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MEMORANDUM

SUBJECT: Occupational Risk Assessment for Molinate

TO: Peter Caulkins
Acting Director
Special Review & Reregistration Division (7508W)

FROM: Stephanie Irene / s /
Acting Director
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Attached is the risk assessment for occupational exposure to Molinate. This assessment estimates the short term, intermediate and long term occupational exposure to mixers/loaders and applicators. HED has provided reproductive margins of exposure and cancer risk estimates. The attached risk assessment incorporates comments and input contributed by RCAB, OREB, TOXI, and TOXII.

Attachment

cc: Jack Housenger (7508W)
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Molinate Team Members: (members responsible for review of technical accuracy, occupational exposure estimates, issues presented and policies as relevant to this risk assessment.)

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MOLINATE

Risk Assessment for Occupational Exposure

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3

MOLINATE
Risk Assessment for Occupational Exposure

I. Executive Summary

HED has completed an occupational risk assessment for molinate. This assessment addresses molinate's use on rice. The granular and emulsifiable concentrate formulations were evaluated for the major application methods as used in California and in the southern regions of the US.

Based on a review of the molinate toxicological database, HED has identified reproductive toxicity and carcinogenicity as the critical toxicological endpoints for regulatory purposes. The HED Peer Review Committee (PRC) evaluated the carcinogenic potential of molinate on September 14, 1992, concluding that molinate should be classified as a Group C carcinogen, possible human carcinogen. The basis for this classification was the finding of male rat kidney cortical adenomas and/or carcinomas. The kidney tumors were considered to be a rare tumor type. The PRC indicated that it is appropriate to conduct a quantitative risk assessment using a linearized low-dose linear extrapolation approach (Q_1^*) to characterize the dose-response of molinate.

The HED Peer Review Committee for Developmental and Reproductive Toxicity met on December 12, 1991 to discuss and evaluate the weight-of-the-evidence on molinate, with particular reference to its potential for reproductive and developmental toxicity. The Committee concluded that clear evidence of male reproductive toxicity is found in dogs, mice, and rats following administration of molinate. HED determined that a NOEL of 0.2 mg/kg/day is appropriate for assessing short term, intermediate and long term occupational exposure to molinate. This NOEL is based on effects of male reproduction (sperm measure and fertility) from the male fertility study in the rat.

HED estimated the exposure to mixers, loaders and applicators using typical molinate products. The occupational exposure estimates for molinate were based on 2 different exposure databases. The granular exposure estimates were based on an actual California granular exposure study performed in 1993 and the emulsifiable concentrate (EC) estimates were based on the Pesticide Handlers Exposure Database (PHED). HED is currently researching possible mitigation options for molinate.

Reproductive margin of exposure estimates and the cancer risk estimates for molinate are contained in Tables 7 and 8. HED estimated cancer risks for occupational use based on the low dose extrapolation model. The excess individual lifetime cancer risk estimates range from 10^{-6} to 10^{-5} for occupational uses of granular molinate and 10^{-6} to 10^{-5} for the EC formulations of molinate as it is used in the southern regions of the US. Margins of exposure for loaders of granular molinate are greater to or equal 100 if the loader uses the carbon impregnated coveralls while direct loading the bulk bags of molinate

4

into airplane hoppers. Trans and direct loading of molinate while wearing Tyvek® suits or carbon impregnated coveralls results in MOEs of less than 100. Margins of exposure for agricultural workers using the EC formulations of molinate are all less than 100 for all job functions and engineering controls evaluated.

II. Background

Molinate is a selective herbicide used only on rice to control a variety of grasses and other weeds. Molinate is the common name for S-Ethyl hexahydro-1H-azepine-1-carbothioate and is often sold under the trade name Ordram®. Zeneca, formerly ICI, is the primary registrant. Molinate is commercially available in 3 granular and 2 emulsifiable concentrate products, and as an emulsifiable concentrate in combination with propanil.

Molinate is applied in all six rice producing states (AR, CA, LA, MO, MS and TX). Nearly 85% of the molinate sold is aerially applied post-emergent as the granular formulation, with the remaining 15% as an emulsifiable concentrate applied pre-emergent by ground equipment or aerially applied post-emergent. Ninety to ninety-five percent of all formulations of molinate are applied commercially by air.

Physical and Chemical Properties:

CAS No.	2212-67-1
Physical State	Amber liquid
Molecular Weight	187.3
Solubility	In water 880 mg/L at 20°C
Vapor Pressure	5.6×10^{-3} mm HG at 25°C
Specific Gravity	1.06 at 20°C
pH	9
Synonyms	Ordram, R-4572
Chemical Formula	$C_9H_{17}NOS$

In 1992, OPP assessed the occupational exposure of agricultural workers and found application crews (i.e., mixer/loaders and applicators) to be the sub-population at high potential risk. Loaders were identified as having the highest potential exposure among the agricultural workers. Current data do not indicate that molinate poses a dietary risk to humans.

The primary alternative to molinate is propanil (3,4-dichlorophenyl propionamide). Propanil is sold as an emulsifiable concentrate or liquid. Propanil has relatively low mammalian toxicity and is expected to be persistent in the environment. In the rat and rabbit developmental toxicity studies, developmental effects did not occur at doses of 100 mg/kg/day and below. A review of a 1993 one year chronic dog study revealed treatment-related blood, kidney and liver effects at doses up to 85 mg/kg/day. The database for propanil has some remaining data gaps.

5

III. Hazard Identification / Dose-Response Evaluation

HED has reviewed the toxicological database for molinate and determined for the assessment of risk to agricultural workers, the critical toxicological endpoints for regulatory purposes are carcinogenicity and reproductive toxicity. Cancer risks are generally estimated over an individual's lifetime of exposure; reproductive toxicity is the appropriate toxicological endpoint for assessing risks to workers exposed to molinate for less than a lifetime (i.e., short-term and intermediate exposure scenarios). Short-term exposure is defined as a duration of 1 to 7 days for occupational exposures. Intermediate exposure is defined as 1 week to several months for occupational exposures. Exposure covering a substantial portion of a lifetime for occupational, residential or dietary exposure is considered long term. Toxicological endpoints which are applicable to exposure of these durations were evaluated and discussed for appropriateness for risk assessment.

A. Carcinogenicity

The HED Peer Review Committee (PRC) classified molinate as a Group C carcinogen (September 14, 1992) and also concluded that it was appropriate to conduct a quantitative risk assessment using a linearized low-dose linear extrapolation approach to characterize the dose-response of molinate (2). The Committee's recommendations are based on male rat kidney (cortical adenoma and/or carcinoma) tumors found in the 2 year rat chronic study which is discussed below. The PRC determined that the kidney tumors were present at numbers above the mean and range for historical controls. The kidney tumors were considered to be a rare tumor type. There was equivocal evidence that molinate induced an increase in testicular tumors. No increases were noted for liver tumors in the rat study. No increases in tumors were noted in female rats or mice of either sex. The evidence for mutagenicity for molinate was considered weak.

The HED Peer Review Committee recommended that risk quantification be based on the male rat kidney (cortical adenoma and/or carcinoma) tumors (2). Therefore, the unit risk (Q_1^*) was estimated to be 1.1×10^{-1} $(mg/kg/day)^{-1}$, based on the kidney tumors in male rats. This unit risk was used to calculate the upper bound lifetime carcinogenicity risk to molinate.

A two year chronic toxicity/carcinogenicity study was conducted in Crl:CD (SD) BR rats (MRID No. 418151-01) at concentrations of 0, 7, 40, or 300 ppm (0, 0.35, 2, or 15 mg/kg/day) with a 600 ppm (30 mg/kg/day) satellite group. [The 600 ppm dose group was dosed for 1 year.] The 600 ppm satellite dose group had reduced body weight and food consumption, significantly decreased red blood cell (RBC) cholinesterase activity, decreased absolute organ weights (brain, kidney and liver of both sexes and testes in males) and increase in number of animals with severity of nervous, muscle and reproductive tissue lesions. The male rats of the 300 ppm dose group had a statistically significant increase by pair-wise comparison to the control group for combined kidney cortical adenomas and/or carcinomas

6

($p<0.05$). The 300 ppm dose group also had decreased body weight/weight gains, possible decrease in food consumption, possible lenticular opacities in males, and significantly decreased RBC cholinesterase. Other effects noted at 300 ppm were muscle "thinness" in males after 12 months on test, and significant decrease in brain and liver weights in both sexes.

The incidence of reproductive histopathologic observations which included oligospermia, atrophy of the epididymides, degeneration with atrophy of the testes were greater in the 300 ppm group when compared to the control group. Also, the number of rats having thecal/interstitial cell vacuolation/hypertrophy of the ovaries was increased in the 300 ppm dose group. Based on effects on body weight, RBC cholinesterase levels and lesions of the nerve, muscle and reproductive tissue in the 300 ppm group, a NOEL was established at 40 ppm (2 mg/kg/day).

The Agency received two submissions from the registrants concerning the ovarian histopathology for this study. In the original 1991 Agency review, the number of rats reported to have thecal/ interstitial cell vacuolation/hypertrophy of the ovaries (grades 1 & 2) were 0/69, 2/60, 4/60, 15/58 and 8/20 for the 0, 7, 40, or 300 ppm and 600 ppm dose groups, respectively. The 1991 review established a NOEL at 40 ppm based on the above data.

In the 1994 submission the registrant concluded that the reevaluation "reaffirms and strengthens the conclusion made previously" that the NOEL was 40 ppm for the incidence of thecal/interstitial cell vacuolation/hypertrophy. The reevaluation report redefined the grading criteria and all available ovaries were reexamined "blind". The incidence of the ovarian lesions were found to be greater than determined previously for each group. The number of rats reported to have thecal/interstitial cell vacuolation/hypertrophy of the ovaries (grades 1 & 2) were 6/69, 3/60, 10/60, 13/58, and 4/20 for the 0, 7, 40, or 300 ppm and 600 ppm dose groups, respectively. In the control and 40 ppm dose levels an additional 6 females were found with this ovarian lesion. Although from a statistical point of view no difference between the 40 ppm and the control groups was attained, the incidence at the 40 ppm (16.7%) was outside the reported historical control range of 6 - 10.3%. Based on the reevaluation, the original NOEL of 40 ppm was not supported by the available data. In HED's 1994 review, the NOEL for the study was lowered to 7 ppm (0.35 mg/kg/day) and the LOEL equals 40 ppm (2 mg/kg/day).

B. Non-Cancer Effects

1. Reproduction Effects

Clear evidence of reproductive toxicity has been found in laboratory studies in the rat, mouse, and dog following administration of molinate. These studies are discussed below.

A fertility study (Accession No. 245675) was conducted in Sprague-

Dawley male rats in 1980. The investigation consisted of the following four parts designed; I) to determine which phase(s) of spermatogenesis were affected, II) to evaluate effect on fertility after 10 weeks of treatment, III) to evaluate effect on male fertility after 5 weeks of treatment, and IV) to evaluate effect of low dose on male fertility after 5 weeks of treatment and to determine a NOEL. The study design was as follows in Table 1.

Table 1: Rat Fertility Study Design

Part	# males	Time dosed (mg/kg)	Design	Parameters monitored
I	12/grp	5 days 0, 12, 60	mated w/ new ♀ each week for 10 weeks	♀ sac. 9-10 days after cohabitation # corpora lutea # implants # viable fetuses # resorptions
II	20/grp	10 weeks 1, 12	mated w/ 2 ♀♀/wk for 2 weeks after treatment	same as Part I, T_3, T_4, TSH, LH, FSH, testosterone concentration, sperm viability, motility, morphology, concentration, adrenal & testes/epididymides wgt. and histology
III	12/grp	5 weeks 0, 12, 30	mated w/ 2 ♀♀ for 1 week	♀ sacrificed 15 d after cohabitation, otherwise design same as Part II
IV	12/grp	5 weeks 0, 0.2, 4	mated w/ 2 ♀♀ for 1 week	same as in Part III

Part I of this investigation found a significant reductions at 60 mg/kg for the following parameters: number of implants and viable fetuses/litter, the implantation index, number of pregnancies at the third mating, significant increase in preimplantation loss at third mating, and a significant reduction in the number of implants/litter during the 4th mating. Part I suggests the major effect was on the late spermatid stage.

All phases of the study showed a reduction in male fertility. Parts II-IV indicate a good correlation between impaired male fertility and statistically significant alterations in sperm viability, morphology and motility. Significant increases were observed in Part III in T_4 at 30 mg/kg, testosterone at 12 and 30 mg/kg and FSH at 30 mg/kg.

Sperm abnormalities at 5 and 10 weeks of treatment at dose levels of 4 mg/kg (Part IV) and greater included detached heads and tails, heads and tails that were bent at abnormal angles and ruptured sperm membranes at head-midpiece and midpiece-tail junctions. The percentage of viable sperm, motile sperm and abnormal sperm were all decreased at 4 mg/kg. Sperm counts, numbers of implants, preimplantation loss and resorptions were also decreased at 4 mg/kg. Therefore, the NOEL was established at 0.2 mg/kg/day.

A 2-generation reproduction study (MRID No. 413334-02) was conducted in Crl:CD (SD) BRVAF/Plus rats in 1989. Molinate was administered to females at dose levels of 0, 6, 50, or 450 ppm (0, 0.3,

2.5, or 22.5 mg/kg/day) prior to mating with untreated males, and through gestation, lactation, and weaning of their offspring for two generations. Based on decreased body weight, body weight gain, food consumption, and significant changes in absolute brain (P_1 generation) and relative kidney weights (P_0 generation) at 2.5 mg/kg/day, the NOEL for systemic (maternal) toxicity was set at 0.3 mg/kg/day. The findings at 22.5 mg/kg/day included reduced body weight, body weight gain, food consumption, fecundity (uterine implants and litter size) and an increased incidence of vacuolation/hypertrophy of the ovary in both generations. In the high dose of the P_0 generation, 16 animals were found to have vacuolation of the ovary at grades 1 & 2 and 9 animals at grade 3. No animals had a grade higher than 3. For the P_1 generation, 18 animals in the highest dose tested were found to be grades 1 & 2 and 9 animals for grade 3. At the mid dose of the P_0 generation, 2 animals were diagnosed as grades 1 & 2 and 4 animals of the mid dose of the P_1 generation were found to be grades 1 & 2. The reproductive NOEL was set at 0.3 mg/kg/day. The reproductive LOEL of 2.5 mg/kg/day was based on reduced fecundity and increased incidence of ovarian histopathological findings (vacuolation/hypertrophy).

An antifertility study (Accession No. 245675) was conducted in male CD-1 mice in 1980. One hundred males of proven fertility were assigned to 5 dose groups which received either 0, 2, 20, 100, or 200 mg/kg/day, respectively for 7 weeks. Fertility was assessed by mating 1 male to 2 females after 2, 4, and 6 weeks of treatment and again after a 4 week recovery period. The mating index was reportedly not affected by treatment. Pregnancies from mating with the treated males in the 100 mg/kg/day dose group were significantly fewer than the mating with the control males after 2 weeks of dosing, the 200 mg/kg/day dose group after 4 weeks of dosing and the 100 and 200 mg/kg/day dose groups after 6 weeks of dosing. There was a significant downward trend with increasing dose for the fertility indices after 2, 4, and 6 weeks of dosing. No significant trend of this kind was observed after the 4 week recovery period. Significant reductions in the numbers of implants and viable fetuses were noted in the 100 mg/kg/day dose group after 2 weeks of dosing and in the 100 mg/kg/day dose group (implants only at week 4) and 200 mg/kg/day dose groups after 4 and 6 weeks of dosing; the number of resorptions remained the same in these groups. No significant differences were observed after the 4 week recovery period. No histological alterations of the male reproductive tissues were attributable to the test compound. The NOEL was set at 20 mg/kg/day based on the lower number of pregnancies, and significant reductions in numbers of implants and viable fetuses in the 100 mg/kg/day dose group.

A one-year dog feeding study (MRID No. 417811-01) was performed at concentrations of 0, 1, 10, 50, or 100 mg/kg/day. Due to toxicity, the 100 mg/kg/day dose group animals were dosed for only 14 weeks. Body weight and body weight gain were decreased at the two highest dose levels in both sexes, although the females did not attain statistical significance during most of the study. However, the magnitude of the decrease was >10% below the control value at all dose levels in females and at the highest dose levels in males from week 8 until study

termination. There was a dose-related increase in relative kidney weights at all dose levels in females and a dose-related decrease in brain weight in females at 10 mg/kg/day and in both sexes at the 50 mg/kg/day dose level. Adrenal weight and liver weight were increased in both sexes at the 50 mg/kg/day dose level and liver weight was also increased in females at the 10 mg/kg/day dose level. Decreases in sperm ejaculate, reduction in the percentage of motile sperm and suggestive testicular atrophy were observed in the 50 mg/kg/day dose group. At 3 months, the dogs were anemic and dogs at the 50 and 100 mg/kg/day dose level lost the ability to bark or had an attenuated bark. Signs of neurotoxicity included ataxia, splayed hind limbs, vacuolation of the medulla, demyelination of the pons and spinal cords, and tremors. Additionally, eosinophilic bodies were observed in the nervous system. The NOEL for effects other than neurotoxicity was set at 10 mg/kg/day. The LOEL was 50 mg/kg/day based on decreased body weight gain, anemia, and decreased ejaculate volume and percent of motile sperm. Because histological lesions in the sciatic nerve/spinal cord occurred at all dose levels in this study and histopathological lesions in the nerve/muscle tissue were displayed at all dose levels in the rat study (discussed above), a definitive NOEL for these effects was determined by a neurotoxicity study (see section 2 below).

A 3 month inhalation and reproduction - fertility study (Accession No. 241965) was conducted in the rat (10 rats/sex/group) at dose levels of 2, 10, or 50 mg/m^3. [The mean actual exposure was 0, 2.2, 11.1, and 42 mg/m^3.] Microscopic examination revealed testicular degeneration in 8 high dose, 3 mid dose, and 4 low dose and 0 control rats. The lesions were more severe and extensive in the high dose animals. Significant numbers of abnormal sperm were observed in the epididymides of all high dose, one mid dose and two low dose rats. The sperm count was also significantly decreased in six high dose and one low dose male rat. The high dose animals exhibited decreased body weight gain, mucus discharge, rapid breathing, decreased brain cholinesterase, decreased reticulocyte, increased adrenal weight, and decreased pituitary weight. The testes of 3 rats in the HDT were smaller than normal. A NOEL was not established for the inhalation phase of the study.

In the reproductive phase of the 3 month study, the body weight of the high and mid dose males were slightly lower than controls. A significant reduction in testicular weight was noted in the high dose group. At the lowest dose tested (LDT) there were significant dose-related reductions in the mean number of implantations and number of fetuses at the one and three month treatment periods. A reproductive NOEL of < 2 mg/m^3 was set for the reproductive phase of this study based on the testicular degeneration and abnormal spermatozoa noted in the 50 mg/m^3 dose group.

A 5 week oral study was conducted in male Crl:CD (SD) BR rats (MRID No. 431582-02) in 1993 to evaluate the effects of molinate on sperm morphology. Molinate was administered by gavage to male rats (12/group) for 35 days at dose levels of 0, 0.5, 1, 2, 3, 4, or 8 mg/kg/day. The rats displayed clear evidence of an effect on sperm morphology. The classification of abnormal sperm was subdivided into head, midpiece and tail abnormalities. The major head abnormality was

listed as headless sperm (detached heads). All dose levels displayed a greater percentage of headless sperm than the control group, but there was no evidence of a dose-response relationship. There was a dose-related increase in midpiece abnormalities at the 2 mg/kg/day and greater levels. Both the number of rats with these midpeice abnormalities and the number of sperm affected were increased with increasing dose. [This study does not satisfy any guideline requirement, but was intended to focus specifically on sperm morphology.]

HED has also evaluated an assessment of fertility in male workers exposed to molinate at the Stauffer Chemical Company that was conducted in 1984. Men at molinate manufacturing facilities in California (n=62), Alabama (n=77), and Arkansas (n=77) were assayed for sperm measurements and reproductive histories. No effects were reported on either parameter at cumulative dose levels of 0-1 mg, 1-20 mg, or 200-1500 mg. A number of shortcomings prevented meaningful interpretation of this study. For example, the plant with the highest range and highest total exposure contributed the lowest number of total samples and samples for pairing. But HED concludes that the possibility does exist that at higher levels of human exposure, and for older workers molinate may alter fertility in male workers.

The HED Peer Review Committee (PRC) for Developmental and Reproductive Toxicity met on December 12, 1991 to discuss and evaluate the weight-of-the-evidence on molinate, with particular reference to its potential for reproductive and developmental toxicity. The Committee concluded that molinate causes effects on male reproduction in dogs, mice, and rats. The lowest NOEL was 0.2 mg/kg/day, found in the rat, based on effects on sperm measures and fertility. Female reproductive toxicity was observed in the rat, and a NOEL of 0.3 mg/kg/day was established based on the histological changes observed in the ovary at higher dose levels. Because there are no data available under the conditions in which both male and female rats are dosed concurrently, a new 2-generation reproduction toxicity study was requested. This new study should be submitted to the Agency in October, 1996. See Appendix A for a listing of the reproductive effects of molinate in animal studies.

2. Neurotoxicity

Neurological effects are another consistent observation in the hen, mouse, rat, and dog studies on molinate. These effects include decreased brain weight, increased incidence of lesions in the sciatic nerve, spinal cord and brain, and increased incidence of several clinical observations indicative of neurological involvement. Molinate also produced axonal degeneration in well-defined tracts of the brain, spinal cord and peripheral nerve of the hen, but these were not accompanied by leg weakness or incoordination. Since animals at all dose levels in both the 2 year rat and the 1 year dog studies displayed histopathological lesions in the nerve/muscle tissue, a definitive NOEL for these neurological effects could not be determined. The registrant was required in 1991 to submit both an acute and a subchronic neurotoxicity study in the rat, which have been recently reviewed.

11

In the acute neurotoxicity study (MRID No. 431880-01) dose levels of 0, 25, 100, or 350 mg/kg were administered as a single gavage dose to Alpk:APfSD rats. Clinical signs suggestive of general systemic toxicity and/or neurological involvement (decreased body weight/gain and food consumption, decreased motor activity, decreased brain and RBC cholinesterase activity, increased foot splay, and increased time to tail flick) were displayed in all dose levels of the study. Neuropathy target esterase (NTE) activity was not affected by treatment. At termination a dose-related and statistically significant decrease in brain weight and brain length were displayed in high dose males when compared to the control group. Microscopically, minimal neuronal cell necrosis was observed in the central nervous system of 4 of the 6 high dose females and in 1 of 6 control females examined. A NOEL was not determined in the study. The reviewer stated that no definitive conclusion regarding a lack of a neurotoxic effect could be made.

A 90-day subchronic neurotoxicity study (MRID No. 432707-01) was conducted in Alpk:APfSD rats at concentrations of 0, 50, 150, or 450 ppm (0, 5, 14, 41 mg/kg/day). Administration of molinate at doses up to 450 ppm resulted in dose-related decreases in body weight/gain, food consumption and food utilization. There were also several differences observed in various functional observation battery (FOB) parameters, which included increased landing foot splay, decreased time to tail flick and decreased forelimb grip strength. No apparent effect was demonstrated on overall motor activity in males, but the females displayed a dose-related increase in motor activity. There was a dose-related decrease in both RBC and brain cholinesterase activities and a dose-related decrease in NTE activity at all dose levels. Absolute brain weight was statistically significantly decreased in both sexes at the high dose level. Microscopically, nerve fiber degeneration in the sciatic nerve and the sural nerve was increased in the high dose males as compared to the control group. A NOEL was not established. Decreased brain cholinesterase in females and decreased NTE activity in both sexes were observed at all dose levels. See Appendix B for a listing of the neurological effects of molinate in animal studies.

3. Dose-Response Assessment

Both short and long term toxicity studies indicate that molinate causes numerous male and female reproductive effects. Dose-response data for reproductive effects are available in numerous mammalian species including the rat, dog, and mouse. The available laboratory data indicate the rat to be the most sensitive mammalian species. The limited human data provide some support for the effects seen in the laboratory studies.

Another consistent observation noted in molinate studies are neurological effects. Dose-response data for the neurological effects are available in the hen, mice, rat, and dog studies. Some of the effects noted were decreased brain weight, increased incidence of lesions in the sciatic nerve, spinal cord and brain.

HED evaluated the toxicological database for molinate using the weight-of-the-evidence approach to select a NOEL for assessing the non-

cancer risk to agricultural workers using molinate. HED focused on evaluating toxicity studies of a short duration because workers mixing/loading and applying molinate are only exposed for approximately 6-12 weeks a year. HED determined that a NOEL of 0.2 mg/kg/day was appropriate for assessing short term, intermediate and long term occupational exposure to molinate. The NOEL of 0.2 mg/kg/day was based on male reproduction effects (sperm measure and fertility) from the male fertility study in the rat. In addition, female reproductive toxicity was observed in the rat and a NOEL of 0.3 mg/kg/day was established based on histological changes in the ovary observed at higher dose levels.

IV. Exposure Assessment

A. Granular Exposure Data

The Occupational and Residential Exposure Branch (OREB) has provided daily exposure estimates for individuals loading granular molinate (3). Two granular molinate exposure studies were reviewed by OREB and they were: 1) Ordram: Biological Monitoring of Persons Exposed to Molinate during Loading and Application (CA - 1992), and 2) Ordram: Biological Monitoring of Persons Exposed to Molinate during Loading and Application (CA - 1993). These studies were originally submitted to the California Department of Pesticide Regulation (CDPR) and were not intended to fulfill USEPA guidelines. No aerial applicator exposure data were reported in either study. The studies estimated the absorbed daily dose for workers loading Ordram 10G and evaluated the effect of personal protective equipment (PPE) and engineering controls required under the 1992 and 1993 California permit conditions.

Both studies monitored individuals who either directly loaded bulk bags (1280-1500 lbs.) of granular molinate into the airplane hopper or who trans-loaded (a 2 step process) granular molinate in a truck hopper by using 50 lb bags which were then emptied into an airplane hopper. Drivers were also monitored during the loading procedure. [Drivers were the individuals driving the vehicles carrying the bulk bags of molinate.] OREB recommended that the exposure values obtained from the 1993 study be used for the current risk assessment. The 1993 study assessed molinate exposure by biological monitoring (urine sampling).

The 1993 study was performed in the rice-growing area of the Sacramento Valley, CA during May and June. The study estimated potential human exposure to granular molinate (Ordram 10G) during loading. Also, the study evaluated the effects of PPE and engineering controls as required under the 1993 California permit. The permit required PPE which consisted of a full face respirator, protective gloves, foot coverings, boots, either Tyvek® or carbon impregnated coveralls. The carbon impregnated coveralls were worn under normal work clothing. [Note this is the same clothing worn during Desert Storm.] Four commercial aerial co-operators were used in the study, but no exposure results were reported for them. A total of 44 subjects

were monitored and these were classified in the following categories:

ten loaders direct-loading wearing Tyvek® suits
nine loaders direct-loading wearing carbon impregnated suits
nine loaders both direct and trans-loading wearing Tyvek® suits
six loaders both direct and trans-loading wearing carbon impregnated suits
five drivers wearing no protective suits
five drivers wearing carbon suits

The trial period for each subject was 4 days, a baseline day followed by 3 days of exposure. Ideally, no exposure would have occurred on the baseline day, but due to commercial practices of aerial applicators this was not always possible. When no molinate was loaded on the intended Day 1, it became the new baseline day and the trial was extended for one day.

Urine samples were collected from all 44 subjects over the entire monitoring period of each trial. Collection started on the baseline morning and finished with the first void in the morning after the monitoring period was completed. The urine samples were analyzed for the major molinate metabolite, 4-hydroxy molinate. An average of 44% of the molinate eliminated in urine was the metabolite, 4-hydroxy molinate. Control and fortified urine samples were prepared at a field laboratory. The results of the urine sampling are summarized in Table 2.

Table 2: Urine samples from the 1993 CA Monitoring Study (Granular)

Job Class	Protective Suit	Loading Method	No. of Subjects	Geometric Mean Dose (µg/kg/d)
Loader	Tyvek	Direct	10	5.65
	Carbon	Direct	9	2.18
	Tyvek	Both	9	4.70
	Carbon	Both	6	9.50
Driver	None	None	5	0.70
	Carbon	None	5	0.49

The above data confirm that the carbon impregnated coveralls will substantially reduce the absorbed dose when compared to Tyvek® suits. This comparison is true except where mixer/loaders direct and trans loaded molinate. Values for the carbon impregnated coveralls were nearly twice that for workers wearing Tyvek®. During this trial the workers alternated the use of PPE. But under actual work conditions this practice probably does not occur. Table 3 presents the daily dose, the average annual daily dose, and the lifetime average daily dose of loaders utilizing different PPE. In California a bag limit of 190 bags/person has been proposed for the entire application season using Ordram 10-G®. The bag limit is a product of 27 use days and

14

7 bags on average per day. Also, there are physical limits on how many acres a single plane can cover (1000 acres for a turbo driven plane and 400 acres for a non-turbo). Using these acreages were the equivalent to 42 and 17 bags per plane per day, respectively.

Table 3: Molinate - GRANULAR exposure (µg/kg/d)

Job Class	Protective Suit	Daily Dose (geo. mean)	Avg. Annual Daily Dose[1]	Lifetime Avg. Daily Dose[2]
Loader (Direct)	Tyvek	5.65	0.418	0.209
	Carbon	2.18	0.161	0.081
Loader (Direct & Trans)	Tyvek	4.70	0.348	0.174
	Carbon	9.50	0.703	0.352
Driver	None	0.70	0.052	0.026
	Carbon	0.49	0.036	0.018

[1] = Assumed 27 use days and 7 bags per day.
[2] = Assumed 35 working years over a 70 year lifetime.

B. Emulsifiable Concentrate Exposure Data

The Occupational and Residential Exposure Branch (OREB) also provided daily exposure estimates for individuals mixing/loading an emulsifiable concentrate (EC) using the Pesticide Handlers Exposure Database (PHED) (4,5). The assessment focuses on ECs applied aerially and by ground boom equipment in the southern regions of the US (i.e., Arkansas, Louisiana, Mississippi, Missouri, and Texas). The Biological and Economic Analysis Division (BEAD) supplied the EC usage information for the southern regions of the US (6 and see Table 4). The EC formulations of molinate are not applied in California aerially, according to the 1992 California Environmental Protection Department's Molinate Risk Assessment for the 1992 use season (7).

Table 4: 1990-1992 Ordram® 8-E Usage on Rice

STATE (1990-92)	ACRES (000)	MULTIPLE ACRES TREATED		POUNDS A.I.	
		(000)	% OF SITE	(000)	% OF TOTAL
ARKANSAS	1,380	5 - 30	<1 - 2	15 - 45	12 - 19
CALIFORNIA	390	15 - 20	4 - 5	25 - 55	15 - 31
LOUISIANA	611	5 - 20	<1 - 3	15 - 45	12 - 19
MISSISSIPPI	278	0	0	0	0
MISSOURI	100	0	0	0	0
TEXAS	346	10 - 75	3 - 22	25 - 255	31 - 61

Source: Resources for the Future. 1991. Herbicide Usage in the United States. United States Department of Agriculture. April, 1991. Rice Situation and Outlook Report.

The following parameters were used in estimating worker exposure. The average farm size was 202 acres with a maximum application rate of 4 lbs ai/acre or a typical application rate of 3 lbs ai/acre. For ground application, HED assumed that 87 acres could be treated in 1 day with a boom width of 28 feet at 4 mph. For aerial application, HED assumed that 416 acres could be treated in 1 day with a spray boom of 35 feet at 100 mph by a commercial aerial applicator. Both scenarios assumed the pesticide would be applied for 8 hours each day. HED assumed that workers weigh 70 kg and wear long pants, long sleeve shirts and gloves. Additional protection factors were employed for the mixer/loader closed pour system exposure estimate because only total deposition data were available. The adjustments for PPE reduction were: hand exposure by 90% for waterproof gloves and dermal exposure by 50% for the addition of coveralls over long pants and long sleeved shirt. OREB assessed several different applicator scenarios: ground boom with open and enclosed cab, aerial applicator, mixer/loader with open and closed pouring systems. The ground boom with open and enclosed cab scenarios were assumed to be private growers. OREB has indicated that even though the PHED exposure data were adjusted by the standard PPE, they believe the protection factors may not reduce exposure due to the high volatility of molinate. Tables 5 and 6 list the worker exposure estimates for the emulsifiable concentrate formulations of molinate.

Table 5: Estimated Worker Exposure during Application of Emulsifiable Concentrate Formulations of Molinate at the Typical Rate

TYPICAL RATE (3 lb ai/acre)					
	Inhalation (mg/kg/d)	Dermal (mg/kg/d)	Total Daily Dose[1] (mg/kg/d)	Total Annual Dose[2] (mg/kg/yr)	Lifetime Avg. Daily Dose[3]
Mixer/loader: open pour	0.002	0.09	0.0416	0.0965	1.32×10^{-4}
Mixer/loader: closed pour	0.0003	0.072	0.032	0.074	1.02×10^{-4}
Ground boom: applicator open cab	0.002	0.067	0.0315	0.0730	1.0×10^{-4}
Ground boom: applicator enclosed cab	0.0002	0.019	0.0086	0.0199	2.73×10^{-5}
AERIAL APPLICATION (1 day)					
Aerial Applicator	0.0011	0.10	0.0451	0.0451	6.18×10^{-5}
Mixer/loader: open pour	0.008	0.435	0.1994	0.1994	2.73×10^{-4}
Mixer/loader: closed pour	0.0015	0.343	0.1524	0.1524	2.1×10^{-4}

[1] - Total daily dose = inhalation + (dermal x % dermal absorption)

[2] - Total annual dose = total daily dose X # application days per year for a 202 acre farm (2.32 days for mixer/loaders and ground boom applicators). Aerial mixer/loaders and applicators treat 416 acres in 1 day.

[3] - $\text{LADD} = \frac{\text{total exposure (mg/kg/yr)}}{\text{365 days/yr}} \times \frac{35}{70}$

Percent dermal absorption = 44%

Table 6: Estimated Worker Exposure during Application of Emulsifiable Concentrate Formulations of Molinate at the Maximum Rate

MAXIMUM RATE (4 lb ai/acre)					
	Inhalation (mg/kg/d)	Dermal (mg/kg/d)	Total Daily Dose[1] (mg/kg/d)	Total Annual Dose[2] (mg/kg/yr)	Lifetime Avg. Daily Dose[3]
Mixer/loader: open pour	0.022	0.12	0.075	0.174	2.38×10^{-4}
Mixer/loader: closed pour	0.0004	0.096	0.043	0.0989	1.36×10^{-4}
Ground boom: applicator open cab	0.003	0.089	0.0422	0.0978	1.34×10^{-4}
Ground boom: applicator enclosed cab	0.0002	0.025	0.0112	0.026	3.56×10^{-5}
AERIAL APPLICATION (1 day)					
Aerial Applicator	0.0014	0.13	0.0586	0.0586	8.03×10^{-5}
Mixer/loader: open pour	0.011	0.58	0.2662	0.2662	3.65×10^{-4}
Mixer/loader: closed pour	0.002	0.46	0.2044	0.2044	2.80×10^{-4}

[1] - Total daily dose = inhalation + (dermal x % dermal absorption)

[2] - Total annual dose = total daily dose X # application days per year for a 202 acre farm ((2.32 days for mixer/loaders and ground boom applicators). Aerial mixer/loaders and applicators treat 416 acres in 1 day.

[3] - $\text{LADD} = \frac{\text{total exposure (mg/kg/yr)}}{365 \text{ days/yr}} \times \frac{35}{70}$

Percent dermal absorption = 44%

HED recommends that the current protective clothing restrictions imposed by California be adopted for all labels; due to the toxicological effects at very low dose levels and the lack of suitable alternatives. These restrictions include full-face respirator, carbon-impregnated suit under the normal work clothes (long sleeve shirt and long pants), chemical resistant gloves, and footwear plus the addition of a knee-length chemical resistant apron for EC use be adopted on all Section 3 labels.

V. Risk Characterization

Cancer risks and margins of exposure for occupational workers exposed to molinate were estimated using oral toxicity data. The primary routes of exposure for workers are via the dermal and inhalation route; although the inhalation route is considered negligible. The carcinogenicity and reproductive toxicity data are based on oral feeding studies making it necessary to adjust for dermal absorption. Based on the data submitted to the Agency, HED has determined that 44% is the best estimate for dermal absorption (8). HED assumed that workers were exposed to molinate for 10 hours before washing any remaining material from the skin. Ten hours corresponds to a typical work day and would result in 44% potentially being absorbed over this time frame.

The principal durations of exposure for molinate would be short-term and seasonal. Even though the typical use season is limited to 6 weeks, the data suggest both short and long term toxicological effects. Therefore, HED characterized both short and long term risks.

A. Cancer Risk Estimates

HED estimated the occupational cancer risk using a low dose linear extrapolation model (Q_1^*). Table 7 presents the excess individual lifetime cancer risks associated with each job function and PPE for granular molinate as it was used in California in 1993. Table 8 presents the excess individual lifetime cancer risks associated with each job function and engineering controls for the emulsifiable concentrate (EC) formulations of molinate as it is used in the southern regions of the US. The cancer risks were calculated using the following equation:

$$\text{Extra cancer risk} = Q_1^* \times \text{LADD}$$

where $Q_1^* = 1.1 \times 10^{-1}\ (\text{mg/kg/day})^{-1}$

$$\text{and LADD} = \frac{\text{exposure (mg/kg/yr)}}{365\ \text{days/yr}} \times \frac{35}{70}$$

The excess individual lifetime cancer risk estimates range from 10^{-6} to 10^{-5} for occupational uses of granular molinate (see Table 7). These cancer risk estimates reflect the typical application rates of granular molinate used in California during 1993. The excess individual lifetime cancer risk estimates range from 10^{-6} to 10^{-5} for occupational uses of the EC formulations of molinate as it is used in the southern regions of the US (see Table 8).

B. Margins of Exposure

HED determined that a NOEL of 0.2 mg/kg/day was appropriate for assessing short term, intermediate and long term occupational exposure to molinate. The margins of exposure (MOE) for occupational uses of molinate are presented in Tables 7 and 8. MOEs were calculated using the following equation:

$$MOE = \frac{\text{NOEL (mg/kg/day)}}{\text{Total Daily Dose (mg/kg/day)}}$$

OPP has traditionally required a margin of exposure greater than 100 to provide an adequate level of protection when the NOEL is based on animal data. A factor of 10 is included to protect sensitive individuals in the human population. An additional factor of 10 is included to account for extrapolation from laboratory animal data.

Margins of exposure for loaders of granular molinate are greater than or equal to 92 if the loader uses the carbon impregnated coveralls while direct loading the bulk bags of molinate into airplane hoppers. The use of Tyvek® suits or carbon impregnated coveralls while trans and direct loading molinate result in MOEs of less than 100. The granular molinate MOEs are based on exposure that is representative of loading molinate only. The CA granular study did not include aerial applicator exposure data. Margins of exposure for agricultural workers using the EC formulations of molinate are all less than 100 for all of the job functions and engineering controls evaluated. OREB is currently examining additional measures to mitigate possible exposure to ECs.

Table 7: Occupational Use
Cancer Risk and Margins of Exposure Estimates for GRANULAR Molinate

Job Class	Protective Suit	Daily Dose (geo. mean µg/kg/day)	Lifetime Avg. Daily Dose (µg/kg/d)	Cancer Risk Estimates	Margins of Exposure
Loader (Direct)	Tyvek	5.65	0.209	2.3×10^{-5}	35
	Carbon	2.18	0.081	8.9×10^{-6}	92
Loader (Direct & Trans)	Tyvek	4.70	0.174	1.9×10^{-5}	43
	Carbon	9.50	0.352	3.9×10^{-5}	21
Driver	None	0.70	0.026	2.9×10^{-6}	286
	Carbon	0.49	0.018	2.0×10^{-6}	408

Table 8: Occupational Use Cancer Risk and
Margins of Exposure Estimates for EC Formulations of Molinate

	TYPICAL RATE				MAXIMUM RATE			
	Total Daily Dose (mg/kg/yr)	Lifetime Avg. Daily Dose (mg/kg/d)	Cancer Risk Estimates	Margins of Exposure	Total Daily Dose (mg/kg/yr)	Lifetime Avg. Daily Dose (mg/kg/d)	Cancer Risk Estimates	Margins of Exposure
Mixer/loader: open pour	0.0416	1.32×10^{-4}	1.45×10^{-5}	5	0.075	2.38×10^{-4}	2.6×10^{-5}	3
Mixer/loader: closed pour	0.032	1.02×10^{-4}	1.12×10^{-5}	6	0.043	1.36×10^{-4}	1.5×10^{-5}	5
Ground boom: applicator open cab	0.0315	1.0×10^{-4}	1.1×10^{-5}	6	0.0422	1.34×10^{-4}	1.47×10^{-5}	5
Ground boom: applicator enclosed cab	0.0086	2.73×10^{-5}	3.0×10^{-6}	23	0.0112	3.56×10^{-5}	3.92×10^{-6}	18
AERIAL APPLICATION (1 day)								
Aerial	0.0451	6.18×10^{-5}	6.8×10^{-6}	4	0.0586	8.03×10^{-5}	8.83×10^{-6}	3
Mixer/loader: open pour	0.1994	2.73×10^{-4}	3.0×10^{-5}	1	0.2662	3.65×10^{-4}	4.0×10^{-5}	0.8
Mixer/loader: closed pour	0.1524	2.1×10^{-4}	2.31×10^{-5}	1	0.2044	2.8×10^{-4}	3.1×10^{-5}	1

C. Strengths and Uncertainties of the Risk Assessment

HED made standard assumptions in estimating occupational risks including interspecies extrapolation and prorating exposure over an individual's working lifetime (i.e., LADD). HED used both biological monitoring data and the PHED. Dermal exposure estimates from the PHED were adjusted for dermal absorption because carcinogenicity and

21

reproductive toxicity data were derived from oral feeding studies and the primary route of worker exposure to molinate is dermal contact. The inhalation exposure estimates from the PHED data were considered negligible in comparison to dermal exposure. Since different sources of exposure data were used in this risk assessment, their strengths and uncertainties will be explained separately below. Also, one must keep in mind that nearly 85% of the molinate sold is the granular formulation, aerially applied post-emergent and the remaining 15% as an emulsifiable concentrate applied pre-emergent by ground equipment, or aerially applied post-emergent.

1. Granular Molinate Exposure Data

The occupational exposure assessment is limited to the 1993 permit conditions used for the state of California. The strict use conditions applicable to California such as bag limits, techniques used for trans- and direct loading into airplane hoppers, plus the differences in PPE requirements may underestimate the potential molinate exposure that might occur in the southern regions of the US. The exposure study did illustrate that with the new type of PPE (carbon-impregnated coveralls) exposure is reduced significantly. Since the California exposure study monitored granular molinate, the data should reflect actual worker exposure, but California's application rates are somewhat lower than the rates used in the southern regions of the US. The MOEs would be smaller with higher application rates.

2. Emulsifiable Concentrate Exposure Data

The emulsifiable concentrate (EC) exposure data were obtained from OREB's Pesticide Handlers Exposure Database (PHED). Adjustments were made to the dermal exposure data for dermal absorption (44%). The MOEs for applicators of the EC formulations are probably an underestimate of exposure. A weakness in using surrogate data (PHED) for molinate is that other compounds might not be as volatile as molinate (30-40% volatility); which could lead to an underestimation of the risk to workers using EC formulations of molinate. An uncertainity concerning the aerial mixer/loaders and applicators is that HED assumed that molinate would be aerially applied for 1 day. Therefore, the risk displayed would be an underestimation of exposure. No information was available on the number of possible application days for a commerical applicator spraying rice. An additional uncertainty is that the agricultural practices used during the collection of the PHED data might not adequately reflect those used for a water-grown commodity such as rice.

D. Summary

HED has provided an assessment of occupational risks associated with the use and application of different formulations of molinate. This risk assessment provides cancer risk and margin of exposure estimates for agricultural use of molinate (Tables 7 and 8). Cancer risks were estimated using a low dose extrapolation model (Q_1^*).

22

Margins of exposure were calculated by comparing daily exposure estimates against a short-term NOEL of 0.2 mg/kg/day. The excess individual lifetime cancer risk estimates range from 10^{-6} to 10^{-5} for occupational uses of granular molinate. Margins of exposure for loaders of granular molinate are greater to or equal 92 if the loader uses the carbon impregnated coveralls while direct loading the bulk bags of molinate into airplane hoppers. The use of Tyvek® suits or carbon impregnated coveralls while trans and direct loading molinate result in MOEs of less than 100. The excess individual lifetime cancer risk estimates range from 10^{-6} to 10^{-5} for occupational uses of the EC formulations of molinate as it is used in the southern regions of the US. Margins of exposure for agricultural workers using the EC formulations of molinate are all less than 100 for all job functions and engineering controls evaluated.

VI. References

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(6) E. Maurer. Molinate Usage by State and Formulation. Memorandum to P. Parsons (November 14, 1994).

(7) L. Nelson. DRAFT Molinate Risk Assessment for the 1992 Use Season. California Environmental Protection Department (January 24, 1992).

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Appendix A:
Summary of Reproductive Findings for Molinate

STUDY	NOEL	LOEL	EFFECTS
Acute Inhalation LC50 rat	0.28 mg/L	0.83 mg/L	↑ body weight & testicular damage
Acute Inhalation LC50 mice	1.1 mg/L	1.8 mg/L	↑ body weight & testicular alteration
13 week feeding rat	8 mg/kg	16 mg/kg	ovarian vacuolation
3 month Inhalation rat	< 2 mg/m^3 (LDT)	2 mg/m^3 (LDT)	testicular degeneration and abnormal sperm
1 year feeding dog	10 mg/kg/day	50 mg/kg/day	↓ sperm ejaculate, ↓ motile sperm & suggestive testicular atrophy
2 year feeding rat	7 ppm (0.35 mg/kg/day)	40 ppm (2 mg/kg/day)	effects on organ weights and ↑ lesions of nerve, muscle and reproductive tissue (ovarian thecal/interstitial cell vacuolation)
18 month oncogenicity mouse	10 ppm (1.5 mg/kg/day)	100 ppm (15 mg/kg/day)	testicular degeneration
Developmental rat	2.2 mg/kg/day MAT = 35 mg/kg/day	35 mg/kg/day MAT = 140 mg/kg/day	↑ post implantation loss, runting, S-T (head) and skeletal variants, and ↓ fetal body weight, ↑ salivation/dehydration, ↓ RBC ChE
Developmental rabbit	20 mg/kg/day	200 mg/kg/day	↓ ossification of sternebrae & extra paired ribs, percent of live fetuses
3-generation rat	0.63 mg/kg/day (HDT)	-	slight ↓ litter size & no. alive day 5 in F_{1b} at 0.63 mg/kg/day
2-generation rat	6 ppm (0.3 mg/kg/day)	50 ppm (2.5 mg/kg/day)	↓ fecundity & ovarian vacuolation/hypertrophy
Fertility mouse	20 mg/kg/day	100 mg/kg/day	↓ no. of implants & pregnancies
Fertility rat	0.2 mg/kg/day	4 mg/kg/day	↓ fertility, # viable fetuses, % viable sperm, % motile sperm, sperm count, # implants/♀, and ↑ % abnormal sperm, slight ↑ in preimplantation loss
Fertility (13 week) Inhalation rat	< 2 mg/m^3 (LDT)	2 mg/m^3	some testicular changes, ↑ in plasma & erythrocyte values
Fertility rabbit	40 mg/kg/day♦	80 mg/kg/day	↑ preimplantation loss, sperm abnormalities, ↓ # fetuses
Spermatogenesis monkey	> 50 mg/kg/day (HDT)	-	no treatment effects on sperm motility, morphology, volume concentration, or total count

♦ = Registrant contends that there are no effects in the rabbit.

24

Appendix B:
Summary of Neurological Findings for Molinate

STUDY	NOEL	LOEL	EFFECTS
Acute Delayed Neurotoxicity hen	0.2 mg/kg♦	0.63 mg/kg	axonal degeneration in well-defined tracts of brain & spinal cord & peripheral nerves, unsteady gait
10-day feeding rat?	75 mg/kg/day	150 mg/kg/day	splayed gait, subdued behavior, hunched posture
Acute neurotoxicity rat	?	25 mg/kg/day (LDT)	decreased body weight/gain and food consumption, decreased motor activity, decreased brain and RBC cholinesterase activity, increased foot splay, and increased time to tail flick in all dose levels. Neuropathy target esterase (NTE) activity was not affected by treatment. Dose-related and statistically significant decrease in brain weight and brain length in high dose males when compared to the control group.
90-day subchronic neurotoxicity rat	?	5 mg/kg/day (LDT)	dose-related ↓ in body weight/gain, food consumption and food utilization. FOB differences - increased landing foot splay, ↑ time to tail flick and ↓ forelimb grip strength. No apparent effect was demonstrated on overall motor activity in males, but the females displayed a dose-related increase in motor activity. Dose-related ↓ in both RBC and brain cholinesterase activities and a dose-related ↓ in NTE activity at all dose levels. Absolute brain weight was statistically significantly dec. in both sexes at the high dose level. Microscopically, nerve fiber degeneration in the sciatic nerve and the sural nerve was increased in the high dose males as compared to the control group.
3-month Inhalation rat	10 mg/m^3	50 mg/m^3	↑ aggressive behavior, closed eyes
2-yr feeding rat	?	7 ppm (0.35 mg/kg/day) (LDT)	↑ degeneration/demyelination (sciatic nerve), ↑ atrophy/reserve cell hyperplasia-skeletal muscle, [ataxia, abducted hindlimbs, atrophied hindlimb/thigh/sacral region, ↓ brain weight (absolute & relative), spinal cord degeneration/eosinophilic bodies observed at 300 ppm
1 yr feeding dog	?	1 mg/kg/day (LDT)	↑ demyelination os sciatic nerve & spinal cord (lumber & thoracic), ataxia, splayed hind limbs, vacuolation of medulla, demyelination of pons and spinal cord, tremors
18-month Onco. mouse	100 ppm (15 mg/kg/day)	1000 ppm (150 mg/kg/day)	hindlimb muscle weakness, abducted hindlimbs, ataxia, splayed hindlimbs, ↓ relative & absolute brain weight, demyelination & Schwann cell hyperplasia- sciatic nerve, eosinophilic bodies in spinal cord & brain
developmental rat	135 mg/kg/day	200 mg/kg/day	abnormal gait (high-stepping & splayed)

♦ = additional data required to define definitive NOEL