UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, O.C. 20460

Office of Prevention, Pesticides
and
Toxic Substances

January 9, 2001

MEMORANDUM

SUBJECT: MOLINATE - Revised Human Health Risk Assessment

DP Barcode: D271384
PC Code: 041402
Case: 818845
Submission: S589909

FROM: Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer
Reregistration Branch I, Health Effects Division (7509C)

TO: Robert McNally/Wilhelmena Livingston
Special Review and Reregistration Division (7508C)

THRU: Whang Phang, Ph.D., Branch Senior Scientist
Health Effects Division (7509C)

Action Requested: Revise Human Health Risk Assessment

Recommendations: Attached is the Revised Human Health Risk Assessment for Molinate. The risk assessment of June 15, 2000, has been revised as follows:

1) The cancer risk assessment sections have been deleted due to a reassessment by the HED Cancer Assessment Review Committee (CARC). The basis for this reassessment was the submission of new data and a reanalysis of the kidney tumor data. The CARC classified the data for molinate into the category "suggestive evidence for carcinogenicity but not sufficient to assess human carcinogenic potential" based on the limited evidence of kidney tumors in rats. The Committee further concluded that quantification of carcinogenic risk is not required.[1]

[1]Molinate - Report of the Cancer Risk Assessment Review Committee dated December 14, 2000.

2) The drinking water exposure and the aggregrate risk assessment sections have been revised based on revised ground and surface water exposure values from EFED.[2]

3) Although not revised, the classification of molinate as a delayed neurotoxicant in the hen, as appears in the June 15, 2000 risk assessment, was explored with Dr. Karl Jensen, a neurotoxicologist at EPA's National Health and Environmental Effects Research Laboratory. He evaluated the hen study (MRIDs 00133562 and 43136601) and concluded that molinate produces delayed neurotoxicity in the hen.

[2] Revised Water Memorandum for Molinate Incorporating Parent Molinate and Degradates of Concern Based on 10-31-00 HED MARC Meeting (DP Barcode D271004) dated December 7, 2000

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HUMAN HEALTH RISK ASSESSMENT

FOR

MOLINATE

U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)

Virginia A. Dobozy, V.M.D., M.P.H., Risk Assessor
December 19, 2000

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APPENDIX

1.0 EXECUTIVE SUMMARY

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has evaluated the molinate data base and conducted a human health risk assessment for the reregistration of the chemical. Molinate is a list B reregistration chemical. It was the subject of a Phase 4 Review dated February 21, 1991. Risk reduction mitigation occurred in 1996 because of concern about the health risks of workers exposed to molinate. Beginning with the 1997 growing season, the use of activated carbon impregnated body suits was required. In addition, the amount of emulsifiable concentrate used by workers in a single growing season was restricted.

Molinate (s-ethyl hexahydro-1H-azepine-1-carbothiate) is a herbicide registered for use primarily for the control of watergrass in rice. Rice is grown in California and the south central/south eastern states of Arkansas, Louisiana, Missouri, Texas and Tennessee. There are four active end-use products (EPs) with food/feed uses registered to Zeneca Ag Products under the trade names Ordram® or Arrosolo® (combination of molinate and propanil). Emulsifiable concentrate (33.1%-90.9% a.i.) and granular (15% a.i.) formulations may be applied to rice preemergence and/or postemergence using ground and aerial equipment. Another registrant, RICECO, recently registered a molinate technical and two end-use products, a granular (15% a.i.) and an emulsifiable concentrate (combination of molinate and propanil) formulation.

Tolerances are presently established (40 CFR §180.228) for residues of molinate *per se* in/on rice and rice straw each at 0.1 ppm. However, HED is recommending that the tolerances for residues in/on rice grain be increased to 0.75 ppm. The tolerances for residues in/on rice straw should be increased to 7.0 ppm. Tolerances for hulls and bran processed from molinate-treated rice grain should be 3.0 and 2.0 ppm, respectively. HED is also recommending that residues to be regulated in plants include molinate and its metabolites 4-hydroxy molinate and molinate acid. Residues of molinate and its metabolites of concern are not expected to transfer to edible livestock commodities at the maximum dietary burden based on current uses.

Molinate is a thiocarbamate. In general, thiocarbamates are less potent cholinesterase (ChE) inhibitors than other carbamates. Multiple studies in various species indicate that molinate produces ChE inhibition (plasma, red blood cell and brain) via multiple routes of exposure. Molinate also inhibits neurotoxic esterase (NTE) and is positive for delayed neurotoxicity in the hen. The findings in multiple studies demonstrate that molinate is a neurotoxin after single and multiple doses *via* the oral, dermal and inhalation routes of exposure and across species (rat, dog, mouse). In neurotoxicity studies of varying durations, clinical signs indicative of nervous system effects, ChE and NTE inhibition and neuropathology were observed. In the subchronic neurotoxicity study, the Lowest Observed Adverse Effect Level (LOAEL) was 4.0 mg/kg/day in males and 4.5 mg/kg/day in females based on decreased red blood cell and brain cholinesterase and neurotoxic esterase in both sexes; a No Observed Adverse Effect Level (NOAEL) was not established.

In the developmental neurotoxicity study, pups born to molinate-treated dams exhibited

treatment-related functional and anatomical nervous system effects. Evidence of reproductive toxicity was found in studies in rats, mice, rabbits and dogs; however, the male rat appeared to be the most sensitive species/sex. A wide range of male reproductive parameters have been altered adversely in the studies with both oral and inhalation exposures, including testes weight, sperm number and morphology, fertility and testicular histopathology. Reproduction studies in both rats and mice demonstrated treatment-related effects on fertility and gestation. In a special five-week fertility study, a dose of 0.5 mg/kg/day in males produced adverse effects on sperm parameters; a NOAEL was not established. There was also evidence that molinate causes increased sensitivity to offspring following prenatal exposure in rats.

Special mechanistic studies have been conducted to demonstrate a proposed mechanism of toxicity for the male reproductive effects. The registrant position's is that the reproductive effects of molinate require the production of molinate sulfoxide and the dependence of the enzyme cholesterol ester hydrolase for steroid sex hormone production. The registrant also concludes this mechanism is specific to rodents and not relevant to humans. The currently available mechanistic studies have been reviewed by the HED Mechanism of Toxicity Assessment Review Committee, which concluded that the data are not adequate to demonstrate the proposed mechanism. Some of the reasons for this conclusion include the following: lack of concordance between dose levels where effects on testosterone and precursor hormone levels are observed and dose levels where fertility/sperm effects are observed; lack of data to show that sulfoxidation is occurring at the dose levels where fertility/sperm effects are observed in the rat; and lack of data demonstrating an inhibition of n-CEH *in vivo* at dose levels where fertility/sperm effects occur.

In the rat combined chronic toxicity/carcinogenicity study, there was an increase in kidney tumors in males at the high dose level. Molinate was reviewed by the HED Cancer Assessment Review Committee (CARC) on November 1, 2000, and based on the kidney tumors, was classified as *Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential* using the 1999 draft Guidelines for Carcinogen Risk Assessment. Dose-response assessments are not recommended for chemicals in this classification.

Molinate was negative in a *Salmonella tymphimurium* assay and for aberrations in cultured human lymphocytes. Because suggestive increases were found for mutations, aberrations, and sister chromatid exchange [SCE] in mouse lymphoma cells, and there was conflicting data in two mouse micronucleus assays, a dominant lethal test was requested. Subsequently, molinate was shown to be negative in this assay.

The metabolism data indicate that molinate is well absorbed and extensively metabolized following both oral and intravenous exposure and is rapidly excreted, mainly in the urine. Data indicate that the metabolism of molinate in mammals is primarily *via* three routes: carbon oxidation, sulfur oxidation, and thiocarbamate cleavage. The data also suggest that carbon oxidation predominates at low doses and sulfur oxidation at high doses of molinate in both rodents and humans. It is not known at what dose level the predominate pathway becomes saturated. The only toxicology studies with any metabolites are mechanistic studies conducted to

demonstrate the mechanism of molinate toxicity on the male reproductive system. Based on a study in the rat with radiolabeled molinate, dermal absorption was determined to be 40%.

The 10x FQPA Safety Factor has been retained based on the following: increased fetal susceptibility observed in the prenatal developmental study in rats; increased fetal susceptibility in the developmental neurotoxicity study in rats; reproductive effects in mice and rats; and uncertainty associated with the molinate surface water exposure in some rice-growing areas.

The toxicology profile for molinate is presented in Table 1 of the Appendix.

The results of the acute and chronic dietary assessments showed that, for all population subgroups (general population, females 13-50, infants <1 year, children 1-6 years and children 7-12 years), risk estimates were below HED's level of concern [<100% of the Population Adjusted Dose (PAD)]. The most highly exposed subgroup was infants (< 1 year) for both assessments consuming 18% of the chronic PAD (cPAD) and 21% of the acute PAD (aPAD) at the 95th percentile of exposure. Even at the 99.9th percentile, the acute risk estimate was approximately 55% of the aPAD.

Exposure to molinate in drinking water is based on monitoring data in rice-growing areas where the chemical is used. Raw water data were used for exposure to ground and surface water for risk assessment purposes. The exposure values were increased by a factor of 1.56 to account for the lack of analyses for molinate metabolites in the monitoring studies.

Aggregate risk assessments using percentage of the PAD calculations were quantitated for dietary exposure to food and water (ground and surface water) for three separate subpopulations (adult males, adult females and children) for acute and chronic exposures. There are no residential uses to be considered in this aggregate assessment. The aggregate risk assessment of acute exposure to food and surface water in children (110% of the aPAD) exceeded HED's level of concern (>100% of aPAD). However, HED thinks that this assessment may overestimate the risk and that refinement of either the food or water exposure may bring the risks into an acceptable range. The anticipated residues in food were based on field trial residues. Monitoring studies closer to the point of consumption or cooking studies would refine exposure.

HED has determined that there is a potential for exposure from handling molinate products during the application process (i.e., mixer/loaders, applicators, flaggers, mixer/loader/applicators) and from entering agricultural areas previously treated with molinate. Occupational postapplication exposures, however, are expected to be minimal because of the nature of the activities associated with rice cultivation (e.g., scouting and water management) and the protective equipment that is commonly used during these activities (e.g., waterproof rubber boots for walking through rice paddies). The exposure and risk for three mixer/loader scenarios were assessed using biomonitoring exposure data. The exposure and risk of another eight scenarios involving mixing/loading, flagging and applying granular and liquid formulations using aerial and ground-based equipment were assessed using PHED data. The short-term and intermediate-

term risks were calculated using the biomonitoring data.

With the PHED data, individual short- and intermediate-term dermal and inhalation risks were calculated and then combined. HED determined that the dermal and inhalation exposures could be combined due to the common endpoints for short-term (neurotoxicity) and intermediate-term (reproductive effects) exposures. Assessing short-term and intermediate-term exposure using biomonitoring data, the risks exceeded the Agency's level of concern for liquid and granular mixer/loaders at the baseline level of personal protective equipment (PPE) and for additional PPE. Assessing short-term dermal risks using PHED data, risks exceeded the Agency's level of concern for all eight scenarios at the baseline level of personal PPE and for additional PPE. With engineering controls, the risks still exceeded the level of concern for five of the scenarios. Short-term inhalation risks using PHED data did not exceed the level of concern for the eight scenarios at the baseline level of PPE. When the short-term dermal and inhalation exposures and risks were combined, the risks exceeded the level of concern for all scenarios at the baseline level and when additional protective clothing/PPE were added. When engineering controls were added, the risks still exceeded the level of concern for pilots applying granular and liquid formulations and for handlers mixing/loading liquids for ground-based application and applying liquids using ground-based equipment.

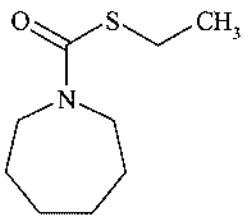
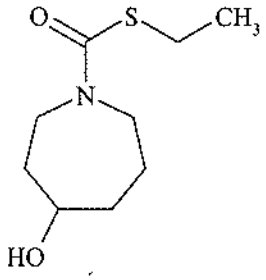
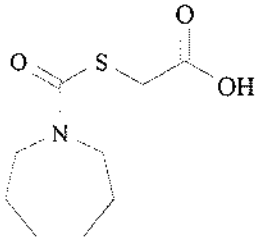
Intermediate-term dermal risks data estimated for eight handler scenarios using PHED data all exceeded the Agency's level of concern at the baseline clothing and additional levels of PPE. With the addition of engineering controls, the risks of six scenarios still exceeded the level of concern. Intermediate-term inhalation MOEs all exceeded the level of concern at the baseline PPE level. The addition of a full face respirator resulted in intermediate-term inhalation risks above the level of concern for all the scenarios. Risks for pilots applying liquids and granulars were only assessed with engineering controls; both exceeded the Agency's level of concern. When intermediate-term dermal and inhalation risks were combined, the risks exceeded the Agency's level of concern for all scenarios at baseline and with added protective clothing/PPE. When engineering controls are added, the risks still exceed the level of concern for pilots applying both granular and liquid formulations and for handlers applying both granular and liquid formulations using ground-based equipment and for handlers mixing/loading liquids for ground-based application.

The toxicology data base is adequate, except the 21-day dermal toxicity study and the acute neurotoxicity study were both unacceptable and not upgradeable. Repeating these studies would complete the data requirements; however, the results may not alter the endpoints and doses selected for risk assessment. Outstanding residue chemistry studies include a multiresidue method testing for molinate, 4-hydroxy molinate and molinate acid and data on residues in irrigated crops for molinate, 4-hydroxy molinate, molinate acid, molinate sulfoxide and molinate sulfone. Outstanding product chemistry requirements are detailed in the October 28, 1999 Product and Residue Chemistry Chapter (Memorandum from Christine Olinger to Virginia Dobozy and Wilhelmena Livingston/Robert McNally).

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Molinate [S-ethyl hexahydro-1H-azepine-1-carbothioate] is a selective thiocarbamate herbicide. The chemical name and structures of molinate and its metabolites of concern are depicted in Figure A.

Figure A. Chemical names and molecular structures of molinate and its metabolites of concern in plants.

Chemical Name **Common Name**	Structure
s-ethyl hexahydro-1*H*-azepine-1-carbothioate **Molinate**	
s-ethyl hexahydro-4-hydroxy-1*H*-azepine-1-carbothioate **4-Hydroxy molinate**	
s-(carboxymethyl)-hexahydro-1*H*-azepine-1-carbothioate **Molinate acid**	

A. Physical Properties of Molinate

Physical state: Liquid
Boiling point: 136.5^{0}C at 10 torr
Solubility: soluble in water at 970 mg/L at 25^{0}C, miscible with acetone, chlorobenzene, ethanol, kerosene, n-octanol and xylenes
Vapor pressure: 5.3 X 10^{-3}mm Hg at 25^{0}C
Specific gravity: 1.0663 at 20^{0}C
Octanol/water partition coefficient (K_{ow}): 756 at 25^{0}C

B. Other Identifying Characteristics and Codes for Molinate

Empirical Formula:	$C_9H_{17}NOS$
Molecular Weight:	187.3
CAS Registry No.:	2212-67-1
Shaughnessy No.:	041402

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

The Toxicology Chapter of the RED was prepared by Dr. Linda Taylor (D249717 dated January 4, 1999). Molinate is a thiocarbamate. In general, thiocarbamates are less potent cholinesterase (ChE) inhibitors than other carbamates. Multiple studies in various species indicate that molinate produces ChE inhibition (plasma, red blood cell and brain) via multiple routes of exposure. Molinate also inhibits neurotoxic esterase (NTE) and is positive for delayed neurotoxicity in the hen. In addition, molinate is a reproductive and developmental toxicant and a suggestive human carcinogen.

The toxicological data base on molinate is **adequate,** except the 21-day dermal toxicity study and the acute neurotoxicity study were both unacceptable and not upgradeable. Repeating these studies would complete the data requirements; however, the results may not alter the endpoints and doses selected for risk assessment. The existing data base supports reregistration eligibility. The quality of the data from the toxicology studies is generally good; however, a NOAEL was not established in several guideline studies, including the subchronic inhalation study, 21-day dermal toxicity study (systemic effects), chronic dog study, combined chronic toxicity/carcinogenicity study in the rat and reproduction study (brain weight effect). In general, molinate was not acutely toxic *via* the oral, dermal, and inhalation routes of exposure in the acute studies required for labeling. It was a mild skin and a moderate eye irritant, but not a dermal

sensitizer. Molinate produced delayed neurotoxicity in the hen [axonal degeneration].[3] Acute and subchronic neurotoxicity studies in the rat demonstrated adverse effects of molinate on motor activity and various functional observational battery [FOB] measurements, in addition to cholinesterase and neurotoxic esterase [NTE] activity inhibition. In the subchronic neurotoxicity study, the Lowest Observed Adverse Effect Level (LOAEL) was 4.0 mg/kg/day in males and 4.5 mg/kg/day in females based on decreased red blood cell and brain cholinesterase and neurotoxic esterase in both sexes; a No Observed Adverse Effect Level (NOAEL) was not established. The subchronic and chronic toxicity studies demonstrated that molinate inhibits cholinesterase activity in plasma, red blood cell [RBC], and brain in rats, dogs, monkeys, and rabbits in a dose-responsive manner. Clinical signs associated with cholinesterase activity inhibition were observed and included ataxia, tremors, salivation, reduced motor activity, splayed/adducted hindlimbs, and abnormal gait.

Delayed fetal development was observed in the rabbit at the same dose level where maternal toxicity was observed. In the rat, developmental toxicity/developmental neurotoxicity were observed [increase in runting/reduction in startle amplitude] at dose levels below the maternal NOAEL. Molinate is a reproductive toxicant, and the rat is the most sensitive species for this effect. Abnormal sperm, decreased percent motile sperm, decreased sperm numbers, decreased litter size, decreased percentage of pups born live, decreased pup viability, increased incidence of microscopic lesions in the ovary, testes, and adrenal, delayed vaginal opening, reproductive organ weight effects, and decreased brain weight were consistent findings in studies in the rat. In a special five-week fertility study, a dose of 0.5 mg/kg/day in males produced adverse effects on sperm parameters; a NOAEL was not established.

It is the registrant's position that the reproductive effect of molinate "requires the production of molinate sulfoxide and the dependence on the enzyme cholesterol ester hydrolase (CEH) for steroid sex hormone production." Additionally, the registrant concludes that the reproductive toxicity in the rat is induced by a mechanism that is specific to rodents. Special studies data submitted to establish the proposed mechanism of toxicity were reviewed and evaluated by the HED Mechanism of Toxicity Assessment Review Committee. The Committee concluded that the submitted studies are not adequate to demonstrate the proposed mechanism of toxicity. The details of the reasons for the Committee's conclusions are included in the memorandum of that meeting. Some of the reasons include the following: lack of concordance between dose levels where effects on testosterone and precursor hormone levels are observed and dose levels where fertility/sperm effects are observed; lack of data to show that sulfoxidation is occurring at the dose levels where fertility/sperm effects are observed in the rat; and lack of data demonstrating an inhibition of n-CEH *in vivo* at dose levels where fertility/sperm effects occur.

In the rat combined chronic toxicity/carcinogenicity study, there was an increase in kidney

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[3]The hen study (MRIDs 00133562 and 43136601) was evaluated by Dr. Karl Jensen, a neurotoxicologist at EPA's National Health and Environmental Effects Research Laboratory (NHEERL). He concluded that molinate produces delayed neurotoxicity in the hen.

tumors in males at the high dose level. Molinate was reviewed by the HED Cancer Assessment Review Committee on November 1, 2000 and, based on the kidney tumors, was classified as *Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential* using the EPA's 1999 draft Guidelines for Carcinogen Risk Assessment. Dose-response assessments are not recommended for chemicals in this classification. (See December 14, 2000 CARC report.)

Molinate was negative in a *Salmonella tymphimurium* assay and for aberrations in cultured human lymphocytes. Because suggestive increases were found for mutations, aberrations, and sister chromatid exchange [SCE] in mouse lymphoma cells, and there were conflicting data in two mouse micronucleus assays, a dominant lethal test was requested. Subsequently, molinate was shown to be negative in this assay.

The metabolism data indicate that molinate is well absorbed and extensively metabolized following both oral and intravenous exposure and is rapidly excreted, mainly in the urine. The data also indicate that the metabolism of molinate involves s-oxidation to form the intermediate molinate sulfoxide, which is either hydrolyzed to hexamethyleneimine or conjugated with glutathione, ultimately forming molinate mercapturic acid; ring hydroxylation at the 3 and 4 positions followed by glucuronide conjugation is also a significant route of metabolism. More recent information indicates that the metabolism of molinate in mammals is primarily *via* three routes: carbon oxidation, sulfur oxidation, and thiocarbamate cleavage, and the proportion of metabolism through each of these pathways varies among the species, including man. The data also suggests that carbon oxidation predominates at low doses of molinate, and this pathway saturates on increasing dose. Then the metabolism switches to sulfur oxidation. It is not known at what dose level the predominate pathway becomes saturated. Based on a study in the rat with radiolabeled molinate, dermal absorption was determined to be 40%.

The toxicology profile for molinate is presented in Table 1 of the Appendix.

3.2 FQPA Considerations

There is evidence of neurotoxicity in multiple studies with several species. Increased susceptibility of offspring was observed in the prenatal developmental toxicity study and the developmental neurotoxicity study in rats. The HED FQPA Safety Factor Committee evaluated the hazard and exposure data for molinate as the bases for making a recommendation on the magnitude of the FQPA Safety Factor. The FQPA Safety Factor Committee recommendation in the December 17, 1998 report of the October 30, 1998 meeting was that the **FQPA Safety Factor be retained at 10X for molinate**. The rationale for the retention of the 10X is:

- Increased susceptibility observed in the prenatal developmental toxicity study in rats.

- Increased susceptibility observed in the developmental neurotoxicity study in rats.

• Reproductive effects *were seen* in mice (anti-fertility study) and rats (sperm morphology study) following oral administration (although there was no evidence of increased susceptibility in the 2-generation reproduction study).

• Uncertainty associated with the lack of characterization for the surface water monitoring data used for drinking water exposure assessments. The environmental fate data base indicates that the parent molinate is persistent and expected to reach surface water. Monitoring data are available, however there is a lack of characterization of the exposure levels for localities downstream of rice fields in the Southeast.

The Committee determined that the 10x FQPA safety factor is applicable for the following:

Acute Dietary Assessment: The Committee determined that the FQPA Safety Factor should be **retained (10x)** for acute dietary risk assessment because the increased susceptibility was demonstrated in both the prenatal developmental toxicity and developmental neurotoxicity studies.

Chronic Dietary Assessment: The Committee determined that the FQPA Safety Factor should be **retained (10x)** for chronic dietary risk assessment because of the concern for the severe reproductive effects seen following repeated oral exposures in studies with rats and mice.

For dietary risk assessments, the target exposure level above which risk is considered to be of concern is referred to as the Population Adjusted Dose (PAD). An acute PAD (aPAD) and a chronic PAD (cPAD) are calculated by dividing the respective acute and chronic RfDs (aRfD and cRfD) by the FQPA Safety Factor (see Table 2).

3.3 Dose Response Assessment and Hazard Endpoint Selection

On October 1 and 7, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database for molinate, re-assessed the existing reference dose, and selected the doses and toxicological endpoints for dietary and non-dietary exposure risk assessments. Table 1 contains the acute toxicity endpoints, which are especially important for labeling purposes. Table 2 contains a summary of the doses and endpoints selected for use in the various human health risk assessments.

Table 1: Acute Toxicity of Molinate

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1 870.1100	Acute Oral - rat	40593301	LD_{50} = 730 mg/kg (679-785) Males = 700 mg/kg (620-791) Females	III
81-2 870.1200	Acute Dermal - rabbit	40593301	LD_{50} > 2000 mg/kg	III
81-3 870.1300	Acute Inhalation - rat	00245675	LC_{50} = 2.9 mg/L (2.5-3.3) Males = 2.4 mg/L (2.2-2.6) Females	IV
81-4 870.2400	Primary Eye Irritation	40593301	moderate irritant	II
81-5 870.2500	Primary Skin Irritation	00247547	mild dermal irritant	IV
81-6 870.2600	Dermal Sensitization	40593302		Negative
81-7 870.6100	Acute Delayed Neurotoxicity (Hen)	00133562 43136601	NOAEL = 0.2 g/kg, based on axonal degeneration in brain and cervical spinal cord; delayed neurotoxicant.	N/A
81-8 870.6200	Acute Neurotoxicity - rat	43188001	↓ motor activity, ↑ time to tail flick; NTE, ChE, GFAP activities were not assessed at appropriate times	N/A Unacceptable

Table 2: SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	LOAEL = 1.8	Developmental neurotoxic effect (reduction in startle amplitude)	Developmental Neurotoxicity
	UF = 300	**Acute RfD = 0.006 mg/kg** Acute PAD = 0.0006 mg/kg	
Chronic Dietary non-carcinogenic effects	LOAEL=0.3	Degeneration/demyelination in sciatic nerve and atrophy/reserve cell hyperplasia of muscle	Rat Chronic Toxicity/Carcinogenicity
	UF=300	**Chronic RfD = 0.001 mg/kg/day** Chronic PAD = 0.0001 mg/kg/day	
Short-Term* (Dermal)	Oral LOAEL = 1.8	Developmental neurotoxic effect (reduction in startle amplitude)	Developmental Neurotoxicity
Intermediate-Term* (Dermal)	Oral NOAEL = 0.2	Reproductive effects including decrease in following: % viable sperm, % motile sperm, % normal sperm, sperm counts, number of implants, number of viable fetuses; increase in implantation loss	5-week rat fertility
Long-Term (Dermal / Non-cancer)	None	The use pattern (1-2 applications per season to rice) does not indicate potential long-term dermal exposure; risk assessment is NOT required.	
Short-Term (Inhalation)	NOAEL = 0.12 mg/L	Hindleg muscle weakness	Acute inhalation - rat
Intermediate-Term (Inhalation)	NOAEL = 0.0003 mg/mL	Reproductive effects including decreased number of implants and increased % of abnormal sperm	4-week inhalation - rat
Long-Term (Inhalation)	None	The use pattern (1-2 applications per season to rice) does not indicate potential long-term inhalation exposure; risk assessment is NOT required.	

* = Since an oral LOAEL was selected a dermal absorption factor of 40% should be used for dermal risk assessments.

NOTE: For Short-term dermal risk assessments, an MOE of 300 is required because a NOAEL was not achieved in the developmental neurotoxicity study; an MOE of 100 is adequate for all other exposure (dermal and inhalation) risks.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Molinate is currently registered for use on rice for grass weed control, including barnyard grass, springletop and broadleaf grass, as well as flatsedge, dayflower and other small seed broadleaf weeds. There are four active end-use products (EPs) with food/feed uses registered to Zeneca Ag Products under the trade names Ordram® or Arrosolo® (combination of molinate and propanil).[4] Emulsifiable concentrate (33.1%-90.9% a.i.) and granular (15% a.i.) formulations may be applied to rice preemergence and/or postemergence using ground and aerial equipment. Another registrant, RICECO, recently registered a molinate technical and two end-use products, a granular (15% a.i.) and an emulsifiable concentrate (combination of molinate and propanil) formulation. Molinate products can be used at various intervals in rice production. The maximum per season application rate range is 6 to 9 lbs a.i./acre. Products may be applied two to three times per growing season.[5] In the southern states, usual planting times typically range from early to mid April through late May. In California, most planting is completed during May.

4.2 Dietary Exposure

4.2.1 Food Exposure

The Product and Residue Chemistry Chapter of the RED was prepared by Christine Olinger (DP Barcode: D249755, dated October 28, 1999). The Acute and Chronic Dietary Exposure Risk Analyses were completed by Felicia Fort (D262577 dated February 9, 2000).

Molinate Residues

Most residue chemistry guideline studies have been submitted. All that are necessary for dietary exposure assessment are available. Tolerances are currently established for residues of molinate *per se* (40 CFR §180.228). The HED Metabolism Committee (Memoranda dated March 2, 1994 and April 25, 1994 from Christine Olinger) has

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[4]Two Zenca products, Ordram 6E and Ordram 10-G, were recently canceled (Federal Register, September 6, 2000, Volume 67, Number 173, page 54113-54128). The cancellation order permits the registrant to continue to sell and distribute existing stocks of the canceled products until January 15, 2001. Existing stocks already in the hands of dealers or users can generally be distributed, sold or used legally until they are exhausted.

[5] Molinate Use Closure Memo from Lois Rossi to Margaret Stasikowski summarizing September 23, 1998 SMART meeting with registrant.

determined that the residues to be regulated in plant commodities are molinate and the metabolites 4-hydroxy molinate and molinate acid. Therefore, the tolerance definition in 40 CFR §180.228 should be amended to include all residues to be regulated.

Sufficient data are available to ascertain the adequacy of the established tolerances for molinate residues in/on rice grain and rice straw. The tolerance for residues in/on rice grain should be increased to 0.75 ppm based on combined residues of <0.73 ppm in/on grain from field trials. The tolerance for residues in/on rice straw should be increased to 7.0 ppm based on combined residues of <6.27 ppm in/on straw from field trials. Molinate *per se* was <0.05 ppm (<LOQ) in/on rice grain and straw from all field trials.

An adequate processing study indicated that residues concentrated in hulls and bran processed from molinate-treated rice grain; tolerances of 3.0 and 2.0 ppm, respectively, are required.

The livestock metabolism studies indicate that molinate residues of concern are not present in tissues, milk, or eggs from animals dosed with molinate at levels greater than the theoretical maximum dietary exposure. These diets are exaggerated and represent the maximum dietary exposure assuming all rice is treated and bears residues at the tolerance level. Tolerances for molinate residues in livestock commodities are not required based on current uses.

Studies which are outstanding include multiresidue method testing for molinate, 4-hydroxy molinate, and molinate acid and data on residues in irrigated crops for molinate, 4-hydroxy molinate, and molinate acid, molinate sulfoxide, and molinate sulfone. Molinate sulfoxide and sulfone were not found in appreciable quantities in commodities when rice was treated with parent molinate. However, the sulfoxide and sulfone can be found in significant quantities in water from rice paddies which may be used to irrigate other crops. No irrigation crop studies have been completed when the sulfoxide and sulfone were measured in the crops.

Anticipated Residues

In a March 31, 1999 Memorandum, the Biological and Economic Analysis Division provided information on the percent of rice treated with molinate. Anticipated residues for chronic and acute dietary exposures were generated based on field trial data for the raw agricultural commodity, rice grain. Anticipated residues generated from the grain are adjusted by a processing factor and include the combined residues of molinate, 4-hydroxy molinate, and molinate acid. USDA and FDA monitoring data are not available for molinate. Rice and its food forms are all considered to be blended; therefore an average residue was used for both the chronic and acute assessments. Although an average concentration was used for the anticipated residue, it is a higher level than that to which

the consumer is likely to be exposed, since the levels are based on field trial residues. A more refined value could be estimated if the registrant were to conduct monitoring studies closer to the point of consumption or if cooking studies were submitted.

Dietary Risk Assessment

The doses and endpoints for dietary risk assessment selected by the HED Hazard Identification Assessment Review Committee (HIARC) were discussed previously and are summarized in Table 2.

Also previously discussed (section 3.2), the HED FQPA Safety Factor Committee determined that the FQPA Safety Factor should be **retained (10x)** for both chronic and acute dietary risk assessment for all populations (B. Tarplee, 12/17/98).

HED conducts dietary risk assessments using the Dietary Exposure Evaluation Model (DEEM™) which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, one-day consumption data are summed and a food consumption distribution is calculated for each population subgroup of interest. The consumption distribution was multiplied by a residue point estimate for a deterministic (Tier # I/II type) exposure/risk assessment. Exposure estimates are expressed in mg/kg bw/day and as a percent of the aPAD. For chronic risk assessments, residue estimates for foods (e.g. apples) or food-forms (e.g. apple juice) of interest are multiplied by the averaged consumption estimate of each food/food-form of each population subgroup. Exposure estimates are expressed in mg/kg/bw/day and as a percent of the cPAD.

The results of both the chronic and acute exposure assessments showed that for all population subgroups, risk estimates were below HED's level of concern (<100% cPAD or aPAD). The most highly exposed subgroup was infants (<1 year) for both assessments consuming 18% of the cPAD and 21% of the aPAD at the 95th percentile of exposure. Even at the 99.9th percentile, the acute risk estimate was approximately 55% of the aPAD. The dietary risk estimates are presented in Table 3.

Table 3. Dietary Risk Estimates for Molinate.

Population Subgroup	Chronic		Acute (95th % ile)		Acute (99.9th % ile)	
	Exposure	%cPAD	Exposure	%aPAD	Exposure	%aPAD
U.S. Population	0.000005	5	0.000039	7	0.000186	31
All Infants (<1 years)	0.000018	18	0.000128	21	0.000328	55
Children (1-6 years)	0.000010	10	0.000083	14	0.000249	42
Children (7-12 years)	0.000006	6	0.000049	8	0.000193	32
Females (13-50 years)	0.000004	4	0.000033	6	0.000152	25

aPAD = 0.0006mg/kg, cPAd = 0.0001 mg/kg/day

4.2.2 Water Exposure

The Drinking Water Assessment for molinate was prepared by James Breithaupt of the Environmental Fate and Effects Division (EFED) (DP Barcode D252252 dated February 16, 1999, D253406 dated March 17, 1999, D254562 dated April 2, 1999, D259945 dated January 13, 2000, D262859 dated February 8, 2000 and D271004 dated December 7, 2000). Potential exposure to molinate in the drinking water is limited to those rice-growing regions where the chemical is used.

To obtain both ground and surface water concentrations for the purpose of risk assessment, EFED received monitoring data from the U.S. Geological Survey (USGS), the State of Arkansas Department of Pollution Control and Ecology, the City of Sacramento, CA, the State of California Department of Environmental Regulation, and the State of Texas. EFED used monitoring data for the drinking water assessment since the data were available for the areas where molinate was applied except for Tennessee, where only 3,000-5,000 acres of rice were grown in Lake County. EFED has conducted a state-by-state regional assessment since molinate was applied only in California and in the south central/south eastern states of Arkansas, Louisiana, Missouri, Texas, and Tennessee. EFED has no official models to generate estimated environmental concentrations (EECs) from aquatic crops.

The effect of water treatment appears to be an important factor in removing molinate from finished water. EFED has reviewed laboratory studies on the efficiency of parent molinate removal simulating the city of Sacramento's water treatment process. If chlorination is the only oxidant chemical used in treatment, up to 80% of molinate has been shown to remain after treatment as the metabolite molinate sulfoxide, which still has the carbamate functional group. Further degradation is likely to be achieved only if more effective oxidants are used (e.g., ozone, chlorine dioxide, $KMnO_4$). Potassium permanganate ($KMnO_4$) appears to be a more effective oxidant for molinate, since it

degrades >98 % of parent molinate to a non-carbamate degradate. However, since the extent of use of stronger oxidants than chlorine is uncertain, EFED recommended using the raw water concentrations.

Adjustment of parent molinate concentrations in ground water and surface water for molinate degradates was necessary since there was no monitoring for any degradates with the exception of the photoproduct 4-keto molinate. At an October 31, 2000 meetint, the HED Metabolism Assessment Review Committee concluded that the following molinate metabolites and degradation products should be included in the water assessment: molinate sulfoxide, molinate sulfone, 3-keto and 4-keto molinate, hydroxy molinate (2, 3, and 4), molinate acid (carboxymethyl molinate), and ring- opened molinate (S-ethyl-5-carboxypentyl thiocarbamate). No meaningful estimates of exposure for molinate sulfone, 3-keto molinate, or ring-opened molinate (S-ethyl-5-carboxypentyl thiocarbamate) could be provided based on the submitted environmental fate studies. However, EFED does not expect significant formation of these metabolites in water. This is based on the fact that volatility is the primary route of dissipation and the other metabolites are formed in relatively low amounts (<10% of applied), with the exception of 4-keto molinate.

Calculation of a factor to account for the lack of monitoring data on the molinate metabolites/degradation products was based on data from laboratory studies and aquatic field dissipation studies for dry-seeded rice (MRID 41421803) and water-seeded rice (MRID 41421804). The field studies provided data on molinate acid and molinate sulfoxide degradates relative to parent. The average percent of parent molinate was 9.4 % for dry-seeded rice and 11 % for water-seeded rice, leading to adjustment factors of 1.094 and 1.11, respectively. To account for 2-, 3-, and 4-hydroxy molinate, the estimated environmental concentrations (EECs) were increased by another 14.7 % (average percent observed in an aerobic aquatic metabolism laboratory study, MRID 44956603). The use of a laboratory study was necessary because no metabolites other than molinate acid and molinate sulfoxide were analyzed for in the aquatic field dissipation studies.

EFED used a recent publication of a study by Joseph Domagalski to recommend increasing molinate exposures by 30% to account for the amount of 4-keto molinate.[6] Monitoring was conducted in the Sacramento Basin below the confluence of the Colusa Drain and the Sacramento River to downstream of the City of Sacramento. The metabolite 4-keto molinate was detected at 10-30 % (one detection of 50 %) of parent molinate in every sample where molinate was detected in surface water from storm water runoff. In the Southern region of the U. S., 4-keto molinate levels in water of 10-50 %

[6] Domagalski, J. Pesticides and Pesticide Degradation Products in Stormwater Runoff: Sacramento River Basin, California, Water Resources Bulletin, Volume 32, Issue 5, October, 1996, pp. 953-964

of detected parent molinate have also been observed.

To adjust for all molinate metabolites and degradates, EFED recommended using a 1.56 adjustment factor for both California and the Southern Region for both surface and ground estimates of parent molinate.

Drinking Water from Ground Water

For estimates of dietary exposure from ground water used as drinking water, EFED recommended the use of 0.056 ug/L for acute and chronic assessment for parent molinate and 0.087 ug/L for total toxic residues of molinate (molinate plus metabolites). The 0.056 ug/L concentration was the maximum observed in recent USGS monitoring data from both California and the Southern Region (Mississippi and Arkansas). Some of the wells in which detections were observed were drinking water wells.

EFED did not run the SCI-GROW2 ground water model because it is inappropriate for rice. SCI-GROW2 assumes vulnerable soils with a shallow water table, but rice fields require impermeable layers to hold the floodwater. Also, SCI-GROW2 does not directly take into account the volatility of a given compound.

Drinking Water from Surface Water

Table 4 provides the estimates of drinking water exposure levels from parent molinate and the residues of toxic concern recommended by EFED for the aggregate risk assessments.

The surface water intakes with the highest exposure are Sacramento and West Sacramento. Maximum concentrations of parent molinate in these areas ranged from 1.52-2.13 ug/L, and the annual mean concentrations ranged from 0.29-0.41 ug/L. The intakes on the Mississippi and Atchafalaya Rivers in Louisiana had similar maximum parent molinate concentrations of 0.109-0.117 ug/L and annual mean concentrations of 0.014-0.018 ug/L. Arkansas, Mississippi, Missouri, and Tennessee have no surface water intakes in rice-production areas, and therefore no exposure in drinking water from surface water. The only intake in Texas found to receive molinate residues was Anahuac. Maximum and annual mean concentrations of molinate were 0.073 and 0.0029 ug/L, respectively.

Table 4. Monitoring estimated environmental concentrations (EECs) for parent molinate and residues of concern that may be used for acute and chronic risk assessment for molinate+

Location (Source of Data) [Population]	Frequency of Detection (Range of detection limits)	Parent Molinate		Adjustment Factor for degradates of concern[2]	Parent + degradates of concern (See Table 3 below)	
		Maximum Concentration (ug/L)	Annual Means (ug/L)[1]		Maximum Concentration (ug/L)	Annual Means (ug/L)
Sacramento, California (Upper 95th percentile of parent molinate levels in raw water from the Sacramento River after holding periods (1991-2000 data), [374,600 people]	65/117 (0.1 ug/L)	1.52	0.29	1.56	2.37	0.45
West Sacramento, California (Upper 95th percentile of parent molinate levels in raw water from the Sacramento River after holding periods (1991-2000 data) adjusted for the percent flow data at City of Sacramento, [30,000 people][3]	65/117 (0.1 ug/L)	2.13	0.41	1.56	3.32	0.64
Arkansas, Mississippi, Missouri, and Tennessee (no surface water intakes in rice-production areas)	Not Applicable	0	0	1.56	0	0
New Orleans Area (Upper 95th percentile of parent molinate levels in raw water from 1996-1999 USGS data in the Mississippi River at St. Francisville, LA), [1.21 million people][4]	13/58 (0.004 ug/L)	0.117	0.014	1.56	0.18	0.022

St. Mary Parish, Louisiana Intakes at Atchafalaya River (Upper 95th percentile of parent molinate levels in raw water from 1996-1999 USGS data at Melville, LA), [61,374 people][4]	15/57 (0.004 ug/L)	0.109	0.018	1.56	0.17	0.028
Lake Anahuac in Texas, (from dilution calculations) [1,960 people][5]	20/20 (0.004 ug/L)	0.073	0.0029[6]	1.56	0.114	0.005[7]

[+] Drinking water exposure estimates from surface water.

[1] Time-weighted annual mean concentrations were requested by the Health Effects Division.

[2] Based on a meeting between EFED and the HED MARC committee, EFED calculated an adjustment factor of 1.56 for the parent molinate monitoring data to account for degradates of concern (See EFED Chapter).

[3] The City of West Sacramento gets all of its water from the Sacramento River, while the City of Sacramento gets 71.4 % of its water from the Sacramento River and 28.6 % from the American River. EFED divided the Sacramento concentrations by 71.4 % to estimate concentrations for West Sacramento. Even though West Sacramento gets more molinate in their water, they do not get taste and odor complaints. The two cities are investigating this discrepancy.

[4] The intakes below the USGS sampling points at St. Francisville in the Mississippi River and at Melville in the Atchafalaya River are at diluted portions, and both rivers are channelized. There are no significant downstream sources of water to dilute the residues further. As a result, EFED expects concentrations similar to the estimates at these intakes. The annual means using zero for non-detections for 1996, 1998, and 1999 were at or below the limit of detection, while the means calculated using the limit of detection were above the limit of detection, indicating high uncertainty in these estimates for these locations.

[5] White's Bayou drains rice fields directly into Lake Anahuac, a drinking water supply for 1,960 people. However, there are other sources of water for this intake and EFED does not know the exact proportions. Also, rice production along White's Bayou has declined by approximately two-thirds since the year the data were generated (1994).

[6] These estimates have additional uncertainty because it is below the lowest detection limit of 0.004 ug/L.

Assumptions, Certainties, Uncertainties, and Limitations

1) Water Treatment

EFED assumed that drinking water facilities use only chlorination as an oxidative process, and therefore 80 % of parent molinate present in raw water would still be present as molinate sulfoxide after treatment. Potassium permanganate may be a more effective oxidant for molinate as it degraded >98% of parent molinate to a non-carbamate degradate in laboratory studies. However, the extent of the use of oxidants rather than chlorine is unknown.

The efficiency of water treatment practices varies from intake to intake. The studies dealing with water treatment were laboratory simulations of the water treatment practices at Sacramento, California. Other intakes may have different practices that may provide very different removal efficiencies. Variables such as spiking rates of oxidants, size of the distribution system, and storage/treatment times may provide different pesticide removal efficiencies. Therefore, using the results of one intake's treatment may not be accurate for another intake.

The water treatment practices at the Mississippi and Atchafalaya River intakes was not provided by the registrant. EFED is assuming that chlorination is the only oxidative treatment at these intakes.

2) Use of Monitoring Data

EFED is very certain about the drinking water conclusions for California, Missouri, Tennessee, and Arkansas for parent molinate. EFED is less certain about the Mississippi and Atchafalaya River intakes in Louisiana because of fewer years of monitoring data (4 years or less) compared to California (19 years). EFED is uncertain about the extent of exposure at Anahuac, Texas, because the amount of water from other sources and the number of days that Lake Anahuac receives rice drainage is unknown.

The amount of the degradate 4-keto molinate exposure in the use season is uncertain. The Domagalski article states that between 10-30 % of detected molinate was present in the Sacramento River in California. However, this study was conducted in January, and molinate is applied in May-June primarily.

The use of monitoring data to assess dietary exposure creates uncertainties. Monitoring

data are not available everywhere for all uses of a given compound. In a given year, it is highly likely that peak concentrations are missed since sampling is not always conducted on a daily schedule or over the time necessary to detect peaks. Also, peak concentrations are not likely to be detected unless sampling is conducted in a stratified sampling pattern in highly vulnerable sites. Sampling is also not necessarily representative of the entire year unless sampling is conducted over a year. Since monitoring data are dependent on the weather in a particular year, data may not always be available for enough years to cover the range of weather in a given area of application. The associated information to interpret monitoring information, such as amount of use and the area treated in a watershed, the timing and amount of rainfall events that drive runoff events, and specific cultural practices are not always available. Inclusion of data from an area where no pesticide is applied tends to bias estimates of exposure downward when considered with data from use areas. In analyzing these data, efforts were made to only include data from areas where molinate was known to have been used.

3) Estimation of degradate concentrations based on field and laboratory studies

Estimation of degradate concentrations in surface water based on laboratory and field studies introduces uncertainties because levels of degradates relative to parent compound vary with time. Degradate concentrations are lowest relative to parent compounds immediately following the application and increase with time. As a result, no single adjustment factor for monitoring data will perfectly represent the contribution of degradates to ecological and drinking water exposure. However, the 1.56 factor is an average number will reasonably represent the contribution of degradates for both ecological and drinking water exposure. Monitoring for all residues of concern is the only certain method to assess exposure.

4)Time-weighting of monitoring data

Time-weighting of monitoring to provide annual exposure data from seasonal data introduces uncertainties because of extrapolation and censored data. Extrapolation introduces potential error because a concentration represents a point in time. Extrapolation of high concentrations increases the estimates. On the other hand, extrapolation of non-detections (censored data) decreases the estimates depending on the level of detection (LOD).

5) Taste and odor issues between Sacramento and West Sacramento

Since 1982, taste and odor complaints associated with molinate and thiobencarb (another rice herbicide) have been reported at Sacramento. Unlike Sacramento, West Sacramento does not receive any taste and odor complaints associated with molinate. This problem is not expected given the fact that molinate exposure is likely be higher at West Sacramento. Sacramento and West Sacramento are conducting further investigations into the molinate exposure problem to determine if water treatment differences or agricultural drains between the two towns are contributing to the taste and odor problem at the City of Sacramento. Even though there is some exposure at these two locations, the levels are below the State of California MCL of 20 ppb for taste and odor in drinking water.

6) Uncertainties of using dilution calculations

Dilution calculations were used to estimate dietary exposure at Lake Anahuac, Texas. At this location, White's Bayou drains rice fields into Lake Anahuac, which is a drinking water source for 1,960 people. However, other sources of water that do not receive rice drainage are used to supplement the lake. Also, rice production along White's Bayou has declined by approximately two-thirds since the year the data were generated (1994). As a result, the predicted EEC's are probably higher than actual exposure. EFED has no information on the proportion of water from the other source and from rice fields and the number of days Lake Anahuac receives rice drainage so that the estimates of drinking water concentrations can be refined.

4.3 Occupational Exposure

The Occupational/Residential Exposure Assessment for the RED was prepared by Steven Weiss (DP Barcode D249751, dated December 21, 1999 and subsequent revisions)

Molinate use on rice differs based on cultural practices (e.g., wet versus dry seeding and water management). Application parameters are generally defined by the physical nature of the use site, by the equipment required to deliver the chemical to the use site, and by the application rate required to achieve efficacy. Molinate applications intended for weed control in rice are predominantly made by aircraft (approximately 90 percent of total applied) while the remaining applications are completed by ground-based equipment designed to apply granulars or by typical groundboom spray rigs. Most ground-based applications occur by pre-plant/incorporation. Information obtained at the September 1998 SMART meeting indicates molinate is apparently sold mostly in bulk packaging. This is supported by the fact that the predominant applicators are pilots who would use larger quantities of molinate compared to a typical grower (i.e., bulk packaging is easier

to handle for larger quantity users).

The predominant rice producing states are Arkansas, California, Louisiana, Mississippi, Missouri, and Texas. Cropping time for rice ranges from approximately 120 to 140 days. In the southern states, usual planting times typically range from early to mid April through late May. In California, most planting is completed during May. Harvest in the southern states can range from the beginning of August through the end of October. Likewise, harvest in California essentially occurs throughout October. The occupational risk assessment does not differentiate risks to workers in the various rice-growing areas.

4.3.1 Handler

HED has determined that there is a potential for exposure from handling molinate products during the application process (i.e., mixer/loaders, applicators, flaggers, mixer/loader/applicators) and from entering agricultural areas previously treated with molinate.

The non-dietary exposure database that has been developed in support of the reregistration of molinate is extensive when compared to that for other similar chemicals. This database contains exposure monitoring data that have been developed using both passive dosimetry and biological monitoring techniques. A molinate-specific epidemiology assessment has also been completed (discussed under 4.5). HED policy dictates that chemical-specific data be used in conjunction with other sources of exposure data commonly used by HED to complete risk assessments (e.g., *Pesticide Handlers Exposure Database*). As such, several data sources were considered in this assessment including the *Pesticide Handlers Exposure Database* (PHED) and the array of molinate-specific data that have been submitted.

HED anticipates that occupational molinate exposures will only occur in a short-term or intermediate-term pattern. HED anticipates that occupational exposures will not be chronic because HED defines chronic exposures as use of the chemical for approximately 180 days per year and it is anticipated that molinate as with other typical pesticide compounds will not be used in this manner.

In October 1998, the Hazard Identification Assessment and Review Committee (HIARC) reassessed toxicological endpoints for non-dietary exposure to molinate. For details on the dose and endpoints selected for risk assessment, see Table 2. For short-term dermal risk assessments, an MOE of 300 is required because a NOAEL was not achieved in the developmental neurotoxicity study; an MOE of 100 is adequate for all

other exposure (dermal and inhalation) risks.

Handler Risk Assessment Assumptions and Factors

A series of assumptions and exposure factors served as the basis for completing the handler risk assessment. The following assumptions and factors were used to complete this assessment:

• Average body weight of an adult handler is 70 kg. This body weight is used in all assessments.

• The number of application days/year, the amount of ai/handled per day by loaders and areas treated/day were defined for each handler scenario.

For aerial applications, the following assumptions were used and are based on information provided to the HED during the SMART meeting on 9/23/98, subsequent conversations with Zeneca, and the best professional judgement of the HED.

* aerial applications of granulars: 27 application days/year with average of 300 acres treated /day

* aerial applications of liquids: 27 application days/year with average of 300 acres treated /day

* loading granulars for aerial applications: 1,680 lb ai handled/day (average in 1993 study MRID# 431656-02 was approximately 900 lb ai handled/day)

* mixing/loading liquids for aerial applications: 900 lb ai handled/day (average in 1996 study MRID# 442122-01 was approximately 300 lb ai handled/day)

No information on the number of application days/year for ground-based applications was provided to HED. Therefore, HED assumed that ground-based applications for liquid or granular formulations could occur for 30 application days/year.

All short-term and intermediate-term handler calculations were completed at the maximum labeled application rate for each scenario.

There are three basic risk mitigation approaches considered appropriate for controlling occupational exposures. These include administrative controls, the use of personal

protective equipment or PPE, and the use of engineering controls. Occupational handler exposure assessments are completed by HED using a baseline exposure scenario and, if required, increasing levels of risk mitigation (PPE and engineering controls) to achieve an appropriate margin of exposure or cancer risk. [Note: Administrative controls available generally involve altering application rates for handler exposure scenarios. These are typically not utilized for completing handler exposure assessments because of the negotiation requirements with registrants.] The baseline clothing/PPE ensemble for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, no chemical-resistant gloves (there are exceptions pertaining to the use of gloves and these are noted), and no respirator. The first level of mitigation generally applied is PPE. This involves the use of an additional layer of clothing, chemical-resistant gloves, and a respirator. The next level of mitigation considered in the risk assessment process is the use of appropriate engineering controls which, by design, attempt to eliminate the possibility of human exposure. Examples of commonly used engineering controls include closed tractor cabs, closed mixing/loading/transfer systems, and water-soluble packets.

Occupational Exposure Patterns

The anticipated use patterns and current labeling indicate 11 major occupational exposure scenarios. These scenarios include:

(1) loading granulars for aerial applications;
(2) truck drivers supporting loading granulars for aerial applications;
(3) pilots applying granulars using aerial equipment;
(4) flagging during aerial application of granulars;
(5) mixing/loading liquids for aerial applications;
(6) pilots applying liquids using aerial equipment;
(7) flagging during aerial application of liquids;
(8) loading granulars for ground-based applications;
(9) applying granulars using ground-based equipment;
(10) mixing/loading liquids for ground-based applications;
(11) applying liquids using ground-based equipment

Estimating Exposure and Risk Using Biomonitoring Exposure Data

Exposure and risk for the three mixer/loading scenarios [(1)loading granulars for aerial applications; (2) truck drivers supporting loading granulars for aerial applications; (5) mixing/ loading liquids for aerial applications] were evaluated using biomonitoring

exposure data. Calculations of exposure (combined dermal and inhalation) and risk were based on the assumption that loaders of granulars are using bulk bags and are wearing long sleeve shirts, long pants, coveralls (Tyvek or carbon), and a full face respirator. Risks for truck drivers were calculated for those wearing carbon suits and those wearing no suits. For loaders of liquids for aerial applications, three levels of PPE were evaluated:

Level 1: Activated carbon suit worn underneath "Kleenguard" coveralls
Level 2: "Kleenguard" coveralls worn over normal work clothing
Level 3: Normal work clothing, recommended as long sleeved shirt and long pants

Estimating Exposure and Risk Using Unit Exposures from PHED

Since adequate biomonitoring data were only usable for the three scenarios, the other eight scenarios [(3) pilots applying granulars using aerial equipment; (4) flagging during aerial application of granulars; (6) pilots applying liquids using aerial equipment; (7) flagging during aerial application of liquids; (8) loading granulars for ground-based applications; (9) applying granulars using ground-based equipment; (10) mixing/loading liquids for ground-based applications; and (11) applying liquids using ground-based equipment] were evaluated using the unit exposures from the Pesticide Surrogate Exposure Guide (8/98).

Short- and intermediate-term risks were calculated for dermal, inhalation and the combined dermal and inhalation exposures. It was concluded that the dermal and inhalation exposures could be combined due to the common endpoint for short-term (neurotoxicity) and intermediate-term (reproductive effects) exposures. Since the short-term dermal endpoint was based on a LOAEL with an additional uncertainty factor of 3, the LOAEL was divided by 3 before calculating the combined short-term dermal and inhalation MOEs. The intermediate-term dermal and inhalation endpoints were both based on a NOAEL so this additional step was not necessary for the combined intermediate MOEs. The combined MOEs were calculated using the following equation:

$$\frac{1}{\frac{1}{\frac{(\text{Dermal MOE})}{3}} + \frac{1}{(\text{Inhalation MOE})}}$$

A combined MOE of less than 100 exceeds the Agency's level of concern.

Summary of Risks to Occupational Handlers Using Biomonitoring Data (Appendix Tables 2-3)

Short-term MOE's estimated for liquid and granular mixers/loaders using biomonitoring data are less than 300 at the baseline level of personal protective equipment (i.e., long pants, long sleeved shirts, gloves) and for the additional PPE of coveralls over long pants, long sleeved shirts, chemical resistant gloves and full face respirators. Short-term total MOEs estimated for truck drivers supporting loading of granulars for aerial applications are greater than 300.

Intermediate-term MOEs estimated for liquid and granular mixer/loaders using biomonitoring data are less than 100 at the baseline and additional levels of PPE (MOEs ranged from 17 to 73). Intermediate-term total MOEs for truck drivers supporting loading of granulars for aerial applications are greater than 100.

Summary of Risks to Occupational Handlers Using PHED Data (Appendix Tables 4-7)

Short-term dermal MOEs estimated for 8 handler scenarios using PHED data are all less than 300 at the baseline clothing and additional PPE levels (MOEs ranged from 32 to 230). Engineering controls resulted in short-term dermal MOEs above 300 for only 3 of the 8 scenarios.

Short-term inhalation MOEs estimated for 8 handler scenarios using PHED data are above 100 at the baseline level of clothing/PPE.

When the short-term dermal and inhalation MOEs are combined, the MOEs were below 100 for all scenarios at the baseline level and when additional protective clothing/PPE are added. When engineering controls are added, the MOEs are still below 100 for pilots applying both granular and liquid formulations and for handlers mixing/loading liquids for ground-based application and applying liquids using ground-based equipment.

Intermediate-term dermal MOEs estimated for 8 handler scenarios using PHED data are all less than 100 at the baseline clothing and additional levels of PPE (MOEs ranged from 4 to 26). Engineering controls resulted in MOEs above 100 for only 2 of the 8 scenarios.

Intermediate-term inhalation MOEs estimated for 8 handler scenarios using PHED data are all less than 100 at the baseline PPE level (MOEs ranged from 8 to 31). The addition of a full face respirator resulted in intermediate-term inhalation MOEs above 100 for 6 scenarios assessed using PHED data. Risks for pilots applying liquids and

granulars were only assessed with engineering controls; the MOEs were 89 and 3, respectively.

When intermediate-term dermal and inhalation risks are combined, the MOEs are less than 100 for all scenarios at baseline and when added protective clothing/PPE are added. When engineering controls are added, the MOEs are still less than 100 for pilots applying both granular and liquid formulations and for handlers applying both granular and liquid formulations using ground-based equipment and for handlers mixing/loading liquids for ground-based application.

The handler assessments are believed to be reasonable high end representations of molinate uses. There are, however, many uncertainties in these assessments. The uncertainties include but are not limited to the following: extrapolating exposure data by the amount of active ingredient handled or applied; not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies.

4.3.2 Postapplication

Occupational postapplication exposures are expected to be minimal because of the nature of the activities associated with rice cultivation (e.g., scouting and water management) and the protective equipment that is commonly used during these activities (e.g., waterproof rubber boots for walking through rice paddies). Thus, a quantitative exposure and risk assessment for post-application activities was not performed. Since the acute toxicity categories for the technical grade are III for oral and dermal, II for primary eye irritation, and IV for inhalation and primary skin irritation, the 24-hour restrictive entry interval (REI) that appears on molinate product labels is in compliance with the Agency's Worker Protection Standard (WPS).

4.4 Residential Exposure

HED has not addressed any residential exposure scenarios because there are no residential uses of molinate. This assessment for molinate reflects the Agency's current approaches for completing residential exposure assessments based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines*, the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment*, and the *Overview of Issues*

Related to the Standard Operating Procedures for Residential Exposure Assessment presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available. This will include expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from other sources already not addressed such as from spray drift; residential residue track-in; exposures to farmworker children; and exposures to children in schools.

4.5 Epidemiology Data

A molinate epidemiology study of exposed male workers, begun in the early 1980s, has been reviewed three times by Dr. Ruth Allen (1991, 1993 and 1999).[7] The purpose of the registrant-sponsored study was to determine whether workers in molinate production and formulation plants showed any adverse reproductive effects, changes in sperm parameters, or reduced fertility. Each successive submission to EPA has been an attempt to upgrade the study report and address deficiencies in previous reviews. The study was published in a peer-reviewed journal in 1999 after a reanalysis of the statistical data.[8]

A total of 225 male workers donated at least two semen samples between 1980 and 1982 at a molinate production plant in Cold Creek, Alabama, and two molinate formulation plants in Richmond, California and in North Little Rock, Arkansas. A total of 43 employees provided semen samples at a single period. Male workers were known by job title and duties to be exposed to molinate in manufacturing and formulating at one of the three facilities.

The study was conducted over four distinct time periods with and without chemical production or formulation. Due to seasonal and individual variation in sperm parameters, each worker served as his own control. Measurements were made on such

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[7] The 1999 review dated December 16, 1999 (D249804 and D260965) provides a summary of the study protocol and results.

[8] Tomenson JA et al (1999) An assessment of fertility in male workers exposed to molinate. J Occup Environ Med 41(9):771-87.

reproductive structure and function indicators as: sperm concentration, motility score, percent normal morphology, percent non-motility, percent live, serum FSH, LH and testosterone. Questionnaire data were also collected on fertility and infertility from 222 wives of workers.

Exposure assessment was based on 660 personal and 335 area air monitoring samples that were collected the year before or during the study period.

The study author concluded "the reanalysis of the study data has provided no evidence of a real molinate exposure effect on sperm or serum hormone parameters despite the use of a wide range of statistical approaches and characterizations of exposure and effect. Supplemental analyses of the fertility or the wives of employees and seasonality patterns of births also provided no indication of a molinate exposure effect."

HED concluded that there was a small decrease in the observed compared to expected number of children at parity 3 and 4+, especially for the high exposure classification, both between production cycles and during peak production exposure. These results are suggestive of a possible effect for the high-exposure group, and a number of subtle questions and issues remain to be clarified. Those issues are as follows:

• Participation Rate. At 49%, the study participation rate is low, and this could introduce error/bias. Study participation rates are needed by population strata, including more highly exposed workers and families at higher parity. A participation rate above 85% is desired. The lower response rate precludes total reliance on this one molinate epidemiology study to make any sweeping health and safety claims. In addition, there was a difference in the demographics of the three plants. At Richmond and Cold Creek, the workers were 75 and 78% white, respectively, whereas those at North Little Rock were 62% black and 10 years younger.

• Exposure Timing and Variability. Job title is an imprecise but commonly used surrogate for actual exposure measurements. The same job title may be associated with different levels of exposure depending on personal hygiene practices and proximity to other concurrent exposures. In addition, molinate was not the only chemical produced or formulated at the various plants.

Within worker variability is not fully examined. The study design is reasonable for the 1980's with multiple testing of the same person. The study does not address timing of exposure adequately and changes in biomarkers, such as increases in FSH via feedback in shorter intervals than 4-6 months. These would not be detected in the intermittent screening of the current design.

• Confidence Intervals. There should be a shift in presentation of results to measure

effects of molinate with characterization of the precision of estimates with confidence intervals not significance testing of patterns and coefficients.

• Chronic Low Level Exposure. Estimates of exposure for each area/job are given. The highest exposure for an area/job was 633 $\mu g/M^3$ (geometric mean TWA), and at each site at least one value reached 250 $\mu g/M^3$. The highest cumulative exposure for a single period of study was 230,000 $\mu g/M^3$.

The current results do not differentiate workers with changing exposure and a possible better outcome compared to chronic low level exposure.

• Confounders. No explanation is given for the marked variability in responses in workers in formulation plants compared production plants.

• Study Power. Study power for analysis is weak for Cold Creek and North Little River plants which raises concerns about the Generalized Estimating Equation (GEE) statistical analysis.

Additional comments regarding the study report can be found in the December 16, 1999 review.

HED recommendations based on review of the epidemiology study:

Molinate is used for weed control in rice fields world-wide (India, Iran, Japan, China, Philippines, Australia, Hungary, Italy, Spain) in addition to various U.S. rice growing regions. In these other countries, use of protective equipment and label compliance are unpredictable and cannot be assured. Any adverse male reproductive health effects could go unreported or under reported. Therefore, prudent public health measures are advised, including labeling products with the National Pesticide Telecommunications Network international phone number or equivalent poison control center in country number to facilitate the use of existing health surveillance and disease reporting system for pesticide poisoning prevention. Reporting of incidents to a central organization would serve as an international biomonitoring of workers exposed to molinate.

Moreover, pesticide poisoning surveillance reporting on adverse health effects is very uneven globally, and efficacy of multi-lingual translations of worker protection label precautionary measures world-wide is uncertain. Therefore, publication of all human health findings from the molinate epidemiology study in the open epidemiologic literature is recommended as a normal part of prudent public health practice and good product stewardship. Given the worldwide use of this chemical, such precautional measures are one responsible way to demonstrate a commitment to public health.

4.6 Incident Data

A review of the incidents of human adverse effects reported with molinate exposure

was prepared by Dr. Ruth Allen (D262407, January 14, 2000). Four separate data bases were consulted with the following results:

1) OPP Incident Data System (IDS) - reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or enough documentation risk mitigation measures may be suggested.

There were 11 incidents in IDS. Two involved ecological (aquatic) effects. Four reported molinate detections in water in California. One was for molinate residues on rice. Two were summaries of incident reports involving multiple pesticides; no details were provided. In an incident from 1999, according to pesticide industry reports, molinate was reportedly associated with 7 individual incidents, including eye irritation and swelling, hives, second degree burns, kidney problems, and ear infections. In another 1999 incident, after molinate was sprayed on rice fields next to a house, dizziness in the whole family was reported due to over spraying.

2) Poison Control Centers - as the result of a data purchase by EPA, OPP received Poison Control Center data covering the years 1993 through 1996 for all pesticides. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 65-70 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc.

A total of 2 exposures were reported to the Toxic Exposure Surveillance System of the American Association of Poison Control Centers. Both cases were in adults. One case did not receive follow up but potentially had moderately toxic effects and the other had symptoms judged unrelated to their exposure. This is too few cases to permit meaningful comparisons with other pesticides.

3) California Department of Food and Agriculture (replaced by the Department of Pesticide Regulation in 1991) - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

There are 13 total reported incidents for molinate. This includes 10 incidents for molinate alone, and 3 incidents for molinate with combinations, including copper sulfate, thiobencarb, and/or bensulfuron methyl.

Eye irritation, burning pain, and/or blurred vision were reported in 1 molinate and two molinate mixture cases. Skin irritation, including rash on contact with dust were reported in 2 molinate and 1 molinate mixture case. These cases were mainly in workers, including flaggers and applicators.

Systemic and respiratory symptoms were reported for 5 molinate cases, including coughing, dizziness, vomiting, nausea, and/ or mild perspiration.

In 1991, a case included non-occupational exposure to molinate when store merchandise was delivered on molinate contaminated pallets and 3000 people were evacuated by the fire dept. from the store with a few being seen by doctors. Also in 1991, a non-employee doing a demonstration at a store developed mild nausea, headaches and dizziness when exposed to the odor of molinate.

In 1992 a shop worker exposed to molinate fumes from a mixer/loader 150 feet away became ill with shortness of breath, headaches and nausea.

In1996, a worker loading a crop duster with molinate experienced eye problems and pain, sought medical help two days later, but the ophthalmologist could not determine the cause of the eye injury, pain and redness in both eyes.

A total of 13 days off work and 0 days hospitalized were reported.

4) National Pesticide Telecommunications Network (NPTN) - NPTN is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.

On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, molinate was not reported to be involved in human incidents.

In summary, the only data base which would provide an accurate gauge of poisoning incidents in workers exposed to molinate is the one from California. Although the number of incidents was small, there were reports of both local and systemic effects. Also, there was no assessment of the number of incidents in relation to the amount of molinate used in the state. No appropriate data bases assess worker incidents in the southern U.S. where rice is also grown.

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

An aggregate exposure risk assessment was prepared for dietary exposure to food and water. These assessments apply only to rice-growing areas. EFED has determined that the monitoring data are suitable for quantification of drinking water risks. Using the suggested raw water concentrations for both ground and surface water and the dietary exposure from DEEM™, HED calculated the percentage of the Population Adjusted Dose (PAD) for acute and chronic risk assessments. The following equations were used:

Adult Males $\quad \text{Water Exposure (mg/kg/day)} = \dfrac{\text{Concentration of water (ug/L)} \times 10^{-3}\,\text{(mg/ug)} \times 2\ \text{L/day}}{70\ \text{kg}}$

Adult Females $\quad \text{Water Exposure (mg/kg/day)} = \dfrac{\text{Concentration of water (ug/L)} \times 10^{-3}\,\text{(mg/ug)} \times 2\ \text{L/day}}{60\ \text{kg}}$

Children $\quad \text{Water Exposure (mg/kg/day)} = \dfrac{\text{Concentration of water (ug/L)} \times 10^{-3}\,\text{(mg/ug)} \times 1\ \text{L/day}}{10\ \text{kg}}$

$$\text{Percentage of PAD} = \frac{\text{Aggregate Exposure (Food + Water) (mg/kg/day)}}{\text{PAD (mg/kg/day)}} \times 100$$

For ground water, EFED determined that 0.087 ug/L (0.056 x 1.56) should be used as an estimate of total residues of molinate in drinking water for acute and chronic aggregate risk assessments. For surface water, HED performed the risk assessment calculations using the data from West Sacramento, California as a worse case [3.32 ug/mL (2.13 x 1.56) for acute exposure and 0.64 ug/mL (0.41 x 1.56) for chronic exposure)].

For food exposure, separate calculations were done for adult males (using general population food exposure), adult females (using females 13-50 food exposure) and children (using infants < 1 year food exposure) for acute (using the 99.9 percentile) and chronic risk assessments.

Greater than 100% of the PAD for the aggregate exceeds the Agency's level of

concern. The data are presented in Table 5.

The percentage of the aPAD for acute aggregate exposure to molinate in food and surface water for children (110%) exceeded the Agency's level of concern. However, HED believes this assessment may overestimate the risk and that refinement of the exposure to either food or water exposure may bring the risks into an acceptable range. The anticipated residues of food were based on field trial residues. Monitoring studies closer to the point of consumption or cooking studies would refine exposure. Better monitoring data for molinate and its metabolites and degradates in water would also refine the risks.

Table 5: Percentage of Population Adjusted Dose (PAD) for Aggregate Dietary (Food and Water) Exposure

Water Exposure (mg/kg/day)			Food Exposure (mg/kg/day)	aPAD/cPAD (mg/kg/day)	Percentage of PAD	
	Molinate	Molinate + Metabolites[a]			Molinate	Molinate + Metabolites[a]
Acute Risk Assessment - Surface Water						
Adult Males	0.000061	0.000095	0.000186	0.0006	41%	47%
Adult Females	0.000071	0.00011	0.000152	0.0006	37%	44%
Children	0.00021	0.00033	0.000328	0.0006	90%	110%*
Acute Risk Assessment - Ground Water						
Adult Males	0.0000016	0.0000025	0.000186	0.0006	31%	31%
Adult Females	0.0000019	0.0000030	0.000152	0.0006	26%	26%
Children	0.0000056	0.000087	0.000328	0.0006	56%	56%
Chronic Risk Assessment - Surface Water						
Adult Males	0.000012	0.000019	0.000005	0.0001	17%	24%
Adult Females	0.000014	0.000022	0.000004	0.0001	18%	26%
Children	0.000041	0.000064	0.000018	0.0001	59%	82%
Chronic Risk Assessment - Ground Water						
Adult Males	0.0000016	0.0000025	0.000005	0.0001	7%	8%
Adult Females	0.0000013	0.0000029	0.000004	0.0001	5%	7%
Children	0.0000056	0.0000087	0.000018	0.0001	24%	27%

a Water exposure values were increased by 56% to account for metabolites not included in the monitoring data.

* >100% exceeds the Agency's level of concern.

6.0 DATA NEEDS

Product Chemisty: the registrant must submit additional studies as described below before all guideline requirements can be considered fulfilled.

- A revised Confidential Statement of Formula (Form 8570-4; the most recent one is dated 11/87).
- The identity and source of a catalyst used in the production is required.
- An explanation on how the upper certified limits for certain impurities were derived.
- Quantitative data demonstrating the stability of the TGAI upon exposure to metals and metal ions are required.
- Data pertaining to the UV/visible absorption of the PAI are required (GLN 830.7050).

Residue Chemistry: Studies which are outstanding include multiresidue method testing for molinate, 4-hydroxy molinate, and molinate acid and data on residues in irrigated crops for molinate, 4-hydroxy molinate, and molinate acid, molinate sulfoxide, and molinate sulfone.

APPENDIX

Table 1. Toxicology Profile of Molinate			
Guideline [§/OPPTS]	Study Type	MRID #	NOAEL/LOAEL
81-1/870.1100	acute oral - rats	40593301	see Table 1: Acute Toxicity of Molinate
81-2/870.1200	acute dermal - rabbits	40593301	see Table 1: Acute Toxicity of Molinate
81-3/870.1300	acute inhalation - rats [0.06, 0.12, 0.28, 0.83, 0.9, 1.6, 2.2, 2.4, 2.8, 4.0, & 4.9 mg/L] mouse (0.034, 0.09, 0.23, 1.1, 1.8, 2.0, 2.3, & 3.2 mg/L)	00245675	NOAEL hindleg weakness = 0.12 mg/L LOAEL hindleg weakness = 0.28 mg/L. NOAEL ataxia = 2.4 mg/L LOAEL ataxia = 2.8 mg/L NOAEL aggression/hyperexcitability = 0.83 mg/L LOAEL aggression/hyperexcitability = 0.9 mg/L no NOAEL for depression/leg weakness. NOAEL decreased testes weight = 1.8 mg/L LOAEL decreased testes weight = 2.0 mg/L NOAEL microscopic lesions of testes = 1.1 mg/L LOAEL microscopic lesions of testes = 1.8 mg/L
81-4/870.2400	primary eye irritation	40593301	see Table 1: Acute Toxicity of Molinate
81-5/870.2500	primary dermal irritation	00247547	see Table 1: Acute Toxicity of Molinate
81-6/870.2600	dermal sensitization	40593302	see Table 1: Acute Toxicity of Molinate
81-7/870.6100	acute delayed neurotoxicity - hen	00133562 43136601	NOAEL = 200 mg/kg LOAEL = 630 mg/kg, based on axonal degeneration in brain & spinal cord [delayed neurotoxicant]
81-8/870.6200	acute neurotoxicity - rat	43188001	no NOAEL; LOAEL = 25 mg/kg, based on decreased motor activity & increased time to tail flick; ChE activity, NTE, & GFAP were not assessed at appropriate times immediately after dosing
82-1/870.3100	subchronic feeding - rats	-	-
82-1/870.3150	subchronic feeding - dog 12-week fertility - male monkey [0.2, 10, 50 mg/kg/day]	- 00246520 42361302	- NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day, based on decreased plasma ChE activity [brain ChE not measured]. Repeat study NOAEL 0.2 mg/kg/day LOAEL 10 mg/kg/day, based on decreased RBC ChE [brain ChE not affected]

Table 1. Toxicology Profile of Molinate			
Guideline [§/OPPTS]	Study Type	MRID #	NOAEL/LOAEL
82-2/870.3200	21-day dermal - rabbits [10, 25, 50 mg/kg/day[	40990601	no NOAEL for RBC ChE inhibition. NOAEL skin effects = 10 mg/kg/day LOAEL skin effects = 25 mg/kg/day, based on skin irritation & acanthosis
82-4/870.3465	90-day inhalation - rodent [2, 10, 50 mg/m^3[4-week inhalation [0.1, 0.2, 0.4, 0.8, 1.6 mg/m^3]	00241965 41589203	no NOAEL; LOAEL = 0.002 mg/L, based on testicular degeneration & abnormal spermatoza, a dose-related decrease in mean number of implantations & mean number of fetuses NOAEL = 0.0003 mg/L; LOAEL = 0.0006 mg/L, based on decreased number of implants & increased % abnormal sperm
82-5/870.6200	subchronic neurotoxicity - rats [50, 150, 450 ppm; males 4, 11.7, 35.5/females 4.5, 13.9, 41 mg/kg/day]	43270701 43965901	no NOAEL; LOAEL = males 4/females 4.5 mg/kg/day, based on decreased brain & RBC ChE activity and decreased NTE in both sexes at all dose levels
83-1(a)/870.4100	chronic toxicity - rats [7, 40, 300 ppm (males: 0.3, 1.8, 13/ females 0.4, 2, 15 mg/kg/day] for 24 months; 600 ppm [≈30 mg/kg/day[for 12 months	41815101	no NOAEL for neurotoxic effects; NOAEL = 7 ppm [males 0.3/females 0.4 mg/kg/day] LOAEL = 40 ppm [males 1.8/females 2.0 mg/kg/day], based on ovarian lesions; at HDT [300 ppm (males 13/females 15 mg/kg/day)] degeneration w/ atrophy of testes & decreased testes weight
83-1(b)/870.4100	chronic toxicity - dog [1, 10, 50 mg/kg/day for 1 year; **100 mg/kg/day for 14 weeks**[	41781101	no NOAEL for neurotoxic effects; NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day, based on decreased BWG, anemia, decreased ejaculate volume & decreased % mobile sperm & increased adrenal weight [both sexes]
83-2/870.4200	carcinogenicity - mice [10, 100, 1000, 2000 ppm [males 1, 10.4, 105, 200 mg/kg/day,/ females 1.3, 13.9, 133, 249 mg/kg/day[	41809201	NOAEL [testicular effects] = 10 ppm [1.0 mg/kg/day]; LOAEL [testicular effects] = 100 ppm [10.4 mg/kg/day[, based on testicular degeneration NOAEL [other effects] = 100 ppm [males 10.4/females 13.9 mg/kg/day] LOAEL [other effects] = 1000 ppm [males 105/females 133 mg/kg/day, based on decreased survival, BW/BWG/FC, increased incidence of non-neoplastic lesions in brain, spinal cord, sciatic nerve & ovaries

Table 1. Toxicology Profile of Molinate			
Guideline [§/OPPTS]	Study Type	MRID #	NOAEL/LOAEL
83-3(a)/870.3700	developmental toxicity - rat [2.2, 35, 140 mg/kg/day]	41473401	maternal NOAEL = 35 mg/kg/day maternal LOAEL = 140 mg/kg/day, based on decreased BW/BWG/FC, increased salivation & dehydration, RBC ChE inhibition. developmental NOAEL = 2.2 mg/kg/day developmental LOAEL = 35 mg/kg/day, based on increase in runting
83-3(b)/870.3700	developmental toxicity - rabbits [0, 2, 20, 200 mg/kg/day]	14021015	maternal NOAEL = 20 mg/kg/day maternal LOAEL = 200 mg/kg/day, based on increased abortions, decreased [negative] BWG during days 14-21, & increased liver weight. developmental NOAEL = 20 mg/kg/day developmental LOAEL = 200 mg/kg/day, based on a delay in fetal development as evidenced by reduced ossification of sternebrae.
	13-week oral - male rabbit [40, 80, 160/120 mg/kg/day	42361301	male fertility NOAEL = 40 mg/kg/day male fertility LOAEL = 80 mg/kg/day, based on sperm effects [increased incidence of atypically-stained heads in ejaculated & epididymal sperm samples[
	8-week oral - male rabbit [10, 100 for 49 days, 200 mg/kg/day for 16 days]	42361304	deaths at 100 & 200 mg/kg/day [fertility assessed only during week 4; limited data at 100 mg/kg/day suggest a reduction in male fertility associated w/ an increased incidence of sperm abnormalities [total & midpiece] & increase in preimplantation loss & decrease in # live fetuses at week 4 due to poor survival, no definitive statement possible w/ respect to male rabbit fertility
	12-week oral - male rabbit [10, 100, 200 mg/kg/day]	42361305	no deaths at ≤250 mg/kg/day; no NOAEL for RBC ChEI LOAEL = 300 mg/kg/day , based on deaths
	28-day oral - male rabbit 2 range-finding studies [100, 200, 300 mg/kg/day] [40, 100, 250 mg/lg/day]	42361306 42361307	

Table 1. Toxicology Profile of Molinate			
Guideline [§/OPPTS]	Study Type	MRID #	NOAEL/LOAEL
83-4/870.3800	2-generation reproduction - rats [both sexes dosed] [♂ 5, 10, 15 ppm (0.4, 0.8, 1.3 mg/kg/day/♀ 20, 50, 300 ppm (1.9, 4.7, 28.8 mg/kg/day)]	44403201	no NOAEL for decreased brain weight LOAEL for decreased brain weight = 5 ppm/20 ppm [males 0.4/females 1.9 mg/kg/day] paternal NOAEL = 5 ppm [0.4 mg/kg/day] paternal LOAEL = 10 ppm [0.8 mg/kg/day], based on increased incidence of abnormal sperm & decreased right cauda weight in F0 males. maternal NOAEL = 20 ppm [1.9 mg/kg/day] maternal NOAEL = 50 ppm [4.7 mg/kg/day], based on microscopic lesions in the ovary & adrenal. neonatal NOAEL = 5 ppm/20 ppm [males 0.4/females 1.9 mg/kg/day] neonatal LOAEL = 10 ppm/50 ppm [males 0.8/females 4.7 mg/kg/day], based on decreased brain weight in F2B females, decreased testes & spleen weights in F1A males, & delayed vaginal opening in females. reproductive NOAEL = 5 ppm/20 ppm [males 0.4/ females 1.9 mg/kg/day] reproductive LOAEL = 10 ppm/50 ppm [males 0.8/ females 4.7 mg/kg/day], based on microscopic lesions in ovary, increased incidence of abnormal sperm morphology [both generations], decreased absolute right cauda weight [F0 males], decreased % pups born live [F1A & F2B], decreased F2B survival & decreased litter size [F1A, F2A, F2B] maternal NOAEL = 6 ppm [0.34 mg/kg/day] maternal LOAEL = 50 ppm [2.9 mg/kg/dny], based on decreased fecundity [F1], increased incidence of vacuolation/hypertrophy of ovary, decreased brain weight [F1 females].
	[only females dosed] [6, 50, 450 PPM]	41333402	reproductive NOAEL = 6 ppm [0.34 mg/kg/day] reproductive LOAEL = 50 ppm [2.9 mg/kg/day], based on occurrence of vacuolation/hypertrophy of ovary. neonatal NOAEL = 6 ppm [0.34 mg/kg/day] neonatal LOAEL = 50 ppm [2.9 mg/kg/day], based on ovarian lesions.
83-5/870.4300	chronic toxicity/carcinogenicity - rat	41815101	see under chronic rat

Table 1. Toxicology Profile of Molinate			
Guideline [§/OPPTS]	Study Type	MRID #	NOAEL/LOAEL
83-6/870.6300	developmental neurotoxicity - rat [0, 20, 75, and 300 ppm (0, 1.8, 6.9, and 26.1 mg/kg/day]	44079201	maternal toxicity NOAEL = 75 ppm [6.9 mg/kg/day] maternal toxicity LOAEL = 300 ppm [26.1 mg/kg/day], based on decreased BW/BWG/FC. no NOAEL for developmental neurotoxicity developmental neurotoxicity LOAEL* = 20 ppm [1.8 mg/kg/day], based on a reduction in startle amplitude in auditory startle test in females on day 23
84-2/870.5100	gene mutation	40918301	-
84-2/870.5375	chromosomal aberration	40946701	-
84-2/870.5300	*in vitro* mammalian cell gene mutation	00163790	-
84-2/870.5550	unscheduled DNA synthesis	41052701 43192301	- -
84-2/870.5450	dominant lethal assay	43986701 44562201	-
85-1/870.7485	metabolism	41781801-41781805	-
85-2/870.7600	dermal penetration	43284101	-
86-1\870.7200	domestic animal safety	-	-

none	5-week fertility [males]
	[0.2, 4, 12, 30, 60 mg/kg/day]
	7-week gavage [males]
	[2, 20, 100, 200 mg/kg/day]
		00245675	NOAEL = 0.2 mg/kg/day
			LOAEL = 4 mg/kg/day, based on decreased % viable sperm % normal sperm, sperm counts, # implants, # viable fetuses, increased resorptions & pre-implantation loss
			NOAEL = 20 mg/kg/day
			LOAEL = 100 mg/kg/day, based on decreased male fertility, # implants, # fetuses/pregnancy

none	vaginal opening [day 7 gestation til day 22 post partum] [300 ppm]	44373601	no NOAEL [only one dose] LOAEL = 300 ppm, based on delayed vaginal opening.
none	male fertility [5 weeks] [0.5, 1, 2, 3, 4, 8 mg/kg/day]	43158202	no NOAEL LOAEL 0.5 mg/kg/day, based on increased incidence of headless sperm, midpiece abnormality, tail abnormality, total abnormal sperm

Table 1. Toxicology Profile of Molinate			
Guideline [§/OPPTS]	Study Type	MRID #	NOAEL/LOAEL
none	mechanistic study - female [gestation days 7-10] [75, 135, 200 mg/kg/day]	42361308	no NOAEL for microscopic lesions in adrenal cortex & ovary; no evidence of effect on ability to maintain a pregnancy, no deaths at 75 mg/kg/day.

♪there is a chronic study available; ♬ ChEI was not monitored; √ only females were administered Molioate;

✖ a 28-day hen study is not available; ✂ NTE, ChE, GFAP activities were not assessed at appropriate times

* altered by HIARC and Toxicology Science Assessment Committee from original Data Evaluation Record

Table 2. Exposure and Risk Assessment for Workers Loading Granulars into Airplane Hoppers from Biomonitoring Study

Using actual exposure from biomonitoring study (MRID 43165602)							
Task	PPE	lb ai handled/ 3 days (mean)	mean body wt (kg)	mg/lb ai handled (geometric mean)	Daily Dose[1] mg/kg/day (geometric mean)	Short-term MOE[2]	Intermediate-term MOE[3]
Dir-Lo	Tyvek	2797	95.0	0.000676	0.0062	290	33
	Carbon	1927	94.7	0.000469	0.0028	660	73
Both	Tyvek	2462	90.9	0.000839	0.0065	280	31
	Carbon	3264	85.7	0.000948	0.0116	160	17
Driver	none	-	82.7	-	0.00081	2,200	250
	carbon	-	81.0	-	0.00059	3,000	340

[1] see Tables 1 through 4 of Appendix C of Occupational/Residential Exposure Chapter

[2] Short-term MOE = Oral LOAEL (1.8 mg/kg/day)/ Daily Dose (mg/kg/day)

[3] Intermediate-term MOE = Oral LOAEL (0.2 mg/kg/day)/ Daily Dose (mg/kg/day)

Using default body weight of 70 kg and unit exposures normalized to mg/lb ai handled									
Task	PPE	lb ai handled/ day		mg/lb ai handled	Default body wt (kg)	Daily Dose[1] mg/kg/day		Short-term MOE[2]	Intermediate-term MOE[3]
		Max	Avg			w\ Max lb ai/day	w\ Avg lb ai/day		
Dir-Lo	Tyvek	1,680	900	0.000676	70	0.0162	0.0087	110	12
Dir-Lo	Carbon	1,680	900	0.000469	70	0.0113	0.0060	160	18
Both	Tyvek	1,680	900	0.000839	70	0.0201	0.0108	90	10
Both	Carbon	1,680	900	0.000948	70	0.0227	0.0122	80	9

[1] Daily Dose (mg/kg/day) = [Max use rate (lb ai handheld/day) x Unit exposure (mg/lb ai handled)] /Body weight

[2] Short-term MOE = Oral LOAEL (1.8 mg/kg/day)/ Daily Dose (mg/kg/day)

[3] Intermediate-term MOE = Oral LOAEL (0.2 mg/kg/day)/ Daily Dose (mg/kg/day)

Table 3. Exposure and Risk Assessment for Workers Loading Liquids into Airplane Hoppers from Biomonitoring Study

Using actual exposures from biomonitoring study (MRID 44212201)							
Work Task	PPE	lb ai [1] handled/ 3 days	Body weight [1] (mean)	Unit exposure [1] mg/lb ai handled (geometric mean)	Daily Dose [1] mg/kg/day (geometric mean)	Short-term MOE[2]	Intermediate-term MOE[3]
Loading Arrosolo (liquid)	Level 1: Activated carbon suit worn underneath 'Kleenguard' coveralls	839	83	0.00076	0.0072	250	28
	Level 2: 'Kleenguard' coveralls worn over normal work clothing	857	82	0.00117	0.0111	162	18
	Level 3: Normal work clothing, recommended as long sleeved shirt and long pants	750	82	0.00340	0.0284	63	7

[1] see Tables 1 through 4 of Appendix D of the Occupational/Residential Exposure Chapter

[2] Short-term MOE = Oral LOAEL (1.8 mg/kg/day)/ Daily Dose (mg/kg/day)

[3] Intermediate-term MOE = Oral LOAEL (0.2 mg/kg/day)/ Daily Dose (mg/kg/day)

Using default body weight of 70 kg, loading rate of 900 lb ai/day, and unit exposures normalized to mg/lb ai handled									
Work Task	PPE	lb ai/ day		body wt (kg)	Unit exposure mg/lb ai handled (geometric mean)	Daily Dose[1] mg/kg/day		Short-term MOE[2]	Intermediate-term MOE[3]
		Max	Avg			w\ Max lb ai/day	w\ Avg lb ai/day		
Loading Arrosolo (liquid)	Level 1: Activated carbon suit worn underneath 'Kleenguard' coveralls	900	300	70	0.00076	0.0098	0.0033	184	20
	Level 2: 'Kleenguard' coveralls worn over normal work clothing	900	300	70	0.00117	0.0150	0.0050	120	13
	Level 3: Normal work clothing, recommended as long sleeved shirt and long pants	900	300	70	0.00340	0.0437	0.0146	41	5

[1] Daily Dose (mg/kg/day) = [Use rate (lb ai handheld/day) x Unit exposure (mg/lb ai handled)] /Body weight

[2] Short-term MOE = Oral LOAEL (1.8 mg/kg/day)/ Daily Dose (mg/kg/day)

[3] Intermediate-term MOE = Oral LOAEL (0.2 mg/kg/day)/ Daily Dose (mg/kg/day)

Table 4: Numerical Inputs from PHED Version 1.1 Used for Molinate Handler Exposure Assessment

No.	Exposure Scenario	Unit Exposures from Pesticide Surrogate Exposure Guide (8/98)						Application Parameters			
		Baseline[a]		Additional PPE[b]		Engineering Controls[c]					
		Dermal (µg/lb ai)	Inhalation (µg/lb ai)	Dermal (µg/lb ai)	Inhalation (µg/lb ai)	Dermal (µg/lb ai)	Inhalation (µg/lb ai)	Application Rate (lb ai/A)[d]		Area Treated (acre/day)[e]	Application Days/year
								Maximum	Typical		
Aerial Applications -Granulars:											
3	pilots applying granulars using aerial equipment	na	na	na	na	1.7	1.3	5	4	300	27
4	flagging during aerial application of granulars	2.75 (single layer, no gloves)	0.15 (single layer, no gloves)	1.17 (additional layer, no gloves)	0.0075 (full-face resp)	0.0462 (enclosed truck cab)	0.003 (enclosed truck cab)	5	4	300	27
Aerial Applications- Liquids:											
6	pilots applying liquids using aerial equipment	na	na	na	na	5.0 (single layer, no gloves, close cab)	0.068 (single layer, no gloves, close cab)	3	3	300	25
7	flagging during aerial application of liquids	11.0 (single layer, no gloves)	0.35 (single layer, no gloves)	10.22 (additional layer, no gloves)	0.018 (full-face resp)	0.22 (single layer, no gloves, enclosed truck cab)	0.007 (single layer, no gloves, enclosed truck cab)	3	3	300	25

No.	Exposure Scenario	Unit Exposures from Pesticide Surrogate Exposure Guide (8/98)						Application Parameters			
		Baseline[a]		Additional PPE[b]		Engineering Controls[c]					
		Dermal (µg/lb ai)	Inhalation (µg/lb ai)	Dermal (µg/lb ai)	Inhalation (µg/lb ai)	Dermal (µg/lb ai)	Inhalation (µg/lb ai)	Application Rate (lb ai/A)[d]		Area Treated (acre/day)[e]	Application Days/year
								Maximum	Typical		
Ground Applications -Granulars:											
8	loading granulars for ground-based applications	6.9 (single layer, gloves, open mixing)	1.7 (single layer, gloves, open mixing)	3.4 (additional layer, gloves)	0.085 (full-face resp)	NF	NF	5	4	80	30
9	applying granulars using ground-based equipment	7.2 (single layer, gloves, open cab)	1.2 (single layer, gloves, open cab)	4.18 (additional layer, gloves)	0.06 (full-face resp)	2.0 (single layer, gloves, enclosed truck cab)	0.220 (single layer, gloves, enclosed truck cab)	5	4	80	30
Ground Applications- Liquids:											
10	mixing/loading liquids for ground-based applications	23 (single layer, gloves, open mixing)	1.2 (single layer, gloves, open mixing)	17.5 (additional layer, gloves)	0.06 (full-face resp)	8.6 (single layer, gloves, closed mixing system)	0.083 (single layer, gloves, closed mixing system)	3	3	80	30
11	applying liquids using ground-based equipment	14 (single layer, gloves, open cab)	0.74 (single layer, gloves, open cab)	11.0 (additional layer, gloves)	0.037 (full-face resp)	5.1 (single layer, gloves, closed cab)	0.43 (single layer, gloves, closed cab)	3	3	80	30

"No Data" or '"na" indicates that no appropriate data are available for incorporation into this cell. "N/F" indicates that this exposure scenario is not considered feasible by HED due to engineering or other practical considerations (e.g., an open cockpit aerial application scenario is not considered feasible as aircraft appropriate for this use are not manufactured with open cockpits).

a Baseline clothing and PPE scenario: Workers wearing single layer clothing, chemical resistant gloves, and no respirator. Also open cab for applicators and flaggers.

Exceptions are noted on an individual basis.

b PPE: Workers typically wear double layer of clothing, chemical resistant gloves, and respirator. Exceptions are noted on an individual basis.

c Engineering controls: Workers wearing single layer clothing and no gloves while using an appropriate engineering control system (e.g., closed mixing, enclosed cabs).

d See **Section 3.2.3.** for derivation of application rates.

e HED believes these values represent a reasonable estimation of the median to upper percentile of what can be treated in a single day based on the exposure scenario of concern. Users of this table are cautioned to note that these values are based on professional judgement when appropriate data are not available.

Table 5. Non-Cancer Risks For Occupational Molinate Handlers at **Baseline Clothing Scenario** (Unit Exposures from PHED)

No.	Exposure Scenario	Absorbed Daily Dose using Max Application Rate (mg/kg/day)		Short-Term Risk (MOE)			Intermediate-Term Risk (MOE)		
		Dermal [a]	Inhalation [b]	Dermal [c]	Inhalation [d]	Combined [e]	Dermal [f]	Inhalation [g]	Combined [h]
	Aerial Applications -Granulars:								
3	pilots applying granulars using aerial equipment								
4	flagging during aerial application of granulars	0.0236	0.0032	76	6500	25	8	24	6
	Aerial Applications- Liquids:								
6	pilots applying liquids using aerial equipment								
7	flagging during aerial application of liquids	0.0566	0.0045	32	4600	11	4	17	3
	Ground Applications -Granulars:								
8	loading granulars for ground-based applications	0.0158	0.0097	110	2200	38	13	8	5
9	applying granulars using ground-based equipment	0.0165	0.0069	110	3000	36	12	11	6
	Ground Applications- Liquids:								
10	mixing/loading liquids for ground-based applications	0.0315	0.0041	57	5100	19	6	19	5
11	applying liquids using ground-based equipment	0.0192	0.0025	94	8200	31	10	31	8

"No Data" indicates that no appropriate data are available for incorporation into this cell. "N/F" indicates that this exposure scenario is not considered feasible by HED due to engineering or other practical considerations (e.g., an open cockpit aerial application scenario is not considered feasible as aircraft appropriate for this use are not manufactured with open cockpits). N/A indicates that an appropriate risk level has been obtained and there is no need for imposition of a more protective level of risk mitigation.

[a] Absorbed daily dermal dose (mg/kg/day) = $\frac{\text{unit exposure (µg/lb ai)*(1E-3 mg/ug) unit conversion * application rate (lb ai/A) * acres treated (acres/day) * dermal absorption (40\%)}}{\text{body weight (70 kg)}}$

[b] Absorbed daily inhalation dose (mg/kg/day) = $\frac{\text{unit exposure (µg/lb ai) *1E-3 mg/ug * application rate (lb ai/A) * acres treated (acres/day) * inhalation absorption (100\%)}}{\text{body weight (70 kg)}}$

[c] Short-Term Dermal MOE = [LOAEL (1.8 mg/kg/day)] /absorbed daily dose (mg/kg/day). MOEs < 300 indicate a risk concern

[d] Short-Term Inhalation MOE = NOAEL (20.9 mg/kg/day)/absorbed daily dose (mg/kg/day). MOEs < 100 indicate a risk concern

$$\text{Combined MOE} = \frac{1}{\frac{1}{\frac{(\text{Dermal MOE})}{3}} + \frac{1}{(\text{Inhalation MOE})}}$$

[f] Intermediate-Term Dermal MOE = NOAEL (0.2 mg/kg/day)/absorbed daily dose (mg/kg/day). MOEs < 100 indicate a risk concern.

[g] Intermediate-Term Inhalation MOE = NOAEL (0.078 mg/kg/day)/absorbed daily dose (mg/kg/day). MOEs < 100 indicate a risk concern.

h Combined MOE = 1 ÷ (1/ Dermal MOE) + (1/Inhalation MOE)

Table 6. Non-Cancer Risks For Occupational Molinate Handlers at **Additionat Protective Clothing and PPE to Mitigate Exposures** (Unit Exposures from PHED)

No.	Exposure Scenario	Absorbed Daily Dose using Max Application Rate (mg/kg/day)		Short-Term Risk (MOE)			Intermediate-Term Risk (MOE)		
		Dermal [a]	Inhalation [b]	Dermal [c]	Inhalation [d]	Combined [e]	Dermal [f]	Inhalation [g]	Combined [h]
Aerial Applications -Granulars:									
3	pilots applying granulars using aerial equipment								
4	flagging during aerial application of granulars	0.010	0.00016	180	130,000	60	20	490	19
Aerial Applications- Liquids:									
6	pilots applying liquids using aerial equipment								
7	flagging during aerial application of liquids	0.0526	0.00023	34	90,000	11	4	340	4
Ground Applications -Granulars:									
8	loading granulars for ground-based applications	0.0078	0.00049	230	43,000	77	26	160	22
9	applying granulars using ground-based equipment	0.0096	0.00034	190	61,000	63	21	230	19
Ground Applications- Liquids:									
10	mixing/loading liquids for ground-based applications	0.0240	0.00021	75	100,000	25	8	380	8
11	applying liquids using ground-based equipment	0.0151	0.00013	120	160,000	40	13	620	13

"No Data" indicates that no appropriate data are available for incorporation into this cell. "N/F" indicates that this exposure scenario is not considered feasible by HED due to engineering or other practical considerations (e.g., an open cockpit aerial application scenario is not considered feasible as aircraft appropriate for this use are not manufactured with open cockpits). N/A indicates that an appropriate risk level has been obtained and there is no need for imposition of a more protective level of risk mitigation.

[a] Absorbed daily dermal dose (mg/kg/day) = $\frac{\text{unit exposure (µg/lb ai)*(1E-3 mg/ug) unit conversion * application rate (lb ai/A) * acres treated (acres/day) * dermal absorption (40%)}}{\text{body weight (70 kg)}}$

[b] Absorbed daily inhalation dose (mg/kg/day) = $\frac{\text{unit exposure (µg/lb ai) *1E-3 mg/ug * application rate (lb ai/A) * acres treated (acres/day) * inhalation absorption (100%)}}{\text{body weight (70 kg)}}$

[c]. Short-Term Dermal MOE = [LOAEL (1.8 mg/kg/day)] /absorbed daily dose (mg/kg/day) MOEs < 100 indicate a risk concern

[d] Short-Term Inhalation MOE = NOAEL (20.9 mg/kg/day)/absorbed daily dose (mg/kg/day). MOEs < 100 indicate a risk concern

[e] Combined MOE = $\dfrac{1}{\dfrac{1}{(\text{Dermal MOE})/3} + \dfrac{1}{\text{(Inhalation MOE)}}}$

[f] Intermediate-Term Dermal MOE = NOAEL (0.2 mg/kg/day)/absorbed daily dose (mg/kg/day). MOEs < 100 indicate a risk concern.

[g] Intermediate-Term Inhalation MOE = NOAEL (0.078 mg/kg/day)/absorbed daily dose (mg/kg/day). MOEs < 100 indicate a risk concern.

h Combined MOE = 1 ÷ (1/ Dermal MOE) + (1/Inhalation MOE)

Table 7. Non-Cancer Risks For Occupational Molinate Handlers at **Engineering Controls to Mitigate Exposures** (Unit Exposures from PHED)

No.	Exposure Scenario	Absorbed Daily Dose using Max Application Rate (mg/kg/day)		Short-Term Risk (MOE)			Intermediate-Term Risk (MOE)		
		Dermal [a]	Inhalation [b]	Dermal [c]	Inhalation [d]	Combined [e]	Dermal [f]	Inhalation [g]	Combined [h]
Aerial Applications -Granulars:									
3	pilots applying granulars using aerial equipment	0.0146	0.0279	120	750	39	14	3	2
4	flagging during aerial application of granulars	0.00040	0.000064	4500	330,000	1,500	500	1,200	360
Aerial Applications- Liquids:									
6	pilots applying liquids using aerial equipment	0.0257	0.00087	70	24,000	23	8	89	7
7	flagging during aerial application of liquids	0.0011	0.000090	1600	230,000	530	180	870	150
Ground Applications -Granulars:									
8	loading granulars for ground-based applications	N/F							
9	applying granulars using ground-based equipment	0.0046	0.0013	390	17,000	130	44	62	26
Ground Applications- Liquids:									
10	mixing/loading liquids for ground-based applications	0.0118	0.00028	150	73,000	51	17	270	16
11	applying liquids using ground-based equipment	0.0070	0.0015	260	14,000	86	29	53	19

"No Data" indicates that no appropriate data are available for incorporation into this cell. "N/F" indicates that this exposure scenario is not considered feasible by HED due to engineering or other practical considerations (e.g., an open cockpit aerial application scenario is not considered feasible as aircraft appropriate for this use are not manufactured with open cockpits). N/A indicates that an appropriate risk level has been obtained and there is no need for imposition of a more protective level of risk mitigation.

[a] Absorbed daily dermal dose (mg/kg/day) = $\frac{\text{unit exposure (µg/lb ai)*(1E-3 mg/ug) unit conversion * application rate (lb ai/A) * acres treated (acres/day) * dermal absorption (40\%)}}{\text{body weight (70 kg)}}$

[b] Absorbed daily inhalation dose (mg/kg/day) = $\frac{\text{unit exposure (µg/lb ai) *1E-3 mg/ug * application rate (lb ai/A) * acres treated (acres/day) * inhalation absorption (100\%)}}{\text{body weight (70 kg)}}$

[c] Short-Term Dermal MOE = [LOAEL (1.8 mg/kg/day)] /absorbed daily dose (mg/kg/day). MOEs < 100 indicate a risk concern

[d] Short-Term Inhalation MOE = NOAEL (20.9 mg/kg/day)/absorbed daily dose (mg/kg/day). MOEs < 100 indicate a risk concern

[e] Combined MOE = $\dfrac{1}{\dfrac{1}{\text{(Dermal MOE)}} + \dfrac{1}{\text{(Inhalation MOE)}}}$

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[f] Intermediate-Term Dermal MOE = NOAEL (0.2 mg/kg/day)/absorbed daily dose (mg/kg/day). MOEs < 100 indicate a risk concern.

[g] Intermediate-Term Inhalation MOE = NOAEL (0.078 mg/kg/day)/absorbed daily dose (mg/kg/day). MOEs < 100 indicate a risk concern.

h Combined MOE = 1 ÷ (1/ Dermal MOE) + (1/Inhalation MOE)

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