundant labeled moiety. The most abundant metabolite was CL 98,724: 1,5-bis(α,α,α-trifluoro-p-tolyl)-1,4-pentadien-3-one. Aldous, 10/24/00.

395-016 993298 This is an old summary of metabolism information, containing a 3-paragraph summary referring to 395-062 126488, above. Aldous, 10/24/00.

395-018 993374 This is not a metabolism study, but rather a brief report of a study to see whether orally ingested antidotes would affect uptake of hydramethylnon. There was no advantage to treatment with "universal antidote" of charcoal:magnesium oxide:tannic acid (2:1:1), nor was magnesium oxide:tannic acid (1:1) of any value. No Medical Toxicology Branch worksheet. Aldous, 10/24/00.

395-018 065618 This is a one-page report, possibly relating to Record No. 126488, above. No reviewable data are included. Aldous, 10/24/00.

395-064 131636 Frantz, S. W. and Beskitt, J. L., "Hydramethylnon: Pharmacokinetics and material balance study following cutaneous administration to male Sprague-Dawley® rats," Bushy Run Research Center (10/93). Laboratory Project ID: 92N1073. Young male rats were dosed on shaved dorsal skin with hydramethylnon as "Maxforce Professional Insect Control Roach Killer Bait Gel" (nominally 2.15% a.i.), using a non-occlusive dressing. Four rats/group were exposed for 10 hr prior to washing application site in all cases. Dose levels of ^{14}C-labeled hydramethylnon ranged from 110 to 167 mg/kg. Sacrifice times for the 4 groups were 10 hr, 24 hr, 7 days, and 14 days, with measurement of urinary and fecal excretion for respective study durations. Urinary excretion never exceeded 0.11% of dose. Maximal fecal excretion was found in the longer duration groups: 0.30 to 0.34% of dose. Dose site washed skin retained 0.90 and 0.93% of dose in the 10 and 24-hr groups, respectively, and 0.22 and 0.04% of dose in respective 1-wk and 2-wk groups. From 89-94% of dose was recovered in the residual gel on the skin surface, body rinses, and dressing in each case. Thus hydramethylnon in this matrix was not efficiently absorbed. Aldous, 5/28/02 (no DPR worksheet).

395-063 131263 Sharp, D. E., "Dermal absorption of AC 217,300 Gel in male rats," Hazleton Wisconsin, Inc., 10/26/93. Lab ID No. HWI 6123-180. Two groups of 4 Sprague-Dawley rats each were dosed on shaved dorsal skin with hydramethylnon as "AC 217,300 Gel," 2.16% active ingredient. Each rat received about 2 mg a.i. in 100 mg of the gel. ^{14}C label was on the phenyl rings. Rats were about 8 wk old and weighed 269-282 g at dosing. Skin was exposed for 10 hr under a non-occlusive dressing, then application sites were washed. One group of rats was sacrificed at this time, and another was maintained for 336 hr. Urine and feces were collected in both cases, and the following were collected at termination: fat, kidneys, liver, lungs, testes, and residual carcass. Only 0.01 to 0.02% of dose was found in urine. No residues were found in 10-

hr group feces, however 0.41% of dose was found in 336 hr group feces. Tissue levels were no more than 0.01% of dose for either group of rats. Residual carcass levels were 0.46% and 0.16% of dose in 10-hr and 336-hr rats, respectively. About 95% of administered dose was found in the skin wash collection. Thus hydramethylnon in this matrix was not efficiently absorbed. Aldous, 5/28/02 (no DPR worksheet).

SUBCHRONIC AND ACUTE/SUBACUTE STUDIES

395-008 993326 Tegeris, A. S., "AC 217,300: 91-day study in the rat," Pharmacopathics Research Laboratories, Incorporated, Laurel, MD, 5/31/79. Sponsor's Report # P-981-78-143-1. Twenty Sprague-Dawley rats/sex/group were dosed in diet with 0, 25, 50, 100, or 200 ppm Hydramethylnon (AC 217,300), 92% purity, for 91 days. This 25 ppm group had been initially dosed at 400 ppm, which proved to be excessively toxic, then dose for this group was reduced to 25 ppm after 2 weeks on study. Estimated achieved dosages for the 50, 100, and 200 ppm groups were 4.5, 8.6, and 17.0 mg/kg/day in males, and 5.0, 9.6, and 19.1 mg/kg/day in females. Incidences of bilateral testicular atrophy were 0, 4, 0, 5, and 20 in respective dosage groups. There was a dose-related decrease in testicular weights in all treated male groups. Given the irregular dosing regimen for the "25 ppm" group, NOEL is best expressed as "< 50 ppm" (LOEL = 4.5 mg/kg/day based on testicular weights: treatment-related testicular atrophy at 8.6 to 17.0 mg/kg/day). Transient food consumption decrement (F) was found at 100 ppm. Ovarian weights were statistically significantly elevated at 100-200 ppm, with no associated histopathology. High dose males had 10 cases of mild prostatic atrophy, compared to none in other groups. There was no other remarkable histopathology. Food consumption was significantly reduced in both sexes at 200 ppm. Body weight decrements after 13 weeks were 12% and 14%, respectively at 200 ppm, with no effects at lower dose levels. Food consumption and body weights were markedly affected at 400 ppm, showing this dose to be excessive. This older study does not meet current guidelines for a subchronic study (deficiencies are noted in DPR review), but provides useful data. Testicular atrophy and low testicular weights are **possible adverse effects**, since findings were not related to apparent general toxicity at 50-100 ppm. Aldous, 6/13/02.

395-007 993325 Fischer, J. E. (Study Director), "Experiment L-1742: 28-day rat feeding study with CL 217,300," American Cyanamid Co., Princeton, NJ, Sept. 5, 1979. Toxicology Report No. AX79-2. Three CD rats/sex/group were dosed in diet with Hydramethylnon (formerly CL 217,300) (91.6% purity) at 0, 50, 100, 200, 400, or 800 ppm for up to 28 days. The 800 ppm group was sacrificed moribund after 2 weeks of treatment. Study design was limited to a few parameters (clinical signs, body weight, food consumption, necropsy, and histopathology). The study pre-dates modern guidelines, and does not address standard data requirements. Small sample sizes make this study of limited value for rigorous evaluation of NOEL's. Apparent NOEL = 50 ppm (5.6 mg/kg/day), based on slight but statistically significant reduction in food consumption in males at 100 ppm, associated with a slight but non-significant reduction in body weight. A similar modest decrement in food consumption (not statistically significant) occurred in females at week 2 only. Testicular lesions (especially focal tubular degeneration and formation of giant cells) occurred at 200 ppm (18.7 mg/kg/day) and above, making the NOEL for organ toxicity = 100 ppm = 10.3 mg/kg/day. These lesions are "possible adverse effects." Supplemental study, suitable mainly as a range-finding study. Aldous, 6/13/02.

395-007 066135 Fischer, J. E. (Study Director), "Experiment L-1743: 28-day rat feeding study with CL 217,300," American Cyanamid Co., Princeton, NJ, 9/24/79. Toxicology Report No. AX 79-4. Six CD rats/sex/group were dosed in diet with hydramethylnon (formerly CL 217,300) (91.6% purity) at 0, 25, 50, 75, and 100 ppm for up to 28 days. In addition to the limited parameters evaluated in the range-finding study conducted at the same facility immediately preceding this study (see Record No. 993325, Cyanamid Toxicology Report No. AX 79-2), the present study included hematology and clinical chemistry (limited to BUN, ALT, and AST). The study pre-dates modern guidelines, and does not address standard data requirements, but provides useful data for parameters evaluated. Apparent NOEL = 75 ppm (9.2 and 9.5 mg/kg/day in M and F, respectively, based on diminished body weight gains in females, and diminished food consumption in both sexes). There were no treatment effects in hematology, clinical chemistry, or gross or microscopic pathology. No adverse effects indicated. The only organs weighed were kidneys and liver: these were unaffected by treatment. Aldous, 6/14/02.

**395-001 993335 Thompson, G. W., "Subchronic 21-day dermal toxicity study of AC 217,300 in rabbits," Hazleton Raltech, Inc., 4/15/82. Raltech Study No. 80033. Ten NZW rabbits per sex per group were dermally exposed on shaved dorsal skin (oleic acid vehicle) for 3 weeks, 6 hr/day, 5 days/week. One-half of animals per group had skin abraded weekly. Test article was hydramethylnon (purity 91.6%), applied 0, 10, 50, or 250 mg/kg per treatment day. Collars prevented disturbance of the taped gauze dressing. Primary parameters evaluated were daily evaluations of treated skin (Draize criteria), and gross examinations and histopathology of treated areas and of a full set of protocol tissues. Hematology and clinical chemistry were performed pre-study and at sacrifice. NOEL = 50 mg/kg/day, based on reduced food consumption and body weights (M and F), and increased relative liver weights (M and F). Plausibly incidental although statistically significant findings seen in only 1 sex at 250 mg/kg/day were decreased platelet counts (F) and elevated cholesterol (M). There were no increases in lesions of treated skin noted in daily clinical observations nor at histopathologic examinations. Except for splenic congestion (5 high dose females vs. 0 control females), no histopathology of non-dermal tissues suggested treatment increases, and this finding is likely to be incidental. Study is acceptable, with no adverse effects. Aldous, 5/24/02.

**009 993327 "AC 217,300: 91-day study in the dog". American Cyanamid Co. Pharmacopathics Research Laboratories, Inc, 5/31/79. Purebred beagles were dosed by gelatin capsule with 0, 3, 6, or 12 mg/kg/day AC 217,300. Occasional slight decrements in food consumption were observed at 3 mg/kg/day. Marked anorexia was observed in both sexes at 6 and 12 mg/kg/day, which led to marked body weight losses and necessitated premature sacrifices. All 12 mg/kg/day dogs died by day 54, and only 1/sex survived to termination at 6 mg/kg/day. Severe inanition preceded these deaths, despite substituting canned dog food, and also milk where indicated, for the normal dry rations. Food consumption was slightly reduced in 3 mg/kg/day dogs compared to controls (statistically significant in 2 of the 13 weeks in each sex). This appears to reflect a mild treatment effect. Body weight gains were not remarkably different between controls and 3 mg/kg/day dogs. Absolute liver weights were slightly but significantly elevated in 3 mg/kg/day males compared to concurrent controls, and to historical controls of comparable age. There was no comparable change in females, and there was no corresponding histopathology. Tremors, occasional convulsions, emaciation, inactivity, and wastage of muscle and subcutaneous fat were commonly observed in males and females at 6 or

12 mg/kg/day. All 6 and 12 mg/kg/day males had mild to moderate bilateral testicular atrophy. This was justifiably considered by investigators to be a result of starvation rather than a primary toxic effect. There were no testicular lesions at 3 mg/kg/day. Study is **acceptable** (as a subchronic study), and **no adverse effect is indicated.** Based on the steep dose-response curve and very mild responses at the low dose level, the NOEL appears to be only slightly below 3 mg/kg/day. C. Aldous, 11/18/88, with 1-liner expanded by Aldous on 6/7/02.

395-072 145824 Glaza, S. M., "Acute subcutaneous toxicity study of hydramethylnon in rats," Hazleton Wisconsin, Inc., 5/13/92. Lab Project ID: HWI 20100567. Ten young male Crl:CD® BR rats/group of average body weight 267 g were dosed once with hydramethylnon (a yellow solid: purity and lot number not stated) in cottonseed oil vehicle (10 ml/kg) at hydramethylnon dose levels of 0, 100, 500, or 1000 mg/kg. Rats were observed for 2 weeks prior to sacrifice, general necropsy, weighing of testes and epididymides, and histopathology of the latter organs plus seminal vesicles. Body weight gain during days 7-14 was reduced slightly at 500 to 1000 mg/kg. Food consumption was reduced during days 8-14 at 500 mg/kg and during days 1-14 at 1000 mg/kg. Clinical signs were limited to the injection site (yellow staining, subcutaneous mass at site, yellow discharge from mass). Body weights were significantly reduced in 1000 mg/kg rats on day 0 (group assignments were not stratified on body weight), and differences were slightly larger at day 14, possibly due to a minor body weight effect of treatment. Average absolute testes weights in respective groups were 1.65, 1.66, 1.58, and 1.71 g. Although absolute weights were comparable, relative weights of testes in 1000 mg/kg group were statistically significantly elevated. There was no gross or histopathologic response in organs examined. Supplemental data, with no adverse effects indicated. Aldous, 6/14/02 (no DPR worksheet).

395-072 145825 Fischer, J. E., "AC 217,300: reproductive performance of male albino rats after receiving a single oral dose with AC 217,300." American Cyanamid Co., 6/1/83, Toxicology Report AX83-5. Ten CD rats/group of initial body weight of 85 g were dosed by gavage with 0 or 800 mg/kg of hydramethylnon (91.6% purity) in corn oil vehicle. Treated males had diarrhea and decreased food consumption during the first 24 hr, followed by rapid recovery. During the 5th week after dosing, these males were mated to untreated females. Males were then sacrificed, and combined testes weights were recorded (there was no dose effect). Males were not further evaluated. There were no differences in parameters evaluated in females: time to impregnation, numbers of viable pups or dead pups, or resorption incidence. This is a supplemental study, which does not address any standard data requirements, and which has little value for hazard evaluation. Aldous, 6/14/02 (no DPR worksheet).

Appendix D

Calculations

Calculation Equations:

1. Conversion of exposure dose mg/kg/day to absorbed dose with absorption factors of 10% and 5%, for oral and dermal exposures, respectively.

$$\text{exposure at mg/kg/day} \times \frac{\text{hours exposed}}{\text{24 days}} \times \frac{\text{days exposed/week}}{\text{7 days/week}} \times \text{absorption factor} = \text{absorbed dose}$$

2. Calculation of Reference Concentration:

The reference concentration is the NOEL (unabsorbed) divided by an uncertainty factor. The uncertainty factor is generally 100 to account for the extrapolation of data from animal to human studies and variation within the human population.

$$\frac{\text{NOEL (mg/kg/day)}}{\text{Uncertainty Factor}} = \text{Reference Concentration}$$

3. Margin of Exposure: Depending on how human exposure was expressed, the NOEL may be in terms of the unabsorbed dose (dietary exposure) or the absorbed dose (occupational/residential exposure).

$$\frac{\text{NOEL (mg/kg/day)}}{\text{Human Exposure (mg/kg/day)}} = \text{Margin of Exposure}$$

Appendix E

Dietary Exposure Assessment

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    California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-98 data)
Residue file: pineapple HMN.RS7                   Adjustment factor #2 NOT used.
Analysis Date: 08-23-2002/14:25:18    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
===============================================================================
```

Summary calculations (per capita):

	95th Percentile			99th Percentile			99.9th Percentile		
	Exposure	% aRfD	MOE	Exposure	% aRfD	MOE	Exposure	% aRfD	MOE
U.S. Population:	0.000018	0.06	164472	0.000196	0.65	15277	0.000981	3.27	3058
Western region:	0.000016	0.05	188798	0.000225	0.75	13324	0.001647	5.49	1821
Hispanics:	0.000019	0.06	154902	0.000366	1.22	8205	0.001560	5.20	1923
Non-hispanic whites:	0.000018	0.06	170742	0.000175	0.58	17122	0.000830	2.77	3612
Non-hispanic blacks:	0.000024	0.08	123979	0.000260	0.87	11534	0.001101	3.67	2723
Non-hisp/non-white/non-black:	0.000014	0.05	215596	0.000298	0.99	10062	0.000978	3.26	3068
All infants:	0.000191	0.64	15676	0.000758	2.53	3956	0.001866	6.22	1608
Nursing infants (<1 yr old):	0.000000	0.00	>1000000	0.000275	0.92	10914	0.001262	4.21	2377
Non-nursing infants (<1 yr old):	0.000239	0.80	12549	0.000790	2.63	3799	0.002052	6.84	1461
Children 1-6 yrs:	0.000150	0.50	20001	0.000703	2.34	4268	0.002140	7.13	1401
Children 7-12 yrs:	0.000058	0.19	51831	0.000328	1.09	9146	0.000757	2.52	3963
Females 13+ (preg/not nursing):	0.000013	0.04	226177	0.000312	1.04	9624	0.000487	1.62	6162
Females 13+ (nursing):	0.000036	0.12	83709	0.001040	3.47	2884	0.001046	3.49	2868
Females 13-19 (not preg or nursing):	0.000010	0.03	295861	0.000070	0.23	42599	0.000580	1.93	5174
Females 20+ (not preg or nursing):	0.000008	0.03	393257	0.000107	0.36	28037	0.000871	2.90	3444
Females 13-50 yrs:	0.000009	0.03	332659	0.000146	0.49	20493	0.001043	3.48	2877
Males 13-19 yrs:	0.000008	0.03	357448	0.000167	0.56	17968	0.000749	2.50	4007
Males 20+ yrs:	0.000005	0.02	548485	0.000087	0.29	34460	0.000468	1.56	6408
Seniors 55+:	0.000008	0.03	381508	0.000081	0.27	36860	0.000358	1.19	8381

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California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-98 data)
Residue file: pineapple HMN.RS7                    Adjustment factor #2 NOT used.
Analysis Date: 08-23-2002/14:25:17    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Acute Reference Dose (aRfD) =   0.030000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
===============================================================================

U.S. Population                     Daily Exposure Analysis  /a
---------------                     (mg/kg body-weight/day)
                                     per Capita    per User
                                    -----------  -----------
            Mean                       0.000008     0.000090
            Standard Deviation         0.000069     0.000213
            Standard Error of mean     0.000000     0.000003
            Margin of Exposure 2/       372,932       33,309
            Percent of aRfD                0.03         0.30

       Percent of Person-Days that are User-Days =  8.93%


  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  -------  ----------  -----  -----------  -------  ---------
10.00     0.000003     0.01 >1,000,000   90.00    0.000220     0.73     13,622
20.00     0.000007     0.02    439,909   95.00    0.000393     1.31      7,642
30.00     0.000011     0.04    279,643   97.50    0.000643     2.14      4,663
40.00     0.000016     0.05    191,247   99.00    0.001046     3.49      2,869
50.00     0.000024     0.08    126,941   99.50    0.001474     4.91      2,035
60.00     0.000035     0.12     85,343   99.75    0.002045     6.82      1,466
70.00     0.000058     0.19     51,918   99.90    0.002187     7.29      1,371
80.00     0.000103     0.34     28,985

===============================================================================

Western region                      Daily Exposure Analysis
--------------                      (mg/kg body-weight/day)
                                     per Capita    per User
                                    -----------  -----------
            Mean                       0.000010     0.000121
            Standard Deviation         0.000093     0.000308
            Standard Error of mean     0.000001     0.000010
            Margin of Exposure          307,994       24,696
            Percent of aRfD                0.03         0.40

       Percent of Person-Days that are User-Days =  8.02%


  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  -------  ----------  -----  -----------  -------  ---------
10.00     0.000002     0.01 >1,000,000   90.00    0.000298     0.99     10,083
20.00     0.000007     0.02    448,603   95.00    0.000656     2.19      4,573
30.00     0.000011     0.04    263,594   97.50    0.000985     3.28      3,047
40.00     0.000017     0.06    178,064   99.00    0.001770     5.90      1,695
50.00     0.000025     0.08    121,659   99.50    0.002065     6.88      1,452
60.00     0.000037     0.12     81,436   99.75    0.002124     7.08      1,412
70.00     0.000052     0.17     57,736   99.90    0.002451     8.17      1,223
80.00     0.000102     0.34     29,368
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California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-98 data)
Residue file: pineapple HMN.RS7                   Adjustment factor #2 NOT used.
Analysis Date: 08-23-2002/14:25:17    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Acute Reference Dose (aRfD) =   0.030000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
==============================================================================

Hispanics                          Daily Exposure Analysis
---------                          (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000012     0.000156
            Standard Deviation        0.000104     0.000342
            Standard Error of mean    0.000001     0.000014
            Margin of Exposure         246,533       19,216
            Percent of aRfD               0.04         0.52

       Percent of Person-Days that are User-Days =  7.79%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000006     0.02    487,583   90.00    0.000447     1.49      6,705
20.00     0.000010     0.03    309,531   95.00    0.000864     2.88      3,470
30.00     0.000015     0.05    198,677   97.50    0.001050     3.50      2,855
40.00     0.000023     0.08    131,021   99.00    0.001707     5.69      1,757
50.00     0.000033     0.11     91,581   99.50    0.002128     7.09      1,410
60.00     0.000047     0.16     64,363   99.75    0.002419     8.06      1,239
70.00     0.000079     0.26     38,008   99.90    0.003507    11.69        855
80.00     0.000153     0.51     19,607
==============================================================================
Non-hispanic whites                Daily Exposure Analysis
-------------------                (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000007     0.000080
            Standard Deviation        0.000060     0.000187
            Standard Error of mean    0.000000     0.000003
            Margin of Exposure         425,093       37,582
            Percent of aRfD               0.02         0.27

       Percent of Person-Days that are User-Days =  8.84%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000002     0.01 >1,000,000   90.00    0.000194     0.65     15,476
20.00     0.000006     0.02    514,543   95.00    0.000319     1.06      9,411
30.00     0.000010     0.03    295,212   97.50    0.000551     1.84      5,442
40.00     0.000015     0.05    198,728   99.00    0.000877     2.92      3,422
50.00     0.000023     0.08    128,314   99.50    0.001213     4.04      2,473
60.00     0.000035     0.12     86,733   99.75    0.001779     5.93      1,686
70.00     0.000055     0.18     54,150   99.90    0.002081     6.94      1,441
80.00     0.000094     0.31     31,785
==============================================================================
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California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-98 data)
Residue file: pineapple HMN.RS7                    Adjustment factor #2 NOT used.
Analysis Date: 08-23-2002/14:25:17    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Acute Reference Dose (aRfD) =   0.030000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
===============================================================================
Non-hispanic blacks                Daily Exposure Analysis
-------------------                (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000010     0.000087
            Standard Deviation        0.000073     0.000202
            Standard Error of mean    0.000001     0.000007
            Margin of Exposure         306,906       34,633
            Percent of aRfD               0.03         0.29

       Percent of Person-Days that are User-Days = 11.28%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000005     0.02    569,715   90.00    0.000252     0.84     11,886
20.00     0.000008     0.03    387,306   95.00    0.000351     1.17      8,541
30.00     0.000011     0.04    281,241   97.50    0.000524     1.75      5,727
40.00     0.000014     0.05    209,552   99.00    0.001098     3.66      2,731
50.00     0.000020     0.07    150,230   99.50    0.001307     4.36      2,294
60.00     0.000029     0.10    102,887   99.75    0.001716     5.72      1,748
70.00     0.000052     0.17     57,238   99.90    0.002539     8.46      1,181
80.00     0.000100     0.33     30,084

===============================================================================

Non-hisp/non-white/non-black       Daily Exposure Analysis
----------------------------       (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000009     0.000146
            Standard Deviation        0.000080     0.000280
            Standard Error of mean    0.000002     0.000019
            Margin of Exposure         317,801       20,497
            Percent of aRfD               0.03         0.49

       Percent of Person-Days that are User-Days =  6.45%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000009     0.03    332,913   90.00    0.000415     1.38      7,221
20.00     0.000013     0.04    227,193   95.00    0.000589     1.96      5,092
30.00     0.000017     0.06    180,223   97.50    0.000974     3.25      3,079
40.00     0.000025     0.08    121,725   99.00    0.001038     3.46      2,889
50.00     0.000037     0.12     80,757   99.50    0.002083     6.94      1,440
60.00     0.000055     0.18     54,956   99.75    0.002140     7.13      1,401
70.00     0.000089     0.30     33,755   99.90    0.002149     7.16      1,396
80.00     0.000236     0.79     12,702
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California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-98 data)
Residue file: pineapple HMN.RS7                   Adjustment factor #2 NOT used.
Analysis Date: 08-23-2002/14:25:17    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Acute Reference Dose (aRfD) =   0.030000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
===============================================================================

All infants                        Daily Exposure Analysis
-----------                        (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000031     0.000289
            Standard Deviation        0.000146     0.000355
            Standard Error of mean    0.000003     0.000021
            Margin of Exposure          98,295       10,395
            Percent of aRfD               0.10         0.96

       Percent of Person-Days that are User-Days = 10.58%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000022     0.07    134,537   90.00    0.000740     2.47      4,056
20.00     0.000042     0.14     71,097   95.00    0.000901     3.00      3,329
30.00     0.000078     0.26     38,565   97.50    0.001062     3.54      2,824
40.00     0.000119     0.40     25,285   99.00    0.001861     6.20      1,612
50.00     0.000179     0.60     16,753   99.50    0.002530     8.43      1,185
60.00     0.000226     0.75     13,279   99.75    0.002546     8.49      1,178
70.00     0.000285     0.95     10,512   99.90    0.002741     9.14      1,094
80.00     0.000463     1.54      6,485

===============================================================================

Nursing infants (<1 yr old)        Daily Exposure Analysis
---------------------------        (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000012     0.000300
            Standard Deviation        0.000091     0.000353
            Standard Error of mean    0.000003     0.000057
            Margin of Exposure         257,059        9,990
            Percent of aRfD               0.04         1.00

       Percent of Person-Days that are User-Days =  3.89%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000044     0.15     68,886   90.00    0.001038     3.46      2,890
20.00     0.000054     0.18     55,609   95.00    0.001192     3.97      2,517
30.00     0.000079     0.26     37,750   97.50    0.001262     4.21      2,377
40.00     0.000136     0.45     22,008   99.00    0.001265     4.22      2,371
50.00     0.000183     0.61     16,398   99.50    0.001266     4.22      2,369
60.00     0.000197     0.66     15,239   99.75    0.001267     4.22      2,368
70.00     0.000253     0.84     11,838   99.90    0.001267     4.22      2,367
80.00     0.000449     1.50      6,679
```

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California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-98 data)
Residue file: pineapple HMN.RS7                   Adjustment factor #2 NOT used.
Analysis Date: 08-23-2002/14:25:17    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Acute Reference Dose (aRfD) =   0.030000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
===============================================================================

Non-nursing infants (<1 yr old)    Daily Exposure Analysis
-------------------------------    (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000038     0.000287
            Standard Deviation        0.000161     0.000355
            Standard Error of mean    0.000003     0.000022
            Margin of Exposure          79,625       10,443
            Percent of aRfD               0.13         0.96

       Percent of Person-Days that are User-Days = 13.12%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000021     0.07    144,822   90.00    0.000734     2.45      4,086
20.00     0.000034     0.11     88,830   95.00    0.000864     2.88      3,471
30.00     0.000078     0.26     38,397   97.50    0.001035     3.45      2,899
40.00     0.000114     0.38     26,408   99.00    0.001880     6.27      1,595
50.00     0.000174     0.58     17,195   99.50    0.002547     8.49      1,178
60.00     0.000226     0.75     13,246   99.75    0.002561     8.54      1,171
70.00     0.000299     1.00     10,027   99.90    0.002750     9.17      1,091
80.00     0.000476     1.59      6,297
===============================================================================

Children 1-6  yrs                  Daily Exposure Analysis
-----------------                  (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000032     0.000174
            Standard Deviation        0.000158     0.000337
            Standard Error of mean    0.000001     0.000007
            Margin of Exposure          95,043       17,200
            Percent of aRfD               0.11         0.58

       Percent of Person-Days that are User-Days = 18.10%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000012     0.04    255,770   90.00    0.000425     1.42      7,053
20.00     0.000020     0.07    150,210   95.00    0.000759     2.53      3,952
30.00     0.000027     0.09    109,928   97.50    0.001125     3.75      2,667
40.00     0.000039     0.13     76,450   99.00    0.001721     5.74      1,743
50.00     0.000059     0.20     50,775   99.50    0.002188     7.29      1,370
60.00     0.000092     0.31     32,520   99.75    0.002604     8.68      1,151
70.00     0.000136     0.45     22,047   99.90    0.003573    11.91        839
80.00     0.000218     0.73     13,755
```

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California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-98 data)
Residue file: pineapple HMN.RS7                   Adjustment factor #2 NOT used.
Analysis Date: 08-23-2002/14:25:17    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Acute Reference Dose (aRfD) =   0.030000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
===============================================================================

Children 7-12 yrs                  Daily Exposure Analysis
-----------------                  (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000013     0.000078
            Standard Deviation        0.000069     0.000154
            Standard Error of mean    0.000001     0.000007
            Margin of Exposure         230,990       38,406
            Percent of aRfD               0.04         0.26

       Percent of Person-Days that are User-Days = 16.63%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000004     0.01    799,698   90.00    0.000212     0.71     14,148
20.00     0.000010     0.03    307,560   95.00    0.000371     1.24      8,090
30.00     0.000013     0.04    226,455   97.50    0.000526     1.75      5,703
40.00     0.000017     0.06    177,305   99.00    0.000660     2.20      4,548
50.00     0.000023     0.08    127,928   99.50    0.000762     2.54      3,937
60.00     0.000035     0.12     86,663   99.75    0.001250     4.17      2,399
70.00     0.000058     0.19     51,764   99.90    0.001767     5.89      1,698
80.00     0.000099     0.33     30,369
===============================================================================

Females 13+ (preg/not nursing)     Daily Exposure Analysis
------------------------------     (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000009     0.000106
            Standard Deviation        0.000052     0.000151
            Standard Error of mean    0.000004     0.000040
            Margin of Exposure         347,299       28,320
            Percent of aRfD               0.03         0.35

       Percent of Person-Days that are User-Days =  8.15%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000002     0.01 >1,000,000   90.00    0.000486     1.62      6,177
20.00     0.000011     0.04    274,777   95.00    0.000486     1.62      6,169
30.00     0.000012     0.04    259,718   97.50    0.000487     1.62      6,164
40.00     0.000013     0.04    224,439   99.00    0.000487     1.62      6,162
50.00     0.000025     0.08    119,806   99.50    0.000487     1.62      6,161
60.00     0.000040     0.13     75,050   99.75    0.000487     1.62      6,160
70.00     0.000144     0.48     20,784   99.90    0.000487     1.62      6,160
80.00     0.000187     0.62     16,030
```

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California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-98 data)
Residue file: pineapple HMN.RS7                   Adjustment factor #2 NOT used.
Analysis Date: 08-23-2002/14:25:17    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Acute Reference Dose (aRfD) =   0.030000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
===============================================================================

Females 13+ (nursing)              Daily Exposure Analysis
---------------------              (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                       0.000032     0.000477
            Standard Deviation         0.000160     0.000411
            Standard Error of mean     0.000018     0.000155
            Margin of Exposure           93,189        6,286
            Percent of aRfD                0.11         1.59

       Percent of Person-Days that are User-Days =  6.75%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000008     0.03    357,338   90.00    0.001042     3.47      2,878
20.00     0.000024     0.08    127,055   95.00    0.001044     3.48      2,872
30.00     0.000038     0.13     79,655   97.50    0.001046     3.49      2,869
40.00     0.000275     0.92     10,916   99.00    0.001046     3.49      2,867
50.00     0.000364     1.21      8,244   99.50    0.001046     3.49      2,866
60.00     0.000367     1.22      8,173   99.75    0.001047     3.49      2,866
70.00     0.000880     2.93      3,409   99.90    0.001047     3.49      2,866
80.00     0.001038     3.46      2,891

===============================================================================

Females 13-19 (not preg or nursing)Daily Exposure Analysis
-----------------------------------(mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                       0.000004     0.000044
            Standard Deviation         0.000034     0.000101
            Standard Error of mean     0.000001     0.000009
            Margin of Exposure          724,079       67,675
            Percent of aRfD                0.01         0.15

       Percent of Person-Days that are User-Days =  9.35%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000002     0.01 >1,000,000   90.00    0.000071     0.24     42,426
20.00     0.000004     0.01    700,947   95.00    0.000274     0.91     10,953
30.00     0.000007     0.02    428,772   97.50    0.000299     1.00     10,042
40.00     0.000008     0.03    362,240   99.00    0.000580     1.93      5,170
50.00     0.000011     0.04    270,569   99.50    0.000698     2.33      4,298
60.00     0.000015     0.05    200,543   99.75    0.000700     2.33      4,288
70.00     0.000021     0.07    141,895   99.90    0.000701     2.34      4,282
80.00     0.000037     0.12     80,083
```

```
California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-98 data)
Residue file: pineapple HMN.RS7                   Adjustment factor #2 NOT used.
Analysis Date: 08-23-2002/14:25:17    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Acute Reference Dose (aRfD) =   0.030000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
===============================================================================

Females 20+ (not preg or nursing)  Daily Exposure Analysis
---------------------------------  (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000005     0.000066
            Standard Deviation        0.000051     0.000180
            Standard Error of mean    0.000001     0.000007
            Margin of Exposure         637,329       45,749
            Percent of aRfD               0.02         0.22

       Percent of Person-Days that are User-Days =  7.18%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000002     0.01 >1,000,000   90.00    0.000146     0.49     20,490
20.00     0.000005     0.02    578,865   95.00    0.000259     0.86     11,570
30.00     0.000007     0.02    402,639   97.50    0.000447     1.49      6,708
40.00     0.000010     0.03    289,444   99.00    0.000980     3.27      3,062
50.00     0.000015     0.05    197,999   99.50    0.001193     3.98      2,513
60.00     0.000025     0.08    121,318   99.75    0.002056     6.85      1,459
70.00     0.000039     0.13     76,502   99.90    0.002063     6.88      1,454
80.00     0.000067     0.22     44,900
California Department of Pesticide Regulation                          Ver. 7.76
===============================================================================

Females 13-50 yrs                  Daily Exposure Analysis
-----------------                  (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000006     0.000077
            Standard Deviation        0.000061     0.000207
            Standard Error of mean    0.000001     0.000010
            Margin of Exposure         504,979       39,129
            Percent of aRfD               0.02         0.26

       Percent of Person-Days that are User-Days =  7.75%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000002     0.01 >1,000,000   90.00    0.000188     0.63     15,973
20.00     0.000005     0.02    643,785   95.00    0.000309     1.03      9,704
30.00     0.000007     0.02    408,977   97.50    0.000599     2.00      5,006
40.00     0.000010     0.03    292,496   99.00    0.001096     3.65      2,736
50.00     0.000014     0.05    215,399   99.50    0.001204     4.01      2,490
60.00     0.000021     0.07    144,394   99.75    0.002066     6.89      1,451
70.00     0.000038     0.13     78,786   99.90    0.002067     6.89      1,451
80.00     0.000068     0.23     43,836
```

```
California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-98 data)
Residue file: pineapple HMN.RS7                   Adjustment factor #2 NOT used.
Analysis Date: 08-23-2002/14:25:17    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Acute Reference Dose (aRfD) =   0.030000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
===============================================================================

Males 13-19 yrs                    Daily Exposure Analysis
---------------                    (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000004     0.000054
            Standard Deviation        0.000037     0.000121
            Standard Error of mean    0.000001     0.000012
            Margin of Exposure         691,113       55,492
            Percent of aRfD               0.01         0.18

       Percent of Person-Days that are User-Days =  8.03%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000002     0.01 >1,000,000   90.00    0.000189     0.63     15,871
20.00     0.000003     0.01    886,844   95.00    0.000260     0.87     11,549
30.00     0.000008     0.03    384,739   97.50    0.000419     1.40      7,152
40.00     0.000009     0.03    352,719   99.00    0.000749     2.50      4,004
50.00     0.000010     0.03    286,827   99.50    0.000750     2.50      3,998
60.00     0.000013     0.04    236,944   99.75    0.000751     2.50      3,995
70.00     0.000021     0.07    143,978   99.90    0.000751     2.50      3,994
80.00     0.000038     0.13     78,603
===============================================================================

Males 20+ yrs                      Daily Exposure Analysis
-------------                      (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000004     0.000056
            Standard Deviation        0.000033     0.000119
            Standard Error of mean    0.000000     0.000005
            Margin of Exposure         853,098       53,548
            Percent of aRfD               0.01         0.19

       Percent of Person-Days that are User-Days =  6.28%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000002     0.01 >1,000,000   90.00    0.000137     0.46     21,858
20.00     0.000005     0.02    555,464   95.00    0.000219     0.73     13,673
30.00     0.000009     0.03    340,757   97.50    0.000335     1.12      8,964
40.00     0.000014     0.05    214,385   99.00    0.000577     1.92      5,199
50.00     0.000020     0.07    148,114   99.50    0.000716     2.39      4,187
60.00     0.000030     0.10    100,011   99.75    0.000860     2.87      3,489
70.00     0.000044     0.15     68,382   99.90    0.001706     5.69      1,758
80.00     0.000069     0.23     43,433
```

```
California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-98 data)
Residue file: pineapple HMN.RS7                   Adjustment factor #2 NOT used.
Analysis Date: 08-23-2002/14:25:17    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Acute Reference Dose (aRfD) =   0.030000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
===============================================================================

Seniors 55+                        Daily Exposure Analysis
-----------                        (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000003     0.000047
            Standard Deviation        0.000025     0.000085
            Standard Error of mean    0.000000     0.000004
            Margin of Exposure         911,364       63,496
            Percent of aRfD               0.01         0.16

       Percent of Person-Days that are User-Days =  6.97%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000003     0.01 >1,000,000   90.00    0.000118     0.39     25,370
20.00     0.000006     0.02    508,030   95.00    0.000227     0.76     13,243
30.00     0.000008     0.03    355,835   97.50    0.000309     1.03      9,712
40.00     0.000012     0.04    249,347   99.00    0.000441     1.47      6,800
50.00     0.000018     0.06    169,954   99.50    0.000512     1.71      5,855
60.00     0.000027     0.09    111,440   99.75    0.000717     2.39      4,181
70.00     0.000038     0.13     79,959   99.90    0.000867     2.89      3,461
80.00     0.000060     0.20     50,039
```

```
California Department of Pesticide Regulation                          Ver. 7.76
DEEM ACUTE Analysis for HYDRAMETHYLNON                            (1994-96 data)
Residue file: pineapple HMN.RS7                   Adjustment factor #2 NOT used.
Analysis Date: 08-30-2002/11:13:43    Residue file dated: 08-23-2002/14:22:23/14
NOEL (Acute) =   3.000000 mg/kg body-wt/day
Acute Reference Dose (aRfD) =   0.030000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "residue = tolerance of 0.05 ppm"
===============================================================================
Custom demographics 1: females 16+
All Seasons, Region(s): West
Sex: F-all/All Races
Age-Low: 16 yrs   High: 65 yrs
-----------------------------------
                                   Daily Exposure Analysis
                                   (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000009     0.000123
            Standard Deviation        0.000093     0.000317
            Standard Error of mean    0.000002     0.000028
            Margin of Exposure         325,520       24,306
            Percent of aRfD               0.03         0.41

       Percent of Person-Days that are User-Days =  7.47%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000001     0.00 >1,000,000   90.00    0.000291     0.97     10,307
20.00     0.000006     0.02    482,773   95.00    0.000751     2.50      3,996
30.00     0.000010     0.03    296,692   97.50    0.001041     3.47      2,881
40.00     0.000015     0.05    205,029   99.00    0.002064     6.88      1,453
50.00     0.000024     0.08    124,826   99.50    0.002066     6.89      1,451
60.00     0.000035     0.12     86,724   99.75    0.002067     6.89      1,451
70.00     0.000044     0.15     68,777   99.90    0.002067     6.89      1,451
80.00     0.000121     0.40     24,719

===============================================================================
Custom demographics 2: males 16+
All Seasons, Region(s): West
Sex: M/F-all/All Races
Age-Low: 16 yrs   High: 65 yrs
---------------------------------
                                   Daily Exposure Analysis
                                   (mg/kg body-weight/day)
                                    per Capita    per User
                                   -----------  -----------
            Mean                      0.000006     0.000096
            Standard Deviation        0.000074     0.000269
            Standard Error of mean    0.000001     0.000017
            Margin of Exposure         463,912       31,211
            Percent of aRfD               0.02         0.32

       Percent of Person-Days that are User-Days =  6.73%

  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.   Exposure    % aRfD     MOE       Perc.  Exposure    % aRfD      MOE
-----  -----------  ------- ----------   ----- -----------  -------  ---------
10.00     0.000002     0.01 >1,000,000   90.00    0.000188     0.63     15,923
20.00     0.000005     0.02    558,060   95.00    0.000488     1.63      6,148
30.00     0.000009     0.03    322,491   97.50    0.000929     3.10      3,228
40.00     0.000014     0.05    208,759   99.00    0.001718     5.73      1,745
50.00     0.000024     0.08    126,754   99.50    0.002063     6.88      1,453
60.00     0.000033     0.11     91,190   99.75    0.002066     6.89      1,452
70.00     0.000043     0.14     69,196   99.90    0.002067     6.89      1,451
80.00     0.000061     0.20     49,478
```

California Department of Pesticide Regulation Ver. 7.76
DEEM Chronic analysis for HYDRAMETHYLNON (1994-98 data)
Residue file name: D:\deem\pineapple HMN chronic res.RS7
Adjustment factor #2 NOT used.
Analysis Date 08-23-2002/14:30:46 Residue file dated: 08-23-2002/14:29:55/14
NOEL (Chronic) = 1 mg/kg bw/day
COMMENT 1: Hydramethylnon residue at 1/2 tolerance (tolerance=0.05 ppm)

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Percent of NOEL	Margin of Exposr 1/
U.S. Population (total)	0.000002	0.00%	435,944
U.S. Population (spring season)	0.000002	0.00%	449,292
U.S. Population (summer season)	0.000002	0.00%	472,478
U.S. Population (autumn season)	0.000002	0.00%	426,785
U.S. Population (winter season)	0.000002	0.00%	400,052
Northeast region	0.000002	0.00%	437,006
Midwest region	0.000002	0.00%	455,773
Southern region	0.000002	0.00%	477,225
Western region	0.000003	0.00%	367,701
Hispanics	0.000003	0.00%	289,074
Non-hispanic whites	0.000002	0.00%	496,463
Non-hispanic blacks	0.000003	0.00%	355,306
Non-hisp/non-white/non-black	0.000003	0.00%	382,936
All infants (< 1 year)	0.000006	0.00%	155,740
Nursing infants	0.000003	0.00%	358,561
Non-nursing infants	0.000008	0.00%	128,207
Children 1-6 yrs	0.000009	0.00%	116,348
Children 7-12 yrs	0.000004	0.00%	260,266
Females 13-19 (not preg or nursing)	0.000001	0.00%	800,192
Females 20+ (not preg or nursing)	0.000001	0.00%	706,964
Females 13-50 yrs	0.000002	0.00%	571,290
Females 13+ (preg/not nursing)	0.000003	0.00%	393,465
Females 13+ (nursing)	0.000010	0.00%	104,782
Males 13-19 yrs	0.000001	0.00%	951,746
Males 20+ yrs	0.000001	0.00%	897,183
Seniors 55+	0.000001	0.00%	952,835

Appendix F

Responses to Comments from the Worker Health and Safety Branch

dpr

Paul Helliker
Director

Department of Pesticide Regulation

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

MEMORANDUM

TO: Gary Patterson
Supervising Toxicologist

FROM: Lori O. Lim
Staff Toxicologist
(916) 324-3515

DATE: April 23, 2003

SUBJECT: RESPONSE TO COMMENTS ON THE HYDRAMETHYLNON RISK CHARACTERIZATION DOCUMENT

I have reviewed the comments from Worker Health and Safety Branch review of the draft Hydramethylnon Risk Characterization Document (RCD, January 7, 2003). My responses to the comments are included in this memorandum.

Page 1, third paragraph: The average dosages from Tables 2 through 4 from WH&S Exposure Assessment Document (EAD) should be amortized (reduced) by a factor of 6 for chronic exposure.

Response: From my discussion with Dr. Michael Dong, the author of the EAD, this change was necessary because of a change in policy on how chronic exposures were calculated. However, the EAD will not be revised to reflect the change. Therefore in the RCD, both the average dosages from the EAD and the amortized values will be presented.

Page 1, third paragraph: For field workers, acute exposure values should be used for seasonal exposure, and amortized (60/365) for chronic exposure, instead of noted as "not estimated".

Response: Table 3 in the EAD showed only upper-bound values; therefore, the draft RCD included only those values for acute exposure. The draft RCD will be revised to include those acute values as seasonal and chronic values (for lack of foliar dissipation data) as indicated in WH&S Branch comments.

Page 2, first paragraph: For the chronic dog study, the draft RCD included the clinical signs of one dog (3 mg/kg/day) in the consideration of the NOEL. WH&S noted that one of the reports stated that data from that one dog was omitted from the report.

Response: The study was reviewed by Dr. Joyce Gee, senior toxicologist for the Data Review Section. She was unable to determine whether the incidences of clinical signs for this dog were included in the summary data. Most other data for this animal were not included in the summaries, at the request of the sponsor. However, it was not known if the request also pertained to the clinical signs data.

Page 2, first paragraph: The summary data appeared to show an increasing trend in clinical signs, starting with the lowest dose group; because of this, an explanation of the NOEL selection would be helpful.

Response: This question was also addressed by Dr. Gee. Her comment was that the data at the lower doses were not of sufficient rigor to use as a definitive NOEL for risk assessment.

Based on the responses of these comments, the following revisions will be made:
1. The average exposure values in Table 28 will be reduced by 6-fold for chronic exposure, where appropriate.
2. Clarification will be provided regarding the clinical sign data for the one dog in question and the selection of the NOEL for the dog study.

cc. Keith Pfeifer
Joyce Gee

dpr

Paul Helliker
Director

Department of Pesticide Regulation

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

MEMORANDUM

TO: Gary T.Patterson, Chief
Medical Toxicology Branch

FROM: Charles M. Andrews, Chief
Worker Health and Safety Branch
(916) 445-4260

for CA

DATE: February 19, 2003

SUBJECT: REVIEW AND COMMENTS ON THE HYDRAMETHYLNON RISK CHARACTERIZATION DOCUMENT

Thank you for routing the Revised Risk Characterization Document (RCD) for Hydramethylnon to the Worker Health and Safety (WHS) Branch for review. I have taken this opportunity to have staff review the document. The RCD is thoughtfully written and the conclusions are presented in a clear fashion.

Exposure Assessment: Except for the following issues, the RCD accurately represents the calculations presented in the Exposure Assessment Document EAD.

Table 28 of the RCD summarizes the upper-bound and average daily dosages for workers and residents as estimated by the Worker Health and Safety Branch. Although the exposure estimates listed in this table are simply those listed in Tables 2 through 4 of the exposure assessment document (EAD), those average dosages used for chronic effects should be amortized (reduced) by a factor of 6 since the exposure frequencies for all groups except user and non-user residents were assumed to be 60 days per season as well as per year (i.e., by a factor of 60 days/365 days ≈ 1/6). This assumption is footnoted in the EAD's Tables 2 and 4 for all commercial handlers, and on p.12 in the EAD for all fieldworkers. This will not affect the RCD conclusions as MOEs for chronic exposure will be even higher. We do feel, however that the values should be changed to correctly reflect the estimated exposure. Furthermore, Table 28 of the RCD indicates that average dosages for fieldworkers were not estimated. In the absence of an average value that can be used for seasonal exposure, we should assume the acute exposure value for 60 days. Since the NOELs are the same for acute and seasonal, and the exposure would be the same, we suggest either showing the values or explaining in the text that the MOEs would be the same as those for the acute. As for chronic exposure, again, they should be taken as the seasonal value amortized by 60/365. Please see p.12 in the EAD for discussion on using acute exposure values.

General Comments on the RCD: We have two specific comments with respect to a study in which dogs were fed gelatin capsules containing hydramethylnon daily for 26 weeks (Wolfe et al., 1980). Interpretation of this study was confounded by the fact that the registrant provided only summary data for incidence of diarrhea, soft stools, and mucoid stools ("clinical signs"). On page 42 of the draft RCD, it says that "it was not possible to determine whether the one male with marked inappetence was disproportionately represented in the summary table." This is in reference to a dog in the highest dose group (3 mg/kg/day), which was twice removed from treatment and reinstated once, due to the dog's extreme weight loss and other signs. However, staff previously noticed a statement in one of the study reports (Wolfe et al., 1980) that data from the dog removed and reinstated to treatment were omitted from the report at the sponsor's request. Furthermore, the NOEL of this study is determined to be 1 mg/kg/day, based on inappetence and clinical signs, as though an increase in clinical signs was considered to have occurred only in the 3 mg/kg/day group. However, the summary data appear to show an increasing trend in clinical signs, starting with the lowest dose group; because of this, an explanation of the NOEL selection would be helpful.

Again, we appreciate the opportunity to review these documents. If you have any questions, please contact me.

cc: Joseph P. Frank (w/out attachment)
Keith Pfeifer (w/out attachment)
Michael H. Dong (w/out attachment)
Sheryl Beauvais (w/out attachment)
Lori O. Lim (w/out attachment)
Susan Edmiston (w/out attachment)

References:

Lim, L.O. 2002. Hydramethylnon Risk Characterization Document. Draft, November 22, 2002. Sacramento, CA: Medical Toxicology Branch, Department of Pesticide Regulation.

Wolfe, G.W., P.M. Marshall, W.M. Weatherholtz, *et al.*, 1980. Twenty-Six Week Toxicity Study in Dogs: AC 217, 300. Unpublished study report prepared by Hazleton Laboratories America, Inc., and submitted by American Cyanamid Co., Princeton, N.J. DPR Volume No. 395-042.

Appendix G

Responses to Comments from Registrants

dpr

Department of Pesticide Regulation

Paul Helliker
Director

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

MEMORANDUM

TO: Gary Patterson
Supervising Toxicologist

FROM: Lori O. Lim
Staff Toxicologist
(916) 324-3515

DATE: April 23, 2003

SUBJECT: RESPONSE TO COMMENTS FROM CLOROX SERVICES COMPANY ON THE HYDRAMETHYLNON RISK CHARACTERIZATION DOCUMENT

I have reviewed the comments from Clorox Services Company review of the draft Hydramethylnon Risk Characterization Document (RCD, January 7, 2003). There was no specific comment pertaining to the toxicology and risk assessment aspects of the RCD. The comments were mainly concerned with exposure and the dermal absorption factor calculated by the Worker Health and Safety Branch.

cc. Keith Pfeifer

dpr

Department of Pesticide Regulation

Paul E. Helliker
Director

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

MEMORANDUM

TO: Ann Prichard, Sr. Environ. Research Scientist
Pesticide Registration Branch

HSM-03009

VIA: Joseph P. Frank, Senior Toxicologist
Worker Health and Safety Branch

FROM: Michael H. Dong, Staff Toxicologist (Specialist)
Worker Health and Safety Branch
(916) 445-4263

MDH

DATE: April 25, 2003

SUBJECT: RESPONSE TO CLOROX' COMMENTS ON THE HYDRAMETHYLNON RCD DRAFT

Below is the response to Clorox Services Company's specific concerns (received March 3, 2003; Tracking No. SBRA-199011-E) over the dermal absorption rate used in the hydramethylnon exposure assessment performed by the Worker Health and Safety Branch (WH&S). The exposure assessment document (EAD) is part of the hydramethylnon risk characterization document (RCD).

In essence, Clorox argued that the use of 5% of the applied dermal dose in the EAD as the dermal bioavailability appears to be overly conservative, as their absorption study using a gel formulation indicated a lower absorption rate of about 1 to 2%.

WH&S used a 5% absorption rate in its EAD because granular formulation for outdoor uses was the target. It is also explained in the EAD (p.6) that the use of a gel formulation in their study *might* underestimate the dermal absorption for the granular formulation. While the exposure assessor does not know for certain that this is indeed the case, the typical formulation used for a dermal absorption study acceptable for exposure assessment is the technical. Also of note is the fact that the EAD already concluded (p.5 & p.14) that the worker and children exposures are insignificant from using the hydramethylnon gel and bait products, due to the little or no direct dermal contact involved.

Clorox Services Company

February 21, 2003

Risk Assessment – (Hydramethylnon)
Attn: Ann Prichard
Pesticide Registration Branch
Department of Pesticide Regulation
1101 I Street, P.O. Box 4015
Sacramento, CA 95812-4015

Reference: Notice to Pesticide Registrants – Hydramethylnon, dated 12/26/02

Dear Ms. Prichard:

Although we are somewhat surprised that DPR is initiating a full review of hydramethylnon, since USEPA has done an in-depth review as part of the Reregistration effort, we are confident that DPR will also find that continued use of hydramethylnon is safe, especially in household insecticide products.

Hydramethylnon-based products play a pivotal role in the control of a wide range of household pests, e.g., cockroaches and ants. The public health benefits that these products provide include removing sources of cockroach allergens, one of the primary causative agents/ triggers of asthma in children, and control of fire ants, the stings of which cause pain and allergic reactions in some individuals.

Our extensive experience in marketing this active in various bait forms (containerized, granular and gel) over the past decade has enabled us to closely monitor its safety aspects. We continue to regularly share our consumer experience with these products with the USEPA under our 6(a)(2) reporting obligation. For example, there were no 6(a) (2) reportable incidents in the past 6 months. Based on these data, we firmly believe that hydramethylnon baits in households provide the widest margin of safety among household insecticides. This is in part due not only to the low levels of active in these products, but also due to the nature of delivery systems(child-resistant bait stations), and relatively inaccessable placement of the baits (such as cracks and crevices) which minimizes consumer exposure to this insecticide. Our gel baits also include Bitrex, a taste aversive agent further mitigating exposure from accidental ingestion.

Dermal Absorption - At least from the study that Clorox has submitted (DPR Vol. 395-064 #131636), a 5% dermal bioavailability appears to be an unlikely scenario, as reflected by the absorbed dose and recovery rates. Also, please note that from the risk assessment perspective, the study concluded that "these results suggest that it would not be likely that any accumulation of Hydramethylnon residues would occur during routine use of this chemical in a gel formulation."

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Pleasanton, California
94566-0803
(925) 425-6100
FAX (925) 463-1187

In the risk assessment exercise and in arriving at a final decision on regulating its use, we urge the agency to consider in earnest hydramethylnon's low toxicity and negligible exposure scenarios in household applications, as well as its role in providing important public health benefits.

If you have any questions or need further clarification on our submission, please contact me by phone at 925-425-6280 or by email at Krishna.reddy@clorox.com

Thank you.

Sincerely yours,

A. Krishna Reddy, Ph.D., D.A.B.T.
Research Associate - PSERC

dpr

Department of Pesticide Regulation

Paul Helliker
Director

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

MEMORANDUM

TO: Gary Patterson
Supervising Toxicologist

FROM: Lori O. Lim
Staff Toxicologist
(916) 324-3515

DATE: April 23, 2003

SUBJECT: RESPONSE TO COMMENTS FROM BASF CORPORATION ON THE HYDRAMETHYLNON RISK CHARACTERIZATION DOCUMENT

I have reviewed the comments from BASF Corporation review of the draft Hydramethylnon Risk Characterization Document (RCD, January 7, 2003). There was only one comment pertaining to the toxicology and risk assessment aspects of the RCD.

Page 1, Appropriate Mammalian Toxicology Study for Potential Short-Term/Intermediate Exposure. The 21-day dermal toxicity study in the rabbit (NOEL of 50 mg/kg/day) is most appropriate study for short-term and intermediate exposure for workers.

Response: The rabbit 21-day dermal toxicity with a NOEL of 50 mg/kg/day was used as the critical NOEL in the RCD to address worker and residential exposure.

Other comments concerned the dermal absorption factor and dislodgeable foliar residue calculations conducted by the Worker Health and Safety Branch.

cc. Keith Pfeifer

dpr

Department of Pesticide Regulation

Paul E. Helliker
Director

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

MEMORANDUM

TO: Ann Prichard, Sr. Environ. Research Scientist
Pesticide Registration Branch

HSM-03010

VIA: Joseph P. Frank, Senior Toxicologist
Worker Health and Safety Branch

FROM: Michael H. Dong, Staff Toxicologist (Specialist) *[original signed by M. Dong]*
Worker Health and Safety Branch
(916) 445-4263

DATE: April 25, 2003

SUBJECT: RESPONSE TO BASF'S COMMENTS ON THE HYDRAMETHYLNON RCD DRAFT

Below is the response to BASF's concerns (received January 3, 2003; Tracking No. SBRA-198658-E) regarding one toxicity-related and two exposure-related estimates used in the risk characterization document (RCD) for hydramethylnon.

BASF suggested that for short-term and intermediate exposures of agricultural handlers, the most appropriate mammalian toxicity study used should be the 21-day rabbit dermal study that had been submitted to the Department for review. The toxicological critical end points are addressed by the Medical Toxicology Branch.

BASF believed that the most appropriate value for dermal bioavailability is derived from the submitted dermal absorption study, which used gel formulations and indicated a lower absorption rate of 1 to 2% (of the applied dermal dose). As stated in an earlier response (Dong, 2003), WH&S used a 5% absorption rate because granular formulation for outdoor uses was the target. It is also explained in the exposure assessment document (p.6) that the use of a gel formulation in the absorption study *might* underestimate the dermal absorption for the granular formulation. While the exposure assessor does not know for certain that this is indeed the case, the typical formulation used for a dermal absorption study acceptable for exposure assessment is the technical.

BASF's third and final concern is that WH&S overestimated the field reentry exposure by using initial deposition values of foliar residues that were based on liquid pesticides sprayed to foliage, instead of those on granular applications. However, WH&S already addressed this issue in its exposure assessment document (p.17) and acknowledged that the hydramethylnon granules, though oily in nature, are likely not as adhesive to the foliage as the sprays that were used in the 21 studies, from which the 95% upper confidence limit of the mean initial deposition foliar residues was derived. The exposure assessor tends to agree with BASF that the dislodgeable foliar residues (DFR) typically are higher from a liquid spray than from a granular application. Nonetheless, this difference cannot be quantified easily even with an extensive review of the limited literature data available today. Based on the data compiled by Klonne (2000), which were referenced by BASF, the difference in DFR between liquid and granular formulations appear to range from approximately 5 to 15% depending on whether geometric or arithmetic

means were used for the comparison. Sears *et al.* (1987) reported similar findings when they compared the DFR of diazinon obtained immediately following application with a liquid and a granular formulation. However, at day 1 post-application and on subsequent days, their data did not show any significant difference in the DFR obtained from treatments with the two different diazinon formulations. Still another uncertainty is that the foliar residue data provided by Sears *et al.* and by Klonne were all on turfgrasses, which typically have slender, shorter, and tender foliage that might be less suitable for the deposition of granules, when compared to the foliage of some other crops on which granular hydramethylnon is allowed. Furthermore, even if adequate data were available to quantify how much the DFR values from the liquid formulation would overestimate those from the granular formulation, the regulatory position would not change as the margins of exposure calculated in the RCD draft were all well above 100, which is the Department's risk assessment benchmark for hydramethylnon.

References

Dong MH, 2003. Review Memo: Response to Clorox' Comments on the Hydramethylnon RCD Draft. HSM-03009. Cal/EPA Department of Pesticide Regulation, dated April 25.

Klonne D, 2000. Evaluation of Transferable Turf Residue Data From Studies Conducted or Purchased by the ORETF. Cal/EPA Department of Pesticide Regulation Data Registration No. 52103-022.

Sears MK, Bowhey C, Braun H, Stephenson GR, 1987. Dislodgeable Residues and Persistence of Diazinon, Chlorpyrifos and Isofenphos Following Their Application to Turfgrass. *Pesticide Science* 20:223-231.

BASF Corporation

JAN 3 0 2003

BY PEST/REGISTRATION
ID# 42641

BASF

Vol. 395-0090

January 22, 2003

Risk Assessment - (Hydramethylnon)
Attn. Ann Prichard
Pesticide Registration Branch
Department of Pesticide Regulation
1001 I Street
Sacramento, CA 95812

Re: Notice to Pesticide Registrants on Identification of Definitive Toxicity/Exposure Studies and Critical Endpoints/NOELS for the active ingredient hydramethylnon

Dear Ms. Prichard:

BASF requests that the comments below be considered during the assessment of human health risks for hydramethylnon.

Appropriate Mammalian Toxicology Study for Potential Short-Term/Intermediate Exposure

When performing estimates for risk assessment for short-term/intermediate exposure of agricultural handlers involved with aerial and/or ground application of hydramethylnon granular insecticide (0.73% a.i.; Amdro® Pro fire ant bait, EPA Reg. No. 241-322; Table 2 of DPR Notice), the most appropriate mammalian toxicology study available is the 21-day dermal study in the rabbit. This 21-day dermal study in the rabbit is most appropriate because dermal exposures constitute the majority of total worker exposures relative to that contributed by inhalation exposure. Moreover, because of its inherent low volatility and its presence in a relatively heavy granule, there exists very low bioavailability of the active ingredient in the respiratory tract.

As mentioned in the Notice to Pesticide Registrants, the NOEL for toxicology effects in the 21-day rabbit dermal study is 50 mg/kg b.w./day, as based on decreased body weights and increased relative liver weights at 250 mg/kg b.w./day. Applying a 100-fold safety factor to the NOEL, the dermal AOEL is calculated as 0.5 mg/kg b.w./day, which may be compared to daily dermal exposure values.

Dermal Absorption

BASF Corporation believes that the most appropriate value for dermal bioavailability is derived from the dermal absorption study performed on the gel formulation (2% a.i.; Siege® gel insecticide, EPA Reg. No. 241-313), which also represents a worst case scenario to provide surrogate data to support proposed uses of the granular formulation (0.73%). Specifically, this dermal absorption study was performed on male rats by applying 2 mg a.i. of gel on a restricted region of skin for a 10-hour period followed by washing of the skin. Direct absorption over a 14-day period was 0.83% with only 0.75% of the dose remaining in the skin at the test site after 14 days (336 hours).

P.O. Box 13528, Research Triangle Park, North Carolina 27709-3528 (919) 547-2000

Thus, the daily-absorbed doses of workers can be calculated using 0.83% of the dermal contact with the Amdro Pro formulation. Finally, margins of exposure (MOE's) can also be derived by comparing the estimated daily absorption of hydramethylnon to the NOEL of 50 ppm (2.5 mg/kg b.w./day) from the most sensitive species, the rat, in an oral toxicity study, and adjusted (multiplied) by the oral bioavailability of 10%. This lowest NOEL of 50 ppm (2.5 mg/kg b.w./day) for the rat was derived from the 90-day rat feeding study, based on small soft testes, decreased testicular weight and testicular atrophy in males at 100 ppm.

Occupational Exposure Endpoints

Table 3 of the DPR notice provides the reentry exposure for fieldworkers and residents. The exposure calculations use a Dislodgeable Foliar Residue (DFR) value of 0.035 µg/cm2. This value is based on DFR values obtained from liquid applications to foliage normalized for the hydramethylnon application rate. The assumption that a DFR value from a liquid application that is intended to uniformly cover foliage is appropriate for an exposure assessment for a granular application is incorrect. Hydramethylnon granules will settle between the leaves of the treated plants or fall to the ground and will be generally unavailable for exposure to workers. In an ORETF report[1], differences in total transferable residues (TTR) between granular and liquid applications were analyzed. Evaluation of 68 granular and 179 liquid application samples indicated the mean transferable residue from a granular application was only 5% of the mean from a liquid application. Although methods for the collection of DFR and TTR data differ, the data can be used to illustrate the differences in potential exposure between granular and liquid applications. Therefore a conservative estimate of the DFR from a hydramethylnon application should be 0.0018 µg/cm2 (5% of 0.035 µg/cm2). This would reduce the estimated exposure following a high crop/high exposure activity to 0.1 µg/kg/day.

If questions arise as the comments are reviewed, please call me at 919-547-2291 or e-mail me at whatlel@basf-corp.com.

Sincerely,
BASF Corporation
Agricultural Products

Laura L. Whatley

Laura L. Whatley, Ph.D.
Senior Registration Scientist

[1]Klonne, D., 2000, Evaluation of Transferable Turf Residue Data From Studies Conducted or Purchased by the ORETF.

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APPENDIX H. Responses to Comments from the Office of Environmental Health Hazard Assessment

Department of Pesticide Regulation

Paul Helliker
Director

MEMORANDUM

Arnold Schwarzenegger
Governor

TO: Gary Patterson, Ph.D.
Supervising Toxicologist
Medical Toxicology Branch

VIA: Keith Pfeifer, Ph.D., DABT
Senior Toxicologist
Medical Toxicology Branch

FROM: Lori O. Lim, Ph.D., DABT
Staff Toxicologist
(916) 324-3515

DATE: January 20, 2004

SUBJECT: RESPONSE TO COMMENTS FROM THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT ON THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR HYDRAMETHYLNON

This memorandum addresses comments from the Office of Environmental Health Hazard Assessment (OEHHA) on the Department's draft Risk Characterization Document (RCD) for the active ingredient hydramethylnon (October 24, 2003). Overall, OEHHA supported the selection of critical endpoints/NOELs, and the evaluation of oncogenicity. They identified areas that needed clarification and additional information. Responses to the specific comments are:

Comment 1: The RCD did not include seasonal dietary exposure. OEHHA suggested that seasonal dietary exposure should be conducted or justification should be provided if not evaluated.

DPR Response: The only human food use for hydramethylnon is on pineapples. Since pineapples are generally available throughout the year, seasonal dietary exposure was not conducted. Single and repeated exposures were addressed by acute and chronic dietary exposure assessments, respectively. This justification will be added to the revised document under IV.B. Exposure Assessment.

Comment 2: OEHHA agreed with DPR that inhalation exposure to hydramethylnon is likely negligible. However, OEHHA considered the discussion in the RCD too limited to support not conducting an inhalation exposure assessment. OEHHA indicated that inhalation exposure should be evaluated or additional justification was needed since U.S. EPA performed such an assessment.

DPR Response: The RCD will add a statement (Table 27 and IV.B.) that the U.S. EPA did not conduct inhalation exposure assessment in the Registration Eligibility Document or in the Final

Rule for the tolerance of pineapple. The rationale, physical chemical/product packaging considerations, was the same as given by DPR.

Comment 3: OEHHA supported DPR's overall evaluation of carcinogenicity for hydramethylnon. Since the evidence showed possible carcinogenicity, OEHHA suggested adding a discussion of applying an additional uncertainty factor. On page 4 of the attachment, OEHHA suggested addition of the incidence data and detailed analyses of the data for adrenal medullary tumors in the CD rat (IRDC, 1982a). This tumor was mentioned in the DPR's testimony before the Proposition 65 Scientific Advisory Panel December 16th, 1988 meeting.

DPR Response: DPR is unclear as to the basis for the suggestion of an uncertainty factor. The U.S. EPA also did not conduct a cancer risk analysis for hydramethylnon in the RED. Furthermore, the U.S. EPA Draft Final Guidelines for Carcinogen Risk Assessment does not have discussion regarding the use of an additional uncertainty factor for possible carcinogenicity for chronic exposures.

The incidence data for adrenal medullary tumor will be discussed within the summary of the study. Detailed analysis of the data will not be conducted since this tumor was not considered as a treatment-related effect in the DPR evaluation of this study.

Comment 4: OEHHA suggested justification for DPR's determination of 10 ppm as the NOEL for decreased fetal body weight for the definitive rabbit developmental toxicity study (IRDC, 1982d). The U.S. EPA established the NOEL at 5 mg/kg/day.

DPR Response: DPR and U.S. EPA used different criteria to select the NOEL for the study. DPR established the NOEL at 10 mg/kg/day because the mean fetal body weight (83% of control) was not statistically significant different than the control. The fetal body weight at 20 mg/kg/day (74% of control) was statistically significant from control. The U.S. EPA established the NOEL at 5 mg/kg/day based on comparison with the historical range. This was explained in the summary for this study and since this difference in the NOELs has no impact on the risk characterization, no further discussion will be added.

Comment 5: OEHHA recommended a brief discussion of other potentially sensitive subpopulations (elderly, medical conditions) be added to the document.

DPR Response: DPR is unclear as to the scientific basis for this comment since OEHHA did not provide rationale for the concerns regarding the exposure of these groups to hydramethylnon.

Comment 6: OEHHA suggested clarification on the use hydramethylnon on pineapples in California.

DPR Response: The revised RCD (under II.B. Regulatory History) will clarify that a tolerance was established for the use of hydramethylnon, not limited to Hawaii.

Comment 7: OEHHA recommended the RCD to include existing (or lack of) specific information on exposure benchmarks such as reference dose, maximum contaminant level, threshold limit value, and permissible exposure limits etc.

DPR Response: The RCD already included reference concentrations. The revised RCD (under II.B. Regulatory History) will include a statement that there are no other standards or limits.

Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 1001 I Street • Sacramento, California 95814
Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

MEMORANDUM

Terry Tamminen
Agency Secretary

Arnold Schwarzenegger
Governor

TO: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1001 I Street, P.O. Box 4015
Sacramento, California 95812-4015

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section
1515 Clay Street, 16th Floor
Oakland, California 946122

DATE: December 19, 2003

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENT HYDRAMETHYLNON

We have completed our review of the draft risk characterization document (RCD) for tetrahydro-5,5-dimethyl-2 (1H)-pyrimidinone {3[4-(trifluoromethyl) phenyl]-1-[2-(4-trifluoromethyl) phenyl] ethenyl]-2-propenylidene} hydrazone (hydramethylnon) prepared by the Department of Pesticide Regulation (DPR).

Hydramethylnon{tetrahydro-5,5-dimethyl-2 (1H)-pyrimidinone {3[4-(trifluoromethyl) phenyl]-1-[2-(4-trifluoromethyl) phenyl] ethenyl]-2-propenylidene} is an insecticide used to control ants (including imported fire ants and leafcutter ants), cockroaches and termites. Hydramethylnon is used on a single food crop (pineapple), on feed (rangeland grasses, and hay) and also has non-food uses (lawns, turfs, golf courses, non-bearing nursery stocks, right-of-ways, houses and other structures). The use of hydramethylnon on pasture and rangeland grass is not permitted in California. Hydramethylnon was first registered with the U.S. EPA in 1980. It belongs to a chemical class of chemicals known as the trifluoromethyl amidinohydrazones. It is listed as a reproductive and developmental toxicant under Proposition 65.

Overall, we support the procedures and approaches used for characterizing the health risk of hydramethylnon in the draft RCD for this chemical. We especially acknowledge efforts made to substantiate the choices of critical studies, discussions of issues that might be raised by reviewers, identification of numerous uncertainties pertinent to risk estimates, and comparison of risk estimates with those estimated by the U.S. EPA. While the current version of the draft RCD is quite thorough, it would benefit from clarifying certain issues and expanding the information provided.

A summary of our comments on the draft RCD for methyl hydramethylnon is found below. For more details please refer to the attachment.

1. While OEHHA supports DPR's choices of critical studies, toxicological endpoints and NOAELS used in the RCD for hydramethylnon, we note that seasonal (subchronic oral) exposures are not evaluated in the document. No support for this decision is provided in the RCD. We suggest that DPR either evaluate this exposure scenario or provide appropriate justification for not evaluating subchronic exposures.

2. OEHHA agrees that inhalation exposure to hydramethylnon is likely negligible, however, only limited discussion is provided in the RCD supporting this assumption. We note that the U.S. EPA performed this assessment, finding that exposure from the inhalation pathway is indeed negligible. We suggest either evaluating this route in the RCD or substantiating that the exposures evaluated by the U.S. EPA are similar enough to those expected in California and cite the federal assessment as additional support for this assumption.

3. We support the overall evaluation for carcinogenicity. The report includes several important analyses. The report would further benefit by discussing the value of applying an additional uncertainty factor for possible carcinogenicity for chronic exposures.

4. Even though a developmental toxicity endpoint was not used for calculating MOEs in the RCD, we suggest that DPR provide further justification for the selection of 10 mg/kg/day as the NOAEL for developmental toxicity instead of the value of 5 mg/kg/day as determined by the U.S. EPA.

5. No potentially sensitive subpopulations are discussed in the RCD other than children and infants. OEHHA recommends a brief discussion of other potentially sensitive subpopulations (elderly, medical conditions) be added to the document.

6. It is unclear if hydramethylnon is applied to pineapples in California. We suggest clarifying this in the RCD.

7. OEHHA recommends including in the RCD specific information regarding existing (or lack of) current exposure benchmarks such as the reference dose, maximum contaminant level, threshold limit value, and permissible exposure limits etc.

Thank you for providing the document for our review. If you have any questions about our comments, please contact Dr. Jolanta Bankowska at (510) 622-3162 or Mr. Robert Schlag at (916) 323-2624.

Attachment

ATTACHMENT

COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR HYDRAMETHYLNON

BACKGROUND INFORMATION

Hydramethylnon{tetrahydro-5,5-dimethyl-2 (1H)-pyrimidinone {3[4-(trifluoromethyl) phenyl]-1-[2-(4-trifluoromethyl) phenyl] ethenyl]-2-propenylidene} is an insecticide used to control ants (including imported fire ants and leafcutter ants), cockroaches and termites. Hydramethylnon is used on a single food crop (pineapple), on feed (rangeland grasses, and hay) and also has non-food uses (lawns, turfs, golf courses, non-bearing nursery stocks, right-of-ways, houses and other structures). The use of hydramethylnon on pasture and rangeland grass is not permitted in California. Hydramethylnon was first registered with the U.S. EPA in 1980. It belongs to a chemical class of chemicals known as the trifluoromethyl amidinohydrazones. It is listed as a reproductive and developmental toxicant under Proposition 65.

Our specific comments are provided below:

COMMENTS

Selection of critical studies and endpoints for risk assessment in RCD:

Acute Toxicity:

An estimated acute NOAEL of 3 mg/kg/day (0.3 mg/kg/day, absorbed dose) was selected to calculate margin of exposures (MOS) for acute dietary exposures to hydramethylnon. This NOEL was estimated from a LOAEL of 30 mg/kg/day that was based on decreased body weight, clinical signs (nasal and perianal area bloody discharges), and reduced fertility in rats given hydramethylnon for five days (Harnois, 1979). The risk from acute dermal exposure was calculated using a NOAEL of 50 mg/kg/day (0.1 mg/kg/day, absorbed dose) based on decreased food consumption in a rabbit 21-day dermal toxicity study (Thompson, 1982) at the next higher dose of 250 mg/kg/day. Health risks from inhalation exposure to hydramethylnon were not assessed because it is unlikely that the chemical will be found in the air (low vapor pressure and low Henry's Law constant).

Subchronic Toxicity:

A NOAEL of 50 mg/kg/day (1.8 mg/kg/day, absorbed dose) was used to calculate the MOEs for subchronic (seasonal) exposure. This NOAEL was derived from a dermal study in rabbits, which showed decreased food consumption at the next higher dose of

250 mg/kg/day (Thompson, 1982). Subchronic oral exposures were not evaluated in the RCD.

Chronic Toxicity:

Chronic dietary exposure was assessed based on an estimated NOAEL of 1 mg/kg/day (0.1 mg/kg/day, absorbed dose) determined in a 26-week gavage dog study (Marshall, 1980). Toxicological effects observed in this study were clinical signs (soft stools, mucoid stools, diarrhea) and weight loss seen at the next higher dose (LOAEL) of 3 mg/kg/day (0.3 mg/kg/day absorbed dose).

While OEHHA supports DPR's choices of critical studies, toxicological endpoints and NOAELS used in the RCD for hydramethylnon, we note that seasonal (subchronic oral) exposures are not evaluated in the document. No support for this decision is provided in the document. We suggest that DPR either evaluate this exposure scenario or provide appropriate justification for not evaluating subchronic exposures.

Absorption of hydramethylnon by different routes of exposure

Exposure estimates and MOEs were calculated in the RCD by using ten percent oral, and five percent dermal absorption. These absorption factors were determined from the results of the study by Zdybak and Robisnson (1992) for oral absorption and for dermal absorption from two studies (Frantz and Beskitt, 1993; Sharp 1993).

Exposure to hydramethylnon via the inhalation route was considered negligible and therefore not assessed in the RCD. This decision is supported by physico-chemical properties of the active ingredient (low volatility and low Henry's Law constant) and formulations used (granular/flake, pellet/tablet/cake/briquette, gel/paste/cream, impregnated material, or dry material).

OEHHA agrees that inhalation exposure to hydramethylnon is likely negligible, however, only limited discussion is provided in the RCD supporting this assumption. We note that the U.S. EPA performed this assessment, finding that exposure from the inhalation pathway is indeed negligible. We suggest either evaluating this route in the RCD or substantiating that the exposures evaluated by the U.S. EPA are similar enough to those expected in California and cite the federal assessment as additional support for this assumption.

Reproductive and developmental toxicity

Hydramethylnon causes reproductive toxicity in rats. Available multiple-generation toxicity studies (Biodynamics, Inc., 1982; Schroeder, 1995) showed non-reversible reduced fertility in rats, the target organ was the testis. An adult NOAEL of 1.66 mg/kg/day (0.017 mg/kg/day absorbed dose) based on adverse effects in the testis, consisting of degeneration of the germinal epithelium and aspermia, and epididymis-

increased cellular debris was identified (Schroeder, 1995) and was used by the U.S. EPA to assess chronic dietary exposure and acute, subchronic and chronic exposures by the dermal and inhalation routes.

Developmental toxicity studies with hydramethylnon in rats and rabbits showed reduced body weight gain, yellow body fats, and clinical signs such as soft stool and anogenital stains (Bio/dynamics Inc., 1979; IRDC 1982c). In the first study a developmental NOAEL 10 mg/kg/day was identified based on decreased fetal weight and ossification variations (attributed to the body weight loss in the dams) at the next higher dose of 30 mg/kg/day. The maternal NOAEL in this study was lower, 3 mg/kg/day, and was based on decreased body weight gain at the next higher dose of 10 mg/kg/day. In the second study (IRDC 1982c) a NOAEL for maternal toxicity of 5 mg/kg/day based on decreased body weight gain and clinical signs such as reduced stool amounts or soft stools, yellow body fat, and matting and/or discharge in anogenital region at the next higher dose of 10 mg/kg/day was identified. A NOAEL of 5 mg/kg/day was also identified in this study for developmental toxicity based on an increase in spontaneous abortions at the next higher dose of 10 mg/kg/day. The NOAEL of 10 mg/kg/day for developmental toxicity based on decreased fetal weight was identified by DPR from the Bio/dynamics Inc., 1979 study as the NOAEL for developmental toxicity. The U.S. EPA selected 5 mg/kg/day from the IRDC, 1982c study as the NOAEL for developmental toxicity.

Even though a developmental toxicity endpoint was not used for calculating MOEs in the RCD, we suggest that DPR provide further justification for the selection of 10 mg/kg/day as the NOAEL for developmental toxicity instead of the value of 5 mg/kg/day as determined by the U.S. EPA.

Groups sensitive to hydramethylnon exposures

Available toxicological data do not provide evidence for increased pre- and post-natal sensitivity when NOAELs for developmental or reproductive toxicity are compared with those for maternal toxicity. Indeed, in both rat and rabbit developmental toxicity studies, maternal NOAELs were equal to or even lower than fetal NOAELs. Significant effects in the fetuses included reduced fetal body weights (rats and rabbits) and ossification variations (rats only). Similarly, no effects were observed in pups at levels lower than those resulting in maternal and/or reproductive effects. In conclusion no additional safety factor is needed to protect infants and children as is required by the Food and Quality Protection Act (FQPA).

No other sensitive group of the human population is mentioned or discussed in the document. OEHHA recommends including a discussion of other potentially sensitive subpopulations (elderly, medical conditions) in the RCD.

Potential oncogenic effects

Hydramethylnon is classified by the U.S. EPA as a possible human carcinogen (group C carcinogen). Available long-term toxicity studies showed treatment-related tumors in the mouse (IRDC, 1982b) but not in the rat (IRDC, 1982a). Tumors (adenomas and carcinomas) were observed in lungs of female mice. Statistical analysis showed significant increases in lung adenomas and combined adenomas/carcinomas at all doses studied versus the controls. We concur with DPR's use of time-dependant statistical analysis of the incidence data for pair-wise analysis and trend analyses. It was especially important for these data due to the differential survival in the treatment groups. It would also be useful to provide time-dependent analysis with including the highest dose group.

There were also lung tumors found in male mice but they were considered not to be toxicologically significant since the incidences were increased only at maximally tolerated dose (MTD). Uterine polyps were also observed in female rats at the MTD and were also considered not significant since the incidences were increased at maximally tolerated doses. However, as indicated in Table 15, there was a statistically significant trend. Consequently, the effect does not appear to be related solely to exceeding the MTD.

We note that Dr. Hathaway in his December 16th 1988 testimony before the Proposition 65 Scientific Advisory Panel states: "the adrenal medullary tumors in CD rats the MTD was exceeded in that. It is an equivocal study. There was some indication at a lower dose, but not statistically significant". It also would be useful to provide the incidence rate and detailed analysis, similar to Table 26, in the report for this tumor cite. Available genotoxicity tests were all negative. The overall weight of evidence evaluation indicates suggestive evidence for oncogenicity, but does not justify performing a carcinogenic risk assessment.

We support DPR's overall weight of evidence evaluation that includes discussion of the U.S. EPA approach, genotoxicity studies and consideration of structure-activity relationships. This is consistent with the California Proposition 65 Scientific Advisory Panel's determination in 1989 to not add hydramethylnon to the list of carcinogens Scientific Advisory Panel 1988, pg. 59). Since there is "suggestive " evidence for hydramethylnon carcinogenicity the RCD would benefit by discussing the value of applying an additional uncertainty factor for possible carcinogenicity for chronic exposures.

Use of hydramethylnon in California

It is not clear in the RCD whether hydramethylnon uses in California are limited solely to non-food applications (see first paragraph on page one and second paragraph on page six) or if it is also registered for use on pineapples. We suggest this issue be clarified in the RCD.

Exposure standards

OEHHA recommends including in the RCD specific information regarding existing (or lack of) current exposure benchmarks such as the reference dose, maximum contaminant level, threshold limit value, permissible exposure limits, etc.

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