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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

May 30, 2007

SUBJECT: **Mefluidide, Diethanolamine Mefluidide, and Potassium Mefluidide-Phase 2 (30- Day Error only Correction), HED Chapter of the Re-registration Eligibility Decision Document (RED). PC Code: 114001, 114002, 114003. Reregistration Case No. 2370. DP Barcode D334500.**

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Attached is Health Effect Division's phase II risk assessment for mefluidide RED. This is a revised risk assessment (from phase I) incorporating registrant's error only comments dated May 22, 2007. The team reviewers who contributed to the disciplinary chapters and the risk assessment are listed below:

Hazard Identification Assessment; Abdallah Khasawinah, D322246, 1/31/07.
Occupational and Residential Exposure Assessment; Yan Donovan, D324823, 2/28/07.
Incident Report; M. Hawkins, D324824, 07/25/06.
Drinking Water Assessment; James Hetrick from EFED, D334508, 03/08/07.

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1.0 EXECUTIVE SUMMARY

A risk assessment is being conducted for mefluidide, mefluidide diethanolamine salt, and mefluidide potassium salt to support the mefluidide RED. For the purposes of this assessment, all of the three active ingredients are collectively referred to as mefluidide.

Mefluidide is a member of the class of anilide. Mefluidide is a plant growth regulator that is applied postemergence when needed. It is used to control ornamental and non-ornamental woody plants, ground cover, hedges trees, turf grasses, grass and broadleaf weeds by inhibiting plant cell division, stem elongation and seed head development. It is also registered for growth control of low maintenance turf on rights-of-ways, airports, public and industrial sites. Mefluidide products can also be used on residential lawns. There are multiple active ingredient products that contain an additional plant growth regulator and herbicides such as paclobutrazol, imazapyr, and imazethapyr. These ingredients are not assessed in this document. Current formulations include granular, liquid ready- to- use, and soluble concentrate/liquid. Mefluidide can be applied as a band treatment, broadcast, spot treatment, and spray. The equipment used to apply mefluidide includes backpack sprayer, groundboom, hand held pump sprayer, handgun sprayer, hose-end sprayer, power sprayer, high pressure handwand, and spreader (push-type and belly grinder).

Based on the structural similarities of mefluidide and its diethanolamine (DEA) and potassium salts, where they all share the same anion- anilide, and the physical and chemical properties of the DEA and potassium salts, where they dissociate 100% back to free mefluidide in aqueous environments, the risk assessment team concluded that mefluidide DEA and potassium salts are biologically equivalent to mefluidide and thus they share the same toxicity as the free mefluidide. Therefore, it is reasonable to bridge mefluidide toxicity data to mefluidide salts and vice versa.

The toxicology data base of mefluidide and its salts is considered adequate for the purposes of hazard and dose response assessment. Mefluidide has low acute toxicity by the oral, dermal and inhalation routes (toxicity category III and IV). It is a weak eye or dermal irritant (toxicity category III and IV). Mefluidide did not cause dermal sensitization in the guinea pig. In rats and rabbits, critical effects of acute toxicity were tremors, hunched posture, salivation, reduced body weight and body weight gain.

Subchronic and chronic toxicity of mefluidide is manifested by decreased body weight and body weight gain in several species tested (rats, rabbits and dogs). Dogs appeared to be most sensitive species with the critical toxicological effects of cortical nephrosis and body weight loss. In rats and rabbits, critical effects observed were tremors, hunched posture, salivation, reduced body weight and body weight gain. Based on lack of evidence of carcinogenicity in both rats and mice, mefluidide was considered as not likely to be carcinogenic to humans. Mefluidide exhibited a negative response in various genotoxicity screening assays.

Developmental effects of mefluidide in rats included increased number of early resorptions and mean postimplantation loss. These effects were observed at the same dose that caused maternal toxicity indicating there was no increased susceptibility to fetuses (LOAEL = 115 mg/kg/day, NOAEL = 58 mg/kg/day). The maternal toxicity included tremors, decreased body weight, weight gain and mortality. In rabbit, the LOAEL/NOAEL for developmental toxicity were above the highest dose tested (60 mg/kg/day). Although this study is not acceptable alone, taking into the consideration of the results from the 14-day rabbit oral study where mortality was seen at 100 mg/kg/day, and tremors and 100% mortality were noted at 200 mg/kg/day, the NOAEL from the rabbit developmental study is acceptable. In the 3-generation rat reproduction toxicity study, the offspring toxicity was characterized by decreased body weights in both sexes and both litters in all generations. The reproductive LOAEL was not observed (NOAEL = 346/604 mg/kg bw/day in males and females).

Endpoints and dose responses have been selected for all exposure routes and durations, except for dermal exposure, where it was determined that no quantitative dermal risk assessment is needed.

There are no agricultural or any food related pesticide uses of mefluidide. Therefore, no dietary exposure from food is expected. However, there is potential for drinking water exposure due to the outdoor uses of mefluidide. A drinking water assessment was conducted by the Environmental Fate and Effects Division (EFED) using Tier II (PRZM-EXAMS) for surface water modeling and Tier 1 (SCI-GROW) for groundwater modeling. The mefluidide acid concentrations in surface water are not expected to exceed 32 µg/L (= 32 ppb) for the 1 in 10 year daily peak concentration, 10 µg/L (= 10 ppb) for the 1 in 10 year annual concentration, and 5 µg/L for the 30 year annual average concentration. Mefluidide acid concentrations in ground water are not expected to exceed 1.0 µg/L.

Dietary (Water only) Exposure and Risk Estimates

Acute and chronic dietary (water only) risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM). The dietary exposure assessments were performed using exposures from surface water only, as there are no food uses for this chemical. The estimated surface drinking water concentration (32 ppb) was used in acute dietary while the 10 ppb was used for chronic. The analysis results indicated that the dietary risks are below the Agency's level of concern. At the 95th percentile, the acute dietary exposure to U.S. population was 0.0017 mg/kg/day, which utilized **< 1%** of the acute reference dose (aRfD). The exposure for all infants, which was the most highly exposed population subgroup, was 0.006 mg/kg/day, which utilized **1% of the aRfD**. For chronic dietary exposure, the exposure for U.S. population was 0.0002 mg/kg/day, which utilized **1%** of the chronic reference dose (cRfD). The exposure for all infants, which was the most highly exposed population subgroup, was 0.0007mg/kg/day, which utilized **5% of the cRfD.**

Residential Exposure and Risk Estimates

None of the labels prohibit use by homeowners. The residential handler risks were assessed using standard assumptions, maximum label rates, Outdoor Residential Exposure Task Force (ORETF) studies and Pesticide Handlers Exposure Database (PHED) unit exposure data. The MOEs are all >100, which means the risks are not of concern.

Residential Post Application Exposure and Risk Estimates

Since no dermal endpoints were selected, the residential post- application assessments were only conducted for Children (through incidental oral). Incidental oral exposures include exposures from hand- to- mouth, object- to- mouth and soil ingestion of treated turf (all considered short-term). Calculations used the Residential SOPs and maximum label rates. The combined MOE is >100 which means that the risk is below EPA's level of concern. The residential post- application exposures to toddlers from ingesting granules that have been applied to residential turf were also assessed using a standard method as outlined in the Residential SOPs. The MOE was then calculated using the acute dietary NOAEL of 58 mg/kg/day and it is > 100. This means that the risks for toddler exposures from granular ingestion are not of concern.

Aggregate Risk Assessment (food + water + residential exposure)

Although an aggregate risk assessment is not required under current Agency policies for non-food use chemicals, to ensure that the public health is adequately protected, a screening level aggregate risk assessment was conducted for mefluidide. For acute and chronic aggregate risks, the only exposure is from drinking water. As stated above, the dietary exposures (drinking water only) do not exceed 1% of the aRfD/cRfD for adult and 5% of the aRfD/cRfD for children. For short- term, no aggregate is needed for adults since there are no residential post- application exposures to adults. When considering the dietary exposure (drinking water only) as a background exposure to Children for short-term risk, the level of dietary exposure (0.0007 mg/kg/day from chronic food) is negligible when compared to the combined incidental oral exposure (0.019 mg/kg/day) or the granule ingesting dose (0.098 mg/kg/day). No intermediate-term residential risk was identified. Therefore, short- and intermediate- term aggregate is not of concern.

Occupational Exposure and Risk Estimates

The MOEs for occupational handler exposures were calculated for short/intermediate term inhalation exposures using standard assumptions and unit exposure data. The unit exposure data were taken from the PHED and the ORETF studies for professional lawn care operators. All of the MOEs are > 100 with baseline personal protective equipment (PPE) which means that the risks are not of concern and respiratory protection is not needed.

Occupational post application dermal risks were not assessed because there is not likely to have occupational post-application scenario. In addition, no dermal endpoints were selected. Mefluidide is only applied outdoors and it is not a volatile compound, inhalation exposures are negligible.

Risk Characterization

All MOEs for occupational and residential handlers are greatly above 100. No refinement is needed. The risk assessments for post- application exposures for Children are conservative because they are based upon day 0 TTRs and soil residue values and did not account for dissipation.

Environmental Justice Considerations:

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research:

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies (listed in Appendix B) have been determined to require a review of their ethical conduct, and have received that review.

2.0 INGREDIENT PROFILE

Mefluidide is a plant growth regulator that is applied postemergence when needed. It is used to control the growth of ornamental and non-ornamental woody plants, ground cover, hedges, trees, turf grasses, grass and broadleaf weeds by inhibiting plant cell division, stem elongation and seed head development. It is registered for uses on low maintenance turf on rights-of-ways, airports, and industrial sites. It can also be used on ornamental and or shade trees, ornamental ground cover, ornamental herbaceous plants, golf course, hospitals/medical institutions premises ornamental lawns and turf, and residential lawns. There are multiple active ingredient products that contain an additional plant growth regulator and herbicides such as paclobutrazol, imazapyr and imazethapyr. Current formulations include granular, liquid ready- to- use, and soluble concentrate/liquid. Mefluidide can be applied as a band treatment, broadcast, spot treatment, and spray. The equipment used to apply mefluidide includes backpack sprayer, groundboom, hand held pump sprayer, handgun sprayer, hose-end sprayer, power sprayer, high pressure handwand, and spreader (push-type and belly grinder). The two registrants for mefluidide, PBI/Gordon (technical and end-use registrant) and The Scotts Company (end-use registrant) are supporting all of the existing uses for reregistration on their respective labels.

2.1. Summary of Registered/Proposed Uses

Based on the information provided by the registrant at the 11-08-06 SMART meeting, all existing mefluidide label uses (total 11 product labels) are supported by the registrant. The registrant also indicated that among all labels, only three have active sales: Embark 2S (EPA Reg # 2217-759), Embark T&O (EPA Reg#2217-768), and Stronghold (EPA Reg#2217-802).

HED has analyzed all existing mefluidide product labels. The label suggested use patterns, formulations, application methods and maximum application rates are summarized in Table 2.1 below.

Table 2.1 – Summary of Use Patterns, Formulations, and Application Rates for Mefluidide.

Product Type	Product Label/names	Application Equipment	Use Sites	Maximum application rates	Maximum Spray dilution
Liquid	2217-759 (EMBARK 2-S)	High pressure handwand	Ornamental trees,	1.0 lbs ai/A	0.01 lbs ai/gallon
		Groundboom, Turfgun	Turfgrass, golf course, rights-of-ways		0.067 lbs ai/gallon
Liquid	2217-763 (EMBARK 1-S)	Groundboom, Backpack sprayer	Turf, commercial-industrial, public area	1.0 lbs ai/A	0.067 lbs ai/gallon
Liquid	2217-765 (EMBARK	Groundboom, Backpack sprayer	Turf, commercial-industrial, public	1.0 lbs ai/A	0.067 lbs ai/gallon

	1-L)		area		
Liquid	2217-766 (EMBARK 2-L)	Groundboom, Backpack sprayer	Turf, commercial-industrial, public area	1.0 lbs ai/A	0.067lbs ai/gallon
Liquid	2217-768 (EMBARK E-Z-TU-USE)	Hand pump (pressure spray), Hose end sprayers	Turf grass	1.0 lbs ai/A	0.008 lbs ai/gallon
			Ornamentals	0.43 lbs ai/A	0.01 lbs ai/gallon
Liquid	2217-802 (EH1135 PGR)	Conventional power spray	Turf, commercial-industrial	0.43 lbs ai/A	0.029 lbs ai/gallon
Granules	538-181 (St. Aug.GR w/Fertilizer)	Spreader	Lawn	0.50 lbs ai/A	N/A
Granules	538-200 (Scotts Turf Manager)	Spreader	Lawn	0.04 lbs ai/A	N/A
RTU	2217-787 (EMBARK R-T-U Northern)	Sprinkler can	Residential areas	0.11 lbs ai/A	N/A
RTU	2217-788 (EMBARK R-T-U Southern)	Sprinkler can	Residential areas	1.23 lbs ai/A	N/A
RTU	2217-809 (ER 721)	Sprinkler can	Residential areas	1.0 lbs ai/A	N/A

RTU = Ready- to- Use

2.2 Structure and Nomenclature

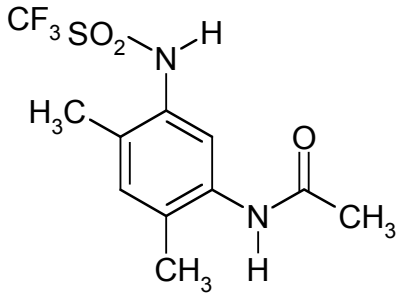
TABLE 2.2a. Test Compound Nomenclature (Mefluidide)	
Chemical Structure	
Empirical Formula	$C_{11}H_{13}F_3N_2O_3S$
Common name	Mefluidide
Company experimental name	MBR 12325
IUPAC name	5′-(1,1,1-trifluoromethanesulfonamido)acet-2′,4′-xylidide
CAS name	*N*-[2,4-dimethyl-5-[[(trifluoromethyl)sulfonyl]amino]phenyl]acetamide
CAS Registry Number	53780-34-0
End-use product/EP	St. Aug.GR w/Fertilizer (Reg. #538-181), Scotts Turf Manager (Reg.#538-200)
Chemical Class	Plant growth regulators
Known Impurities of Concern	None

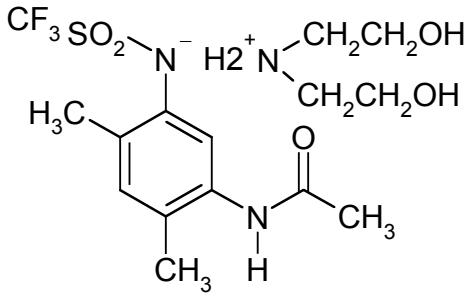
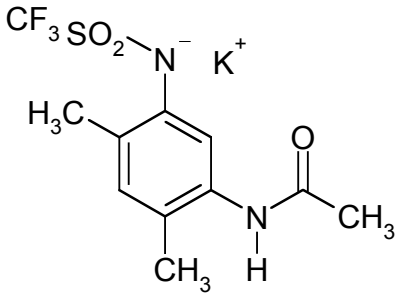
TABLE 2.2b. Test Compound Nomenclature (Diethanolamine Mefluidide)	
Chemical Structure	
Empirical Formula	$C_{15}H_{24}F_3N_3O_5S$
Common name	Diethanolamine Mefluidide
Company experimental name	MBR 12325
IUPAC name	5′-(1,1,1-trifluoromethanesulfonamido)acet-2′,4′-xylidide - 2,2′-iminodiethanol (1:1)
CAS name	*N*-[2,4-dimethyl-5-[[(trifluoromethyl)sulfonyl]amino]phenyl]acetamide compound with 2,2′-iminobis[ethanol] (1:1)
CAS Registry Number	53780-36-2 (This substance is a derivative of mefluidide [53780-34-0]).
End-use product/EP	EMBARK 2-S (Reg.# 2217-759), EMBARK 1-S (Reg.# 2217-763), EMBARK E-Z-TU-USE (Reg.# 2217-768), EH1135 PGR (Reg.# 2217-802), EMBARK R-T-U Northern (Reg.# 2217-787), EMBARK R-T-U Southern (Reg.# 2217-788), ER 721 (Reg.# 2217-809)
Chemical Class	Plant growth regulators
Known Impurities of Concern	None

TABLE 2.2c. Test Compound Nomenclature (Potassium Mefluidide)	
Chemical Structure	
Empirical Formula	$C_{11}H_{12}F_3KN_2O_3S$
Common name	Mefluidide
Company experimental name	MBR 12325
IUPAC name	potassium (*EZ*)-*N*-[5-(1,1,1-trifluoromethanesulfonamido)-2,4-xylyl]acetamide
CAS name	*N*-[2,4-dimethyl-5-[[(trifluoromethyl)sulfonyl]amino]phenyl]acetamide monopotassium salt
CAS Registry Number	83601-83-6
End-use product/EP	EMBARK 1-L (Reg.# 2217-765), EMBARK 2-L (Reg.# 2217-766)
Chemical Class	Plant growth regulators
Known Impurities of Concern	None

2.3 Physical and Chemical Properties

TABLE 2.3.a Physicochemical Properties (Mefluidide)		
Parameter	Value	Reference
Molecular Weight	310.3	HED memo of 3/13/89, A. Smith. Accession No. 259274. RCB No. 126
Melting point/range	183-185 °C	
pH	4.6 @ 25°C (1% aqueous dispersion)	
Density	Not available	
Water solubility (25 °C)	0.18g/L at 25°C	
Solvent solubility (temperature not specified)	N-Octanol. = 17 g/L	
Vapor pressure (25°C)	<1.0E-4 mmHg @ 25°C	
Dissociation constant, pKa	pKa = 4.6	
Octanol/water partition coefficient, $Log(K_{OW})$ (25 °C)	Remain outstanding	
UV/visible absorption spectrum	Max at 287 nm	

TABLE 2.3b. Physicochemical Properties (Diethanolamine Mefluidide)		
Parameter	Value	Reference
Molecular Weight	413.3	HED memo of 3/2/93, C. Olinger, D166847 and D179233. MRIDs 41913301 and 02, 422513 01 through 04, 42309901, 42283301 through 03, 42331401 and 02.
Melting point/range	106-108 °C	
pH	6.98 @ 25°C (1% aqueous dispersion)	
Density	0.69 g/cm3 typical @ 25°C	
Water solubility (20 °C)	566 mg/g at 25°C	
Solvent solubility (temperature not specified)	N-Octanol. = 22 mg/g	
Vapor pressure (25°C)	<1.0 E^{-7} mmHg @ 25°C	HED memo of W. Smith, 2/16/93, D183266. MRID Nos: 42355501.
Dissociation constant, pKa	100% dissociates in aqueous solution. Mefluidide pKa = 4.6	HED memo of 3/2/93, C. Olinger, D166847 and D179233. MRIDs 41913301 and 02, 422513 01 through 04, 42309901, 42283301 through 03, 42331401 and 02.
Octanol/water partition coefficient, $Log(K_{OW})$ (25 °C)	3.2 $x10^{-2}$	
UV/visible absorption spectrum	Max at 254 nm	

TABLE 2.3c. Physicochemical Properties (Potassium Mefluidide)		
Parameter	Value	Reference
Molecular Weight	348.4	HED memo of 11/24/92, F. Toghrol, D179244. MRIDs: 42251401 through 05, 42282001, 42282002, 42302301, and 42323501.
Melting point/range	118- 120 °C	
pH	8.6 @ 25°C (1% aqueous dispersion)	
Density	0.85 g/cm3 typical @ 25°C	
Water solubility (25 °C)	510 mg/g	
Solvent solubility (temperature not specified)	N-Octanol. = 57 mg/g	
Vapor pressure (25°C)	< 1.0 E^{-7} mmHg @ 25°C	
Dissociation constant, pKa	100% dissociates in aqueous solution. Mefluidide pKa = 4.6	
Octanol/water partition coefficient, $Log(K_{OW})$ (25 °C)	Not available	
UV/visible absorption spectrum	Not available	

Based on the structural activities of mefluidide and its DEA and potassium salts, where they all have similar structures (identical benzene ring and functional groups, i.e., share the same anion-anilide), and the above physical and chemical properties of the salts where they dissociate 100% back to free mefluidide in aqueous environment, the risk assessment team determined that mefluidide DEA and potassium salts are biologically equivalent to mefluidide and thus they share the same toxicity as the free mefluidide. Therefore, it is reasonable to bridge mefluidide toxicity data to mefluidide salts and vice versa.

3.0 METABOLISM ASSESSMENT

3.1 Rat Metabolic Profile

Mefluidide was almost completely absorbed following oral ingestion (approximately 96%) and rapidly eliminated within 24 hours. A majority of dose was eliminated in urine (86-89 %) and remainder in feces after a single oral dose in 24 hours. Residue consisted of mefluidide (97%) and 2 unidentified metabolites (1.2% and 0.5%) and unidentified polar material (0.7%). Excretion of the radioactivity in expired air was not detected. The chemical is unlikely to accumulate in body since it was excreted almost completely within 24 hrs and steadily declined thereafter.

3.2 Nature of the Residue in Foods

Not applicable. There are no food uses.

3.3 Environmental Degradation

The only identified degradation product was 5-amino-2, 4-dimethyltrifluoromethanesulfonilide. It was found at a maximum daily concentration of 2.8% of applied dose (MRID 43162201, aerobic soil). The risk assessment team concluded that this degradate is not of concern based on its structure (structurally similar to the parent, there fore it is not likely to be significantly more toxic than the parent), and the fact that it is a minor degradate (<10% of the applied dose). The residue of concern for drinking water assessment is parent only.

4.0 HAZARD CHARACTERIZATION/ASSESSMENT

4.1 Hazard characterization

Mefluidide has shown low acute toxicity by the oral, dermal and inhalation routes (Toxicity Category III and IV). It is a weak eye or dermal irritant (Toxicity Category III and IV). However, the precursor of mefluidide (S-15733: manufacturing starting material) caused eye irritation (Toxicity Category II). Mefluidide did not cause dermal sensitization in the guinea pig. In rats and rabbits, critical effects of acute oral toxicity (occurring at doses of 100 mg/kg/day and above) were tremors, hunched posture, salivation, reduced body weight and body weight gain.

Mefluidide and its diethanolamine salt subchronic and chronic toxicity are manifested by decreased body weight and body weight gain in several species tested (rats, rabbits and dogs). Dogs are most sensitive to these effects, which occur at doses as low as 15 mg/kg/day in diets fed for one year. In addition, dogs fed with mefluidide for one year exhibited chronic cortical nephrosis at doses of 150 mg/kg/day. Increased incidence of liver hyperplastic nodules in both sexes was observed in mice fed with mefluidide at doses of 270 mg/kg/day and higher, but there was no oncogenic response in mice at doses as high as 900 mg/kg/day. Rats fed with mefluidide at doses up to 300 mg/kg/day did not exhibit any carcinogenic response either. Based on lack of carcinogenic response in both rats and mice, mefluidide is considered as not likely to be carcinogenic to humans.

Mefluidide exhibited a negative response in various genotoxicity screening assays (bacterial reverse mutation, *in vitro* mouse lymphoma gene mutation, *in vitro* mammalian chromosome aberration, *in vivo* sister chromatid exchange, unscheduled DNA synthesis).

Mefluidide and its DEA salt were not dermally toxic when tested in rabbits at limit doses of 1000 mg/kg/day for 21 days. Effects were limited to slight erythema at the application site at the 1000 mg/kg/day dose.

Mefluidide or its DEA salt has not been tested for subacute or subchronic inhalation toxicity. However, both of them are in category IV for acute inhalation toxicity.

Developmental effects of Mefluidide in rats included increased number of early resorptions and mean postimplantation loss. These effects were observed at the same dose that caused maternal toxicity indicating there was no increased susceptibility to fetuses. The maternal toxicity included tremors, decreased body weight, weight gain and mortality. In rabbit, the LOAEL/NOAEL for developmental toxicity were above the highest dose tested (60 mg/kg/day). In the 3-generation reproduction toxicity study in rats, the offspring toxicity was characterized by decreased body weights in both sexes and both litters in all generations. The reproductive LOAEL was not observed (NOAEL = 346/604 mg/kg bw/day). The offspring toxicity was observed at the highest dose tested (346 mg/kg/day) that also produced maternal toxicity indicating there was no increased post-natal susceptibility for the mefluidide.

There is no evidence of increased pre- or post-natal susceptibility in the developmental study or in the multi-generation reproduction study in rat. Although the LOAEL/NOAEL for developmental toxicity in the rabbits were not established, the concern is low for the increased susceptibility to the rabbit fetuses since the developmental effects were not seen at the highest dose tested (60 mg/kg/day) which is above the developmental NOAEL in rat (58 mg/kg/day) and well above (40X) the dose that is used to establish chronic RfD (1.5 mg/kg/day). Therefore, there is no residual uncertainty for pre- and/or post natal susceptibility.

The toxicology profile of mefluidide does not indicate a potential concern for estrogens, androgen and/or thyroid mediated toxicity.

The toxicology profile of mefluidide and its DEA salt is adequate for the purposes of hazard and dose response assessment.

Table 4.1a. Acute Toxicity of Mefluidide and its salts (114001, 114002, 114003)

Guideline No.	Study Type	MRID	Results (LD_{50}/LC_{50})	Toxicity Category
870.1100 (81-1)	Acute Oral (female rat) Mefluidide tech	>4000 mg/kg MRID 00047118		III
870.1100 (81-1)	Acute Oral (mouse) Mefluidide tech	1920.2 mg/kg MRID 00047117		III
870.1100 (81-1)	Acute Oral (mouse) Mefluidide tech	829.8 mg/kg MRID 00047116		III
870.1100 (81-1)	Acute Oral (dog) Mefluidide tech	Not established MRID 00049627; emesis precluded evaluation at 100, 500, 2000 mg/kg doses		III
870.1200 (81-2)	Acute Dermal (female rabbit) Mefluidide tech	>4000 mg/kg MRID 00047122 & 00049628 & 00083817		IV
870.1300 (81-3)	Acute inhalation – rat DEA salt of Mefluidide	>5.2 mg/L MRID 41888801		IV
870.1300 (81-3)	Acute inhalation – rat Mefluidide tech.	>5.4 mg/L MRID 41964601		IV
870.2400 (81-4)	Primary Eye Irritation (rabbit) Mefluidide tech	minimal irritation MRID 00047126, 00049630		III
870.2400	Primary Eye Irritation	minimal irritation		III

(81-4)	(rabbit) DEA Mefluidide	MRID43481203	
870.2500 (81-5)	Primary Skin Irritation (rabbit), Mefluidide tech	Not a dermal irritant MRID 00047124, 00049629, 00083819	IV
87.2600 (81-6)	Dermal Sensitization (guinea pig), Mefluidide	Not a dermal sensitizer MRID 41887701	N/A
87.2600 (81-6)	Dermal Sensitization (guinea pig), Mefluidide	Not a dermal sensitizer MRID 00082076	N/A

Table 4.1b Toxicity Profile of Mefluidide and its salts (114001, 114002, 114003)		
Guideline No./ Study type	**MRID No.(year)/Doses/ classification**	**Results**
Non-guideline 21-day Oral - dog	00047137, (1975) 0, 1000, 3000, 10000 ppm Vistar tech, 93% a.i./d (0, 25, 75, 250 mg/kg/d) One dog/sex/dose range finding **Acceptable/non-guideline**	**LOAEL** = not established. **NOAEL** > 250 mg/kg/d,
Non-guideline 5-week - mouse	00082072, (1976) 0, 1800, 6000 ppm Vistar tech, 93% a.i./d (0, 270, 900 mg/kg/d) (Dietary 5/sex/dose) range finding **Acceptable/non-guideline**	**LOAEL** = not established **NOAEL** = 900 mg/kg/d,
None-guideline 28-Day oral dietary [rat]	00047135, (1973), 0, 1000, 3000 or 10000 ppm Vistar tech, 93% a.i. (0, 100, 300, 1000 mg/kg/d) (Dietary 5 rats/sex/dose) range finding **Acceptable/non-guideline**	**LOAE**L = not established. **NOAEL** > 1000 mg/kg/d,
870.3100 (82-1a) 90-Day oral dietary [rat]	00047136, (1975), 0, 300, 1000 or 6000 ppm Vistar tech, 93% a.i. (0, 15, 50, 300 mg/kg/d) (10 rats/sex/dose) 00047140 (1975) 0, 300, 1000, 3000 ppm (0, 15, 50, 150 mg/kg/day). (10 females/dose) **Acceptable/Guideline**	**LOAEL** = 300 mg/kg/d, based on decreased body weight, body weight gain and food consumption in the females. **NOAEL** = 150 mg/kg/d (in conjunction with MRID # 00047140),
870.3150 82-1(b) 90-Day oral dietary [dog]	00047141, **(IBT Study**, 1977), 0, 300, 1000 or 6000 ppm Vistar tech, 93% a.i. (0, 7.5, 25, 150 mg/kg/d) (4/sex/dose) **Unacceptable/guideline** (LOAEL was not observed)	**LOAE**L = not established. **NOAEL** = 150 mg/kg/d.
870.3200 82-2 21-Day Dermal toxicity - rabbit	00082073, (1977) 0, 1, 3, 10 ml of 2S formulation/kg/day (Formulation containing 24% a.i., equivalent to 0, 240, 720, or 2400 mg mefluidide/kg/day) (4 rabbits/sex/dose) **Acceptable/Non-guideline** (NOAEL was not observed) Note: This study assessed the dermal	**Dermal LOAEL** = 240 mg/kg/day, based on irritation, inflammation and necrosis at test sites. **Systemic LOAEL** = 240 mg/kg/day, based on clinical chemistry (increased alkaline phosphatase and alanine aminotransferase) and organ weights (decreased spleen weight in females and increased liver weights in males). Edema and swelling with myelin loss in sciatic nerve was seen in 720 and 2400 mg/kg/day dose group. Dehydration observed at 2400 mg/kg/day dose.

Table 4.1b Toxicity Profile of Mefluidide and its salts (114001, 114002, 114003)		
Guideline No./ Study type	**MRID No.(year)/Doses/ classification**	**Results**
	toxicity of 24 % formulation mefluidide	**Dermal and systemic NOAELs** were not established.
870.3200 82-2 21-Day Dermal toxicity - rabbit	42029601 (1991) 0, 100, 500 or 1000 mg a.i./kg/d Mefluidide 58.2% a.i. (5/rabbits/sex/dose) **Acceptable/guideline**	Dermal toxicity **LOAEL** = 1000 mg/kg/day based on erythema at the test site. Dermal toxicity **NOAEL** = 500 mg/kg/day Systemic toxicity **LOAEL** was not established. Minor hematological and clinical chemistry findings at 1000 mg/kg/day dose reported, that were within normal biological variation and did not correlate to histopathological findings. Systemic toxicity **NOAEL** = 1000 mg/kg/day
870.3200 82-2 21-Day Dermal toxicity - rabbit	41972901 (1991) 0, 100, 500 or 1000 mg a.i./kg/d Mefluidide DEA salt 28.78% a.i. (5/rabbits/sex/dose) **Acceptable/ guideline**	Dermal and systemic toxicity **LOAEL** was not established. Minor incidences of erythema at 500 mg and 1000 mg/kg/day dose. Increased liver weight (absolute and relative) noted at 1000 mg/kg dose but no correlating histopathological findings. Minor statistical increases in liver enzymes AST and ALT. Dermal and systemic **NOAEL** = 1000 mg/kg/day
Non-guideline 1-year feeding (Rat)	00132993, (1981) 0, 60, 200, 600 ppm Vistar tech, 93% a.i. (0, 3, 10, 30 mg/kg/d) (20 rats/sex/dose) Addendum to 2-year feeding study. **Acceptable/non-guideline**	**LOAEL** = not established **NOAEL** = 30 mg/kg/d,
870.4100b 83-1b Chronic Oral Feeding [dog]	00132995, (1982) 0, 60, 600, 6000 ppm Vistar tech, 93% a.i. (0, 1.5, 15, 150 mg/kg/d) (6 dogs/sex/dose) **Acceptable/guideline**	**LOAEL** = 15 mg/kg/d, based on decreased body weight (15%) and body weight gain (50%) in the males. Chronic cortical nephrosis was observed at 150 mg/kg/day dose. **NOAEL** = 1.5 mg/kg/d,
870.4100b 83-2b Carcinogenicity Dietary [mouse]	00082747, (1979) 0, 600, 1800, 6000 ppm Vistar tech, 93% a.i. (0, 90, 270, 900 mg/kg/d) (60 mice/sex/dose) **Acceptable/guideline**	**LOAEL** = 270 mg/kg/day, based on increased incidence of liver hyperplastic nodules in both sexes. **NOAEL** = 90 mg/kg/day. No oncogenicity up to and including the highest dose tested.
870.4300 83-5 2-year feeding/carcinogenicity [rat]	00061930, 00082737 (1979) 0, 600, 1800, 6000 ppm Vistar tech, 93% a.i. (0, 30, 90, 300 mg/kg/d) (50 rats/sex/dose) **Acceptable/guideline**	**LOAEL** = 30 mg/kg/d, based on body weight loss. **NOAEL** < 30 mg/kg/d, No oncogenicity up to and including the highest dose tested.
870.3700a 83-3(a) Developmental Toxicity, gavage [rat]	00132992, (1981) 0, 15, 30, 60 mg/kg/d **Unacceptable/guideline** (LOAEL was not observed)	**Maternal LOAEL** = not established. **Maternal NOAEL** > 60 mg/kg/day, **Developmental NOAEL** > 60 mg/kg/day, **Developmental LOAEL** = not established.

Table 4.1b Toxicity Profile of Mefluidide and its salts (114001, 114002, 114003)		
Guideline No./ Study type	**MRID No.(year)/Doses/ classification**	**Results**
870.3700a 83-3(a) Developmental Toxicity Gavage [rat]	42097201 (range finding) 42097701 (teratology), 1991 Range finding: 0, 100, 200, 400, 600 or 800 mg a.i./kg/d Teratology study: 0, 50, 200 or 400 mg a.i./kg/d Mefluidide technical 58.2% a.i. **Acceptable/Guideline**	**Maternal LOAEL** = 400 mg/kg/d based on reduced gain and food consumption. Higher dose in the range finding study of 600 mg/kg/day produced excessive mortality. **Maternal NOAEL** = 200 mg/kg/d **Developmental LOAEL** = 400 mg/kg/d based on slight fetal toxicity as indicated by a slight nonstatistical increase in 14th rib. **Developmental NOAEL** = 200 mg/kg/d
Non-guideline Range Finding Developmental Toxicity , gavage[rat]	42026101, (1991) 0, 100, 200, 400, 600or 800 mg **diethanolamine salt of mefluidide** (28.78%)/kg/d (6 female rats/dose) Range finding **Acceptable/non-guideline**	**Maternal LOAEL**: 115 mg a.i./kg/day based on clinical signs (tremors, hunched posture, and salivation), maternal body weight gain and food consumption. **Maternal NOAEL**: 58 mg a.i./kg/day; **Developmental LOAEL**: 230 mg a.i. /kg/day based on significantly decreased fetal body weight. **Developmental NOAEL**: 173 mg a.i. /kg/day, The dosage levels of 0, 50, 200 and 400 mg of the 28.78% formulation/kg/day were selected for the definitive developmental study.
870.3700a 83-3(a) Developmental Toxicity, gavage [rat]	42026102, (1991) 0, 50, 200 400 mg **diethanolamine salt of mefluidide** (28.78%)/kg/d (25 females/dose) Doses adjusted for 100 % purity were 0, 14, 58, or 115 mg/kg/day. **Acceptable/guideline**	**Maternal LOAEL** = 115 mg a.i./kg/day based on mortality, clinical signs (tremors, stained nose, urine and vaginal discharge), decreased body weight and weight gain. **Maternal NOAEL** = 58 mg a.i./kg/day), **Developmental LOAEL** = 115 mg a.i./kg/day based on increased number of early resorptions and mean post-implantation loss. **Developmental NOAEL**: 58mg a.i./kg/day
Non-guideline 14-Day Oral gavage [rabbit]	00047138, (1975) 0, 100, 200, 400, 800 mg/kg/d Vistar tech, 93% a.i. 4 females/dose range finding **Acceptable/non-guideline**	**LOAEL** = < 100 mg/kg/day (females), based on mortality (1/3 deaths) at 100 mg/kg/d. Tremors and 100% mortality were noted at the levels of 200 mg/kg/d and above. Histopathology not reported. **NOAEL**: not established,
870.3700b 83-3(b) Developmental Toxicity, gavage [rabbit]	00047139, (1975) 0, 15, 30, 60 mg technical MBR 12325/kg/d (purity not reported). Unacceptable by itself, however, if combined with the 14-day oral study (00047138), it is acceptable.	**Maternal LOAEL** = not established. **Maternal NOAEL** = 60 mg/kg/day, **Developmental LOAE**L = not established. **Developmental NOAEL** = 60 mg/kg/day,
870.3800 (83-4) 3-generation	00082748, (1979) 0, 600, 1800, 6000 ppm, 93% a.i. (M/F:	**The parental systemic LOAEL** = 346/604 mg/kg bw/day (M/F), based on decreased body weights. **The parental systemic NOAEL** = 102/183 mg/kg

Table 4.1b Toxicity Profile of Mefluidide and its salts (114001, 114002, 114003)		
Guideline No./ Study type	**MRID No.(year)/Doses/ classification**	**Results**
reproduction [rat]	0/0, 34/60, 102/183, 346/604 mg/kg/d) **Acceptable/guideline**	bw/day in males/females. **The offspring LOAEL** = 346/604 mg/kg bw/day in males/females, based on decreased body weights in both sexes and both litters in all generations. **The offspring NOAEL** = 102/183 mg/kg bw/day in males/females. **The reproductive LOAEL** was not observed. **The reproductive NOAEL** = 346/604 mg/kg bw/day in males/females.
870.5100 84-2 Bacterial reverse mutation	00132996, (1983) EL-565 (Lily compound 151065: mefluidide technical) tested at 0.1 – 1000 µg/ml **Acceptable/Guideline**	No reverse mutations were noted in any of 8 tester strains of *Salmonella typhimurium* and two tryptophan autotrophs of *E. coli with or without metabolic activation*
870.5100 84-2 Bacterial reverse mutation	41888804, (1991) 0, 100, 333, 667, 1000, 3330, or 5000 µg/plate **diethanolamine salt of mefluidide (28.78%)**/ **Acceptable/guideline**	DEA mefluidide did not increase the number of histidine revertants per plate in any of the tester strains with or without metabolic activation.
870.5300 84-2 *In-vitro* Mouse lymphoma - gene mutation	00132996, (1983) EL-565 (Lily compound 151065: mefluidide technical)0, 1, 25, 50, 100, 250, 500, 750 or 1000 µg/ml **Acceptable/guideline**	There was no evidence of mutation in the presence or absence of metabolic activation.
870.5375 84-2 *In-vitro* mammalian chromosome aberration test	41888803, (1991) **Diethanolamine salt of mefluidide (28.8%)** 500,- 5010 µg a.i. /ml (without S9 mix) or 500, - 5000 (with S9 mix) **Acceptable/guideline**	No significant increase in structural chromosomal aberration with or without metabolic activation was seen, however, the results were considered equivocal.
' 84-2 In-vitro mammalian chromosome aberration test	(1992) concentrations of 1250 to 5000 Φg/ml (w S9 mix) or 200-1600 (wt S9 mix)	Not mutagenic in Chinese Hamster Ovary cells
870.5550 84-2 Unscheduled DNA Synthesis	41888802, (1991) **Diethanolamine salt of mefluidide (28.8%)** Concentrations of 100, 250, 500, 1000, 2000, 3000 µg/ml in trial 1; 1000, 1500, 2000, 3000, 3500 µg/ml in trial 2. **Acceptable/guideline**	No unscheduled DNA synthesis response in the absence of moderate to severe cytotoxicity.
870.5550 84-2 Unscheduled DNA	00132996, (1983) EL-565 (Lily compound 151065: mefluidide technical)	No indication of DNA repair synthesis was observed in cultured rat heapatocytes treated with the test material (EL-565 (Lily compound 151065:

Table 4.1b Toxicity Profile of Mefluidide and its salts (114001, 114002, 114003)		
Guideline No./ Study type	**MRID No.(year)/Doses/ classification**	**Results**
Synthesis	Tested at 0.5 to 1000 nmoles/mL	mefluidide technical))
870.5915 84-2 *In-vivo* Sister Chromatid Exchange	00132996, (1983) EL-565 (Lily compound 151065: mefluidide technical) (0, 12.5, 25, 50, or 100 mg/kg. **Acceptable/Guideline**	Negative in sister chromatid exchange in *in-vivo* bone marrow of Chinese hamster assay.
870.5915 85-1 Metabolism- male rat	MRID is not known: Steifer, LJ (1978). 3M Company Report Number 852 (1-26-78) Dose: 1 or 10 mg/kg of C-14, labeled mefluidide **Acceptable/None-Guideline**	By 24 hrs of post-treatment, 86-89% of the dose was found in urine with the remainder in the feces. Residue consisted of mefluidide (97%) and 2 unidentified metabolites (1.2% and 0.5%) and unidentified polar material (0.7%).
870.6200 81-8 Demyelination study - Chicken	0097684 (1977) 1000, 3000, 5000, 10,000 and 20,000 mg/kg/day. **Non-Acceptable/Non-Guideline**	NOAEL< 1000 mg/kg/day; LOAEL: 1000 mg/kg/day based on clinical signs (hypoactivity, ataxia, tremors, lethargy and dyspnea) that were subsided by 48 hrs following dosing. The test material did not induce delayed neurotoxicity in hens at the LD 50 dosage of 8500 mg/kg. (Limit dose - 1 g/kg).

M = Males; F = Females

4.2 Hazard considerations For Women and Children

4.2.1. Adequacy of the Toxicity Database

The toxicology database for mefluidide is considered adequate. The following acceptable studies are available:

- Developmental toxicity studies in rats
- Developmental toxicity studies in rabbits
- Two-generation reproduction study in rats

4.2. 2. Evidence of Neurotoxicity

Acute and subchronic neurotoxicity studies were not performed. Clinical signs of neurotoxicity (such as tremors, ataxia, atonia, decreased limb tone, salivation) were seen in several studies (14-day oral in rabbit at or above 200 mg/kg/day, demyelination study in chickens at 1000 mg/kg/day and two developmental toxicity studies in rats at 115 mg/kg/day. Edema and swelling with myelin loss in sciatic nerve was observed in a dermal toxicity study in rabbits at doses of 720 mg/kg and above. However, these effects were not seen in an additional dermal test of similar duration using a 58.2% mefluidide formulation or diethanolamine salt of mefluidide 28.8%.

4.2.3. Developmental Toxicity Study Conclusions

Developmental Toxicity Study - Rabbits:

In a developmental toxicity study (MRIDs 00047139 and 00047138), technical MBR 12325 (Lot #9) in 4% gum acacia was administered to 16-20 New Zealand White rabbits/dose group via gavage at dose levels of 0, 15, 30, or 60 mg/kg bw/day from gestation days (GD) 6-18.

There were no treatment-related effects on survival, clinical signs, body weight, food consumption, or cesarean parameters.

The maternal LOAEL was not observed. The maternal NOAEL is 60 mg/kg bw/day (the highest dose tested).

There were no effects of treatment on the numbers of litters, live fetuses, dead fetuses, or resorptions, or on fetal body weights, sex ratio, or post-implantation loss. There were no treatment-related external, visceral, or skeletal variations or malformations.

The developmental LOAEL was not observed. The developmental NOAEL is 60 mg/kg bw/day (the highest dose tested).

This developmental toxicity study in rabbits has a number of deficiencies: a LOAEL was not observed; test material purity was not provided; no information on dose formulation preparation

or storage was provided; and no analyses of homogeneity, stability, or concentration were reported. However, when combined with the 14-day oral gavage study in rabbits (MRID 00047138), where a LOAEL of <100 mg/kg bw/day based on mortality and tremor was established, this developmental toxicity study is considered acceptable and satisfies the guideline for a developmental toxicity study (OPPTS 870.3700b; OECD 414) in rabbits.

Developmental Toxicity Study - Rats:

In a developmental toxicity study (MRID 42026102), Diethanolamine salt of Mefluidide (28.78% a.i. Lot # JB0624) in distilled water was administered to pregnant Sprague Dawley Crl:CD BR VAF/Plus (25/dose) by gavage at dose levels of 0, 50, 200 or 400 mg/kg bw/day (adjusted doses for 100 % purity were 0, 14, 58, or 115 mg/kg/day, respectively) from days 6 through 15 of gestation.

Animals were checked daily for clinical signs, mortality. Body weights were measured on gestation day 0, 6, 9, 12, 16 and 20. Unscheduled deaths, scheduled sacrifice and c-sections were subjected to gross necropsy examination. Each fetus was examined for external/visceral/skeletal anomalies, sexed and then weighed.

Evidence of maternal toxicity included transient clinical signs (tremors, dark material around the nose, few feces, urine stain and reddish vaginal discharge), decreased body weight gain (11-61%), decreased food consumption and mortality (2/25 females found dead on GD 11 and 16) observed at the 400 mg/kg/day levels. At the 400 mg/kg dose, the clinical signs of toxicity appeared within 2 days after dosing in few animals, and after few days of dosing in some others and more than half of the animals at this dose were free from clinical signs of toxicity. No external malformations or developmental variations were observed associated with any fetus. Fetal toxicity was manifested by increase in the number of early resorptions which resulted in increase in mean postimplantation loss at 400 mg/kg/day dose.

After adjusting to the pure active ingredient, the maternal NOAEL is 58 mg/kg/day and the LOAEL is 115 mg/kg/day based on clinical signs (tremors, dark material around the nose, urine stain and reddish vaginal discharge), decreased body weight gain, decreased food consumption and mortality (2/25 females). The developmental toxicity NOAEL is also 58 mg/kg/day, the LOAEL is 115 mg/kg/day based on increase in the number of early resorptions and increase in mean postimplantation loss.

This developmental toxicity study is classified **acceptable/Guideline** and it does satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

4.2.4. Reproductive Toxicity Study

In a three-generation reproduction study (MRID 00082748), MBR 12325 (Mefluidide; 93% a.i., Lot #25) was administered in the diet to 20 male and 40 female Charles River CD® rats/dose group at dose levels of 0, 600, 1800, or 6000 ppm (equivalent to Males/Females - 0/0, 34/60,

102/183, and 346/604 mg/kg bw/day). When approximately 100 days old, the P generation animals were mated (1 male: 2 females) for up to 15 days to produce the F1a litter. Following weaning of the F1a litters, 50 F1a offspring/sex/dose were selected for a 2-year chronic feeding study, and the remaining F1a offspring were discarded. The P generation was reduced to 10 males/20 females per dose group. After a 10-day post-weaning rest period, these P animals were mated again to produce the F1b litter. Upon weaning, 10 male and 20 female F1b offspring/dose group were selected to be parents of the F2 generation. This study design was continued for three generations with 2 litters per generation.

There were no effects on food consumption, organ weights, gross pathology, or histopathology.

Numerous absolute and relative (to bw) organ weights in the 6000 ppm parents were significantly ($p<0.05$) different from the controls, however, none of these differences were corroborated by any macroscopic or microscopic findings indicating these decreases were most likely not related to treatment. Thus, it is likely that they were attributable to decreased body weights at this dose.

The only deaths included one 6000 ppm F1 female, one 6000 ppm F2 male, and one 1800 ppm F2 female. It was stated that macroscopic and microscopic findings in these animals were unremarkable. Therefore, these deaths were considered incidental and were not treatment related.

At 6000 ppm, body weights were decreased by 1-8% in males and 1-12% in females throughout the study in the P generation, attaining significance ($p<0.05$) at Week 18 in the males and Weeks 8, 18, 19, and 27 in the females. In the F1 generation at this dose, body weights were decreased throughout the study in the males (decr. 13-21%) and females (decr. 10-21%), attaining significance ($p<0.01$) at Weeks 27, 37, and 56 in both sexes. Similarly in the F2 generation, body weights were decreased throughout the study in the 6000 ppm males (decr. 14-21%) and females (decr. 11-23%), attaining significance ($p<0.01$) at Weeks 57, 66, and 85 in both sexes.

At 1800 ppm, only minor and infrequent decreases in body weights were noted. There were no treatment-related findings at 600 ppm.

The parental systemic LOAEL is 6000 ppm (346/604 mg/kg bw/day in males/females), based on decreased body weights in both sexes in all generations. The parental systemic NOAEL is 1800 ppm (102/183 mg/kg bw/day in males/females).

There were no effects of treatment on post-natal survival (i.e., viability and lactation) indices in the pups at any dose. There were no treatment-related findings at 600 or 1800 ppm.

At 6000 ppm, body weights were decreased by up to 27% compared to controls throughout the post-natal period in both litters in each generation (i.e., F1a, F1b, F2a, F2b, F3a, and F3b litters). These decreases attained significance in both sexes at PND 21.

The offspring LOAEL is 6000 ppm (346/604 mg/kg bw/day in males/females), based on decreased body weights in both sexes and both litters in all generations. The offspring NOAEL is 1800 ppm (102/183 mg/kg bw/day in males/females).

There were no effects of treatment on male or female fertility indices or gestation survival index.

The reproductive LOAEL was not observed. The reproductive NOAEL is 6000 ppm (346/604 mg/kg bw/day in males/females).

This study is **acceptable/guideline** and satisfies the guideline requirement for a three-generation reproductive study (OPPTS 870.3800; OECD 416) in rats.

4.2.5. Additional Information from Literature sources

There was no published information on this subject.

4.3. Hazard Identification and Toxicity Endpoint Selection

4.3.1. Acute Reference Dose (aRfD)

Females age 13-49 : Acute dietary endpoint for child bearing females (females 13+ years old) was determined from the developmental toxicity study in rat (MRID 42026102). A NOAEL of 58 mg/kg/day was derived based on developmental toxicity (increased number of early resorptions and mean post-implantation loss) at a LOAEL of 115 mg/kg/day. An UF of 100X (10-fold for inter-species extrapolation, 10-fold for intra-species variability) was applied to the NOAEL of 58 mg/kg/day to derive the aRfD.

Acute RfD (Females 13-50 years old) = $\frac{58 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}}$ = **0.58 mg/kg**

Acute Reference Dose (aRfD) - General Population

The acute RfD for the general population including infants and children was determined from the developmental toxicity study in rat (MRID 42026102). A NOAEL of 58 mg/kg/day was derived based on maternal toxicity (clinical signs: tremors) at a LOAEL of 115 mg/kg/day. An UF of 100X (10- fold for inter-species extrapolation, 10-fold for intra-species variability) was applied. The selected endpoint of toxicity is appropriate for this exposure since clinical signs of toxicity occurred within two days of dosing.

Acute RfD (general population) = $\frac{58 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}}$ = **0.58 mg/kg**

4.3.2. Chronic Reference Dose (cRfD)

The cRfD of 0.015 mg/kg/day was determined on the basis of the Chronic Oral Feeding – dog (MRID 00132995); NOAEL of 1.5 mg/kg/day and LOAEL of 15.0 mg/kg/day based on decreased body weight (15%) and body weight gain (50%) in the males. This study provided the lowest NOAEL (1.5 mg/kg/d) in the database that provides the most protective limits for human effects. An UF of 100X (10-fold for interspecies extrapolation, 10-fold for intraspecies variability) was applied to the NOAEL of 1.5 mg/kg/day to derive the cRfD to give and RfD of 0.015 mg/kg/day.

4.3.3. Incidental Oral Exposure (Short-and Intermediate-term durations: 1 day – 6 months)

Points of departure for these scenarios were based on the rat developmental study (MRID 42026102). NOAEL = 58 mg/kg bw/day, LOAEL = 115 mg/kg bw/day based on mortality and clinical signs. These data were also supported by the rabbit developmental study (NOAEL = 60 mg/kg bw/day) and rabbit 14 day oral study (LOAEL = 100 mg/kg bw/day based on mortality). The level of concern for residential exposure is for MOEs = 100 and for occupational exposure is for MOEs =100.

4.3.4. Dermal Absorption Factor

A dermal penetration study is not available. A dermal absorption factor is derived by extrapolation from the rabbit 21-day dermal (MRID 41972901) and rabbit 14 day oral (MRID 00082073) studies. The dermal systemic NOAEL in the 21-day study is 1000 mg/kg/day based on minor increases in liver enzymes. In the 14 day rabbit oral study(MRID 00047138), the LOAEL is less than 100 mg/kg/day based on mortality and clinical signs (tremors) and the NOAEL is <100 mg/kg/day, therefore, the calculated dermal absorption factor would at the most be (100/1000) x 100 = 10%.

4.3.5. Dermal Exposure (Short and Intermediate: (1-30 days and 30 d-180 days)

Three subacute (21-day) dermal toxicity studies were considered. The two more recent studies (MRID 42029601 and 41972901) showed no systemic effects at the limit dose. Only one study (MRID 00082073) with 24% active ingredient showed toxic effects (Edema and swelling with myelin loss in sciatic nerve at 720 and 2400 mg/kg/day). These effects were not seen in the more recent GLP dermal studies using a 58.2% mefluidide formulation (MRID 42029601) or diethanolamine salt of mefluidide 28.8% (MRID 41972901). The risk assessment team determined that no quantitative dermal assessment is needed due to the following:

1) Two 21-day dermal toxicity studies with rabbits indicated no dermal systemic toxicity at 1000 mg/kg/day (the highest dose tested). The one study that showed toxicity indicated that effects only occurred at high doses.

2) The rat developmental study indicated no developmental concern (developmental NOAEL equals to maternal NOAEL),

3) The acute dermal toxicity of mefluidide, where the acute dermal LD50 is >4000 mg/kg, it is not a skin irritant and is not a dermal sensitizer.

4.3.6. Inhalation (Short- and Intermediate-Term)

Endpoint for this scenario was determined from the rat developmental study. NOAEL = 58 mg/kg bw/day, LOAEL = 115 mg/kg bw/day based on mortality and clinical sings. These data were also supported by the rabbit developmental study (NOAEL = 60 mg/kg bw/day) and rabbit 14 day oral study (LOAEL = 100 mg/kg bw/day based on mortality). Since oral study was selected for inhalation exposure assessment an inhalation-absorption factor of 100% oral equivalent should be used.

4.3.7. Margins of Exposure

These are summarized in the following table:

Route Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)
Occupational (Worker) Exposure		
Dermal	NA	NA
Inhalation	100	100
Residential (Non-Dietary) Exposure		
Oral	100	100
Dermal	NA	NA
Inhalation	100	100

4.3.8. Classification of Carcinogenic Potential

Mefluidide was negative for carcinogenicity in mouse (MRID 00082747) and rat (MRID 00061930 7 00082737) bioassays. It was also evaluated for genotoxicity in several tests and found negative. It is unlikely that mefluidide will pose a cancer risk to humans.

Table 4.3. Summary of Toxicological Dose and Endpoints for Mefluidide and its salt (114001, 114002, 114003) Used in Human Risk Assessment				
Exposure Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (general population)	**NOAEL = 58 mg/kg/day**	**UF_A = 10X** **UF_H = 10X**	**Acute RfD = <u>Maternal NOAEL</u> UncertaintyFactor = 0.58 mg/kg /day**	MRID 42026102 Developmental toxicity - rat; LOAEL= 115.0 mg/kg/day based on mortality(within 5 days of dosing) and clinical signs (within 2 days of dosing), and the NOAEL of 58 mg/kg/day.
Acute Dietary (Females 13+)	**NOAEL = 58 mg/kg/day**	**UF_A = 10X** **UF_H = 10X**	**Acute RfD = <u>Develop. NOAEL</u> UncertaintyFactor = 0.58 mg/kg**	MRID 42026102 Developmental toxicity - rat; LOAEL= 115.0 mg/kg/day based on increased number of early resorptions and mean postimplantation loss. NOAEL = 58 mg/kg/day
Chronic Dietary (All populations)	**NOAEL = 1.5 mg/kg/day**	**UF_A = 10X** **UF_H = 10X**	**Chronic RfD = <u>NOAEL</u> Uncertainty Factor = 0.015 mg/kg/day**	MRID 00132995 Chronic Oral Feeding - dog; LOAEL= 15.0 mg/kg/day based on decreased body weight (15%) and body weight gain (50%) in the males at 15 mg/kg/day.
Short-Term Incidental Oral (1-30 days) Intermediate-Term Incidental Oral (1-6 months)	**NOAEL = 58 mg/kg/day**	**UF_A = 10X** **UF_H = 10X**	Residential LOC for MOE = 100	MRID 42026102 Developmental toxicity - rat; NOAEL = 58 mg/kg bw/day, LOAEL = 115 mg/kg bw/day based on mortality and clinical sings. These data were also supported by the rabbit developmental study (MRID 00047139) (NOAEL = 60 mg/kg bw/day) and rabbit 14 day oral study (LOAEL = 100 mg/kg bw/day based on mortality).
Short-Term Dermal (1 to 30 days) Intermediate-Term Dermal (1 to 6 months)	Dermal NOAEL = 1000 mg/kg/day	**UF_A = 10X** **UF_H = 10X**	No quantitative dermal assessment is needed.	Three subacute (21-day) dermal toxicity studies were considered. The risk assessment team determined that no quantitative dermal assessment is needed due to the following: 1) Two 21-day dermal toxicity studies with rabbits indicated no dermal systemic toxicity at 1000

Table 4.3. Summary of Toxicological Dose and Endpoints for Mefluidide and its salt (114001, 114002, 114003) Used in Human Risk Assessment				
Exposure Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
				mg/kg/day (the highest dose tested). The one study that showed toxicity indicated that effects only occurred at high doses. 2) the rat developmental study indicated no developmental concern (developmental NOAEL = maternal NOAEL), 3) Acute toxicity of mefluidide, where acute dermal LD50 is >4000 mg/kg, not a skin irritant and is not a dermal sensitizer.
Short-Term Inhalation (1 to 30 days) Intermediate-Term Inhalation (1 to 6 months)	Oral NOAEL = 58 mg/kg/day (inhalation-absorption rate = 100% oral equivalent)	**UF_A = 10X** **UF_H = 10X**	Residential LOC for MOE = 100; Occupational LOC for MOE = 100	MRID 42026102 Developmental toxicity - rat; NOAEL = 58 mg/kg bw/day, LOAEL = 115 mg/kg bw/day based on mortality and clinical sings. These data were also supported by the rabbit developmental study (NOAEL = 60 mg/kg bw/day) and rabbit 14 day oral study (LOAEL = 100 mg/kg bw/day based on mortality).
Cancer	Mefluidide was negative for carcinogenicity in mouse (MRID 00082747) and rat (MRID 00061930 7 00082737) bioassays. It was also evaluated for genotoxicity in several tests and found negative.			

Point of Departure (POD) = a data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. UF = uncertainty factor, UF_A = extrapolation from animal to human (intraspecies), UF_H = potential variation in sensitivity among members of the human population (interspecies), NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, RfD = reference dose (a = acute, c = chronic), MOE = margin of exposure, LOC = level of concern, NA = Not Applicable. Safety Factor = UF = 100.

5.0 Public Health Data

5.1 Incident Reports

(HED memo of 07/25/06, M. Hawkins, D324824)

The following data bases have been consulted for the poisoning incident data on the active ingredient Mefluidide and salts:

1) OPP Incident Data System (IDS) - No reports for mefluidide or its salts in the Incident Data

System.
2) Poison Control Centers - No reports located in the Poison Control Center records from 1993 through 2003 involving mefluidide.
3) California Department of Pesticide Regulation - Detailed description of 1 case submitted to the California Pesticide Illness Surveillance Program (1982-2003) was reviewed. In the case, a worker reported a rash on the side of their face after several workers passed a vehicle that sprayed the product.
4) National Pesticide Information Center (NPIC) - From 1984-1991 inclusively, mefluidide was not reported to be involved in human incidents.
5) National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR) - Of 5,899 reported cases from 1998-2003, none involved mefluidide.

In conclusion, there was only one report of an ill effect from exposure to mefluidide in the available data bases.

6.0 EXPOSURE CHARACTERIZATION/ASSESSMENT

6.1 Dietary Exposure/Risk Pathway

6.1.1 Food Exposure/Risk Pathway

None. No food uses.

6.1.2 Water Exposure/Risk Pathway

Drinking water Assessment; James Hetrick (D334508, 03/08/07)

Possible routes of dissipation for mefluidide are photodegradation on soil surfaces and microbial-mediated degradation. Mefluidide is not prone to abiotic hydrolysis or photolysis in sterile buffer solutions within the environmentally relevant pH range of 4 to 9. There are data showing mefluidide undergoes rapid photodegradation ($t_{1/2}$ = 2 to 3 days) in natural well water. On soil surfaces, mefluidide photodegraded with a half-life of 116.4 hours. Mefluidide in aerobic soils degraded with a half-life of 12 days. The only degradation product was 5-amino-2,4-dimethyltrifluoromethanesulfonilide. It was found at a maximum daily concentration of 2.8% of applied dose (MRID 43162201, aerobic soil). Mefluidide dissipated with a half-life of 2.0 to 3.3 days in warm-season turf soil in Georgia and 1.2 to 1.4 days in cool-season grass soil in Missouri. Mefluidide dissipated from grass foliage at half-lives of 1.7 to 6.91 days (upper 90th percentile of mean half-life= 4.0414 day, k= 0.1715 days$^{-1)}$.

No surface or ground water monitoring data were found for mefluidide. Drinking water assessment was conducted using Tier II (PRZM-EXAMS) for surface water modeling and Tier 1 (SCI-GROW) for groundwater modeling. Because mefluidide use is associated with turf, the aquatic exposure assessment was conducted using the PA and FL turf scenarios. These use scenarios were selected to represent of rights-of-way, residential turf, industrial areas with turf (i.e., airports, etc.), and golf courses. The turf scenarios are expected to be conservative estimate of mefluidide runoff potential because they assume 100% of the watershed is treated with

mefluidide as well as the runoff scenarios are located in areas with high runoff potential. The mefluidide acid concentrations in surface water are not expected to exceed 32 µg/L for the 1 in 10 year daily peak concentration, 10 µg/L for the 1 in 10 year annual concentration, and 5 µg/L for the 30 year annual average concentration. Mefluidide acid concentrations in ground water are not expected to exceed 1.0 µg/L. These concentrations have not been adjusted for any crop area factor (CAF) because the crop area factors do not account for non-agricultural uses such as turf, ornamentals, etc. Uncertainty in the assessment is the persistence of mefluidide acid in aerobic aquatic environments. This assessment was conducted using an estimated aerobic aquatic half-life of 72 days (Guidance for Chemistry and Management Practice Input Parameters for Use in Modeling the Environmental Fate and Transport of Pesticides, Version 2, 11/7/2000). Because this estimated half-life was designed to approximate upper 90th percentile of the mean half-life, it is anticipated to be a conservative estimate of mefluidide acid persistence in aquatic environments.

6.2 Dietary Exposure Estimates

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03) which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998.

Acute Dietary Exposure from Drinking Water

An acute dietary exposure assessment was performed for mefluidide considering exposures from surface water only, as there are no food uses for this chemical. An estimated drinking water concentration (EDWC) for surface water (32 ppb) provided by the Environmental Fate and Effects Division (EFED) was used in this assessment. Ground water sources were not included, as the EDWCs for this water source are minimal in comparison to surface water. The drinking water exposure analysis result in dietary risk estimates for surface water only are below the Agency's level of concern for acute exposure. At the 95th percentile, the exposure to U.S. population was 0.0017 mg/kg/day, which utilized **<1%** of the acute reference dose (aRfD). The exposure for all infants, which was the most highly exposed population subgroup, was 0.006 mg/kg/day, which utilized **1% of the aRfD**. Conservative screening-level drinking water estimates were used in this assessment (i.e., the highest peak surface water level for a one in ten year concentration), therefore the dietary risk estimates were reported at the 95th percentile of exposure.

Chronic Dietary Exposure from Drinking Water

A chronic dietary exposure from drinking water only was also performed using surface water EDWC value (10 ppb). For the U.S. population the exposure was 0.0002 mg/kg/day, which utilized **1%** of the chronic reference dose (cRfD). The exposure for all infants, which was the most highly exposed population subgroup, was 0.0007mg/kg/day, which utilized **5% of the cRfD.**

Table 6.2. Summary of Drinking Water Exposure and Risk for Mefluidide						
Population Subgroup	Acute Dietary 95th Percentile			Chronic Dietary		
	aRfD (mg/kg/day)	Dietary Exposure (mg/kg/day)	% aRfD	cRfD (mg/kg/day)	Dietary Exposure (mg/kg/day)	% cRfD
General U.S. Population	0.58	0.001672	<1	0.015	0.000211	1
All Infants (< 1 year old)		**0.006303**	**1**		**0.000691**	5
Children 1-2 years old		0.002623	<1		0.000313	2
Children 3-5 years old		0.002396	<1		0.000293	2
Children 6-12 years old		0.001668	<1		0.000202	1
Youth 13-19 years old		0.001356	<1		0.000152	1
Adults 20-49 years old		0.001549	<1		0.000197	1
Adults 50+ years old		0.001399	<1		0.000207	1
Females 13-49 years old		0.001558	<1		0.000196	1

For detailed DEEM input and result files, please see Attachment I.

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

Occupational and Residential Exposure Assessment; Yan Donovan, D324823, 2/28/07.

Mefluidide is intended for both occupational and residential uses. None of the labels prohibit use by homeowners. The residential products are typically formulated as granules, or as liquid concentrates, or ready- to- use sprinkler can sprays. Spot and broadcast treatments are both included on the labels. Exposures are expected to be short term in duration.

6.3.1. Residential Handler Exposure and Risks

Residential Handler Scenarios, Data Sources and Assumptions

Scenarios

Based on the product labels, the following scenarios were assessed.

1. Load/Apply Granules with Belly Grinder
2. Load/Apply Granules with a Broadcast Spreader
3. Mix/Load/Apply with a Hose-end Sprayer (Mix your own)
4. Mix/Load/Apply with Hand Held Pump Sprayer.

Data Sources

Exposure data for scenario #1 was taken from PHED because no unit exposure data is available from ORETF for this specific scenario. Exposure data for scenarios #2 and #3 were taken from the residential portion of the ORETF Handler Study. Exposure data for scenario #4 was taken from MRID 44459801, a study involved low pressure handwand and RTU trigger sprayer application of carbaryl to home vegetable plants. This study was reviewed by Jeff Dawson in document D287251, has since been purchased by ORETF.

Assumptions Regarding Residential Applicators

- Broadcast spreaders and hose end sprayers would be used for broadcast treatments and the other application methods would be used for spot treatments only.
- The application rate of 1.0 lb ai/acre is from mefluidide labels.
- An area of 0.023 acre (1000 square feet) would be treated per application during spot treatments and an area of 0.5 acre would be treated during broadcast applications.

Residential Handler Exposure and Risk Estimates

A summary is included in Table 6.3.1. The MOEs are > 100 and the risks are below EPA's level of concern.

Table 6.3.1- Mefluidide Short Term MOEs for Homeowner Applications to Lawns					
Scenario	**Application Rate**	**Area Treated or Amount Applied**	**Inhalation Unit Exposure (per lbs ai handled)**	**Inhalation Dose (mg/kg/day)**	**Inhalation MOE**
Load/Apply granules with Belly Grinder (spot treatment)	0.5 lb ai/acre	0.023 acre/day	62 µg (PHED)	1.0E-05	6,000,000
Load/Apply Granules with a Broadcast Spreader	0.5 lb ai/acre	0.5 acre/day	0.91 µg (ORETF)	3.3E-06	18,000,000
Mix/Load/Apply with a Hose-end Sprayer (Mix your own)	1.0 ai/acre	0.5 acre/day	16 µg (ORETF)	1.1E-04	500,000
Mix/Load/Apply with Hand Held Pump Sprayer (use on turf)	1.0 lb ai/acre	0.023 acre/day	9 µg (MRID44459801)	3.0E-06	20,000,000
Mix/Load/Apply with Hand Held Pump Sprayer (use on ornamentals)	0.01 lbs ai /gallon	5 gallons	9 µg (MRID44459801)	6.0E-06	9,000,000

6.3.2. Residential Post Application Exposure and Risks

Residential Post Application Exposure Scenarios, Data Sources and Assumptions

Scenarios

The following exposure scenario was assessed for residential turf post application risks:

Short Term Incidental Oral Exposures of Toddlers Playing on Treated Turf

General Assumptions

The following general assumptions are taken from the Standard Operating Procedure (SOPs) of December 18, 1997 and ExpoSAC Policy #12 "Recommended Revisions to the Standard Operating Procedures for Residential Exposure Assessments of February 22, 2001.

- An assumed initial TTR value of 5% of the application rate is used for assessing hand to mouth exposures.
- An assumed initial TTR value of 20% of the application rate is used for assessing object to mouth exposures.
- Soil residues are contained in the top centimeter and soil density is 0.67 mL/gram.
- Three year old toddlers are expected to weigh 15 kg.
- Hand-to-mouth exposures are based on a frequency of 20 events/hour and a surface area per event of 20 cm^2 representing the palmar surfaces of three fingers.
- Saliva extraction efficiency is 50 percent meaning that every time the hand goes in the mouth approximately ½ of the residues on the hand are removed.

- An exposure duration of 2 hours per day is assumed for toddlers playing on turf.

Assumptions Specific to Mefluidide

The following assumptions that are specific to mefluidide are used for assessing residential post application exposures.

- The application rate of 1.0 lbs ai/acre as stated in the label was used. Although RTU product (EPA Reg # 2217-788) has the highest application rate of 1.23 lbs ai/acre, this product is considered to be used as spot treatment. As a result, the 1.23 lbs ai/acre is not considered a representative rate for turf use.

Calculation Methods

The above factors were used in the standard residential SOP formulas to calculate the incidental oral exposures from hand- to- mouth, object- to- mouth and soil ingestion on treated turf. These formulas are described in the cited ORE memo. The MOEs were calculated using the short/intermediate term incidental oral endpoint which has a NOAEL of 58 mg/kg/day.

The MOEs are summarized in Table 6.3.2A. All of the MOEs exceeded 100. This means that the risks are below EPA's level of concern.

Table 6.3.2A - Mefluidide MOEs for Residential Post Application Turf Exposures
(Application Rate = 1.0 lb ai/acre)

Toddler Exposure Scenario	TTR and soil Residue Levels	Dose (mg/kg/day)	MOE
Hand to Mouth Ingestion	0.56 ug/cm^2	0.0150	4,000
Object to Mouth Ingestion	2.2 ug/cm^2	0.0037	16,000
Soil Ingestion	7.5 ppm	5.0E-05	1,000,000
Total of Above		0.019	3,000

The risk assessment for toddler turf exposures are conservative because it is based on day zero TTRs and soil residues and does not account for dissipation. The combined MOE is considered highly conservative since each of the single scenarios (hand-to-mouth, object-to-mouth, or soil ingestion) is assessed based on conservative assumptions, and that the likelihood of all three scenarios occur at the same time is very rare.

Residential Turf Granule Ingestion Exposure and Risks

Scenarios

The following exposure scenario was assessed

Assumptions

The following assumptions were used to assess the risk of incidental oral ingestion of granules:

- The assumed ingestion rate is 0.3 gram/day based on the Residential SOP 2.3.1. This is based on the assumption that if 150 lbs of product were applied to a ½ acre lawn, the amount of product per square foot would be 3 g/ft^2 and a child would consume one-tenth of the product available in a square foot.
- Three year old toddlers are expected to weigh 15 kg.
- The granules contain a maximum of 0.49 percent mefluidide ai based upon product #538-181.

Calculation Methods and Risks

The above factors were used to calculate the potential dose rate and the absorbed dose using the Residential SOP 2.3.1 formulas as shown in Table 6.3.2B. MOEs were then calculated using the acute dietary NOAEL of 58 mg/kg/day and they exceed 100. This means that the risks for toddler exposures from granular ingestion are below EPA's level of concern.

Table 6.3.2B - Granule Ingestion Risks for Mefluidide

Percent ai	Potential Dose Rate[1] (mg/day)	Absorbed Dose[2] (mg/kg/day)	Acute MOE[3]
0.49	1.47	0.098	590

1. Potential Dose Rate (PDR) = 0.3 gram/day * (Percent ai/100)* 1000 mg/gram
2. Absorbed Dose = PDR/BW
3. MOE = NOAEL/Dose where the NOAEL = 58 mg/kg/day

7.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

7.1 Aggregate Risk

Aggregate Risk Assessment (food + water + residential exposure)

Although an aggregate risk assessment is not required under current Agency policies for non-food use chemicals, to ensure that the public health is adequately protected, a screening level aggregate risk assessment was conducted for mefluidide. For acute and chronic aggregate risks, the only exposure is from drinking water. As stated above, the dietary exposures (drinking water only) do not exceed 1% of the aRfD/cRfD for adult and 5% of the aRfD/cRfD for children. For short- term, no aggregate is needed for adults since there are no residential post- application exposures to adults. When considering the dietary exposure (drinking water only) as a

background exposure to Children for short-term risk, the level of dietary exposure (0.0007 mg/kg/day) is negligible when compared to the combined incidental oral exposure (0.019 mg/kg/day, Table 6.3.2A above) or the granule ingesting dose (0.098 mg/kg/day, Table 6.3.2B above). No intermediate-term residential post application exposure was identified. Therefore, short- and intermediate- term aggregate is not of concern.

7.2 Cancer Risk

Based on lack of evidence of carcinogenicity in both rats and mice, mefluidide was considered as not likely to be carcinogenic to humans. No cancer assessment is needed.

8.0 CUMULATIVE RISK CHARACTERIZATION/ASSESSMENT

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to mefluidide and any other substances and mefluidide does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that mefluidide has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 OCCUPATIONAL EXPOSURE/RISK PATHWAY

(Occupational and Residential Exposure Assessment; Yan Donovan, D324823, 2/28/07).

Mefluidide products are intended for both occupational and residential uses.

9.1 Short/Intermediate-Term Handler Risk

Based upon the application methods listed in Table , the following exposure scenarios were identified and assessed.

Mix/Load Liquid Formulations
Groundboom Application
Turfgun Application
Right of Way Application
Mix/Load/Apply Liquids with a Backpack Sprayer
Mix/Load/Apply Liquids with a Turfgun
Load/Apply Granules with a Push Cyclone

Occupational Handler Exposure Assumptions and Data Sources

Exposure Assumptions

The following assumptions and factors were used in order to complete the exposure and risk assessments for occupational handlers/applicators:

- The daily acreages treated were taken from EPA Science Advisory Council for Exposure Standard Operating Procedure #9 "Standard Values for Daily Acres Treated in Agriculture," Revised July 5, 2000.
- The maximum application rate for turf areas is 1.0 lbs ai per acre as listed in the Mefluidide labels.
- The maximum application rate for ornamental trees is 0.01 lbs ai per gallon based upon the Label #2217-759.
- A body weight of 70 kg was assumed because the endpoint is not gender specific.
- The inhalation absorption rate is 100%.
- Baseline indicates that no respirator is worn.

Handler Exposure Data Sources

The handler exposure data were taken from the Pesticide Handler Exposure Database (PHED) and the Outdoor Residential Exposure Task Force (ORETF). The PHED data were used primarily for the golf course, ornamental trees, and rights- of - ways (ROW) scenarios and the ORETF data were used for lawn care scenarios. The detailed values specific to each exposure scenario can be found in the above cited ORE memo.

Occupational Handler Exposure and Risk Estimates

Daily inhalation doses and Margins of Exposure (MOEs) were calculated using standard HED methodology. The MOEs for occupational handlers are summarized in Table 9.1. All of the MOEs are > 100 with baseline PPE which means that the risks are not of concern and respiratory protection is not needed.

Table 9.1 – Mefluidide Inhalation MOEs for Occupational Handlers					
Exposure Scenario	**Use Site**	**Application Rate**	**Daily Amount Treated or Applied**	**Inhalation Unit Exposure at Baseline (µg/lb ai handled)**	**MOE at Baseline Level[1]**
Mixer/Loader (M/L)					
M/L Liquids for Turfgun (20 PCOs)	PCO[2] Turf	1.0 lb ai/acre	100 acres	1.2	34,000
M/L Liquids for High pressure Handwand	Ornamental trees	0.01lb ai/gallon	1000 gallons	1.2	340,000
M/L Liquids for Groundboom	Golf Courses	1.0 lb ai/acre	40 acres	1.2	85,000
M/L Liquids for ROW Sprayer	Right of Way	0.067 lb ai/gallon	1000 gallons	1.2	50,000
Applicator					
Groundboom Application	Golf Courses	1.0 lb ai/acre	40 acres	0.74	140,000
ROW Sprayer Application	Non Turf Areas[3]	0.067 lb ai/gallon	1000 gallons	3.9	16,000
Turfgun Application	PCO Turf	1.0 lb ai/acre	5 acres	1.0	812,000
Mixer/Loader/Applicator (M/L/A)					
M/L/A Liquid Flowables with Turfgun	PCO Turf	1.0 lb ai/acre	5 acres	1.9	427,000
M/L/A Liquids with Backpack Sprayer	Non Turf Areas	0.067 lb ai/gallon	40 gallons	30	50,000
M/L/A Granules with Push Cyclone	PCO Turf	0.5 lb ai/acre	5 acres	7.5	217,000

1. Baseline PPE indicates no respirator.
2. PCO Turf includes residential lawns, commercial lawns and other lawn areas treated by a Pest Control Operator (PCO).
3. Non Turf Areas include roadsides, Rights of Way (ROW) and other similar non-crop areas.

Occupational Handler Risk Characterization

All the MOEs for occupational handlers are greatly above HED's level of concern (100), no refinement is needed. However, HED recommends the level of PPE required on the current labels are not to be changed as a result of this assessment.

9.2 Post-application Exposure and Risk

Occupational post application dermal risks were not assessed because there is not likely to have occupational post-application scenario. In addition, no dermal endpoints were selected. Mefluidide is only applied outdoors and it is not a volatile compound, inhalation exposures are negligible (Vapor pressures are < 1.0E-4 torr at 25° C for mefluidide, < 1.0E-7 torr at 25° C for mefluidide DEA salt and potassium salt).

10.0 DATA NEEDS AND LABEL REQUIREMENTS

None.

Attachment I

Filename: C:\Documents and Settings\ydonovan\DEEM Files\Mefluidide\Mefluidide.R98
Chemical: Mefluidide and Salts
RfD(Chronic): .015 mg/kg bw/day NOEL(Chronic): 1.5 mg/kg bw/day
RfD(Acute): .58 mg/kg bw/day NOEL(Acute): 58 mg/kg bw/day
Date created/last modified: 03-22-2007/09:27:32/8 Program ver. 2.03
Comment: Acute Exposure from drinking water only

EPA Code	Crop Grp	Commodity Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
86010000	O	Water, direct, all sources	0.032000	1.000	1.000	
86020000	O	Water, indirect, all sources	0.032000	1.000	1.000	

U.S. Environmental Protection Agency Ver. 2.02
DEEM-FCID ACUTE Analysis for MEFLUIDIDE AND SALTS (1994-98 data)
Residue file: Mefluidide.R98 Adjustment factor #2 NOT used.
Analysis Date: 03-22-2007/09:46:53 Residue file dated: 03-22-2007/09:44:59/8
NOEL (Acute) = 58.000000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "Exposure from drinking water only"
==========

Summary calculations (per capita):

95th Percentile			99th Percentile			99.9th Percentile		
Exposure	% aRfD	MOE	Exposure	% aRfD	MOE	Exposure	% aRfD	MOE
U.S. Population:								
0.001672	0.29	34696	0.003140	0.54	18472	0.006282	1.08	9232
All infants:								
0.006303	1.09	9202	0.009035	1.56	6419	0.016185	2.79	3583
Children 1-2 yrs:								
0.002623	0.45	22112	0.004380	0.76	13240	0.006371	1.10	9104
Children 3-5 yrs:								
0.002396	0.41	24206	0.003756	0.65	15443	0.006130	1.06	9462
Children 6-12 yrs:								
0.001668	0.29	34771	0.002774	0.48	20912	0.003788	0.65	15312
Youth 13-19 yrs:								
0.001356	0.23	42768	0.002282	0.39	25420	0.004104	0.71	14133
Adults 20-49 yrs:								
0.001549	0.27	37449	0.002594	0.45	22362	0.004692	0.81	12362
Adults 50+ yrs:								
0.001399	0.24	41469	0.002000	0.34	28997	0.003244	0.56	17881
Females 13-49 yrs:								
0.001558	0.27	37238	0.002507	0.43	23137	0.004446	0.77	13046

Filename: C:\Documents and Settings\ydonovan\DEEM Files\Mefluidide\Mefluidide-Chronic.R98
Chemical: Mefluidide and Salts
RfD(Chronic): .015 mg/kg bw/day NOEL(Chronic): 1.5 mg/kg bw/day
RfD(Acute): .58 mg/kg bw/day NOEL(Acute): 58 mg/kg bw/day
Date created/last modified: 03-22-2007/09:44:59/8 Program ver. 2.03
Comment: Chronic Exposure from drinking water only

EPA Code	Crop Grp	Commodity Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
86010000	O	Water, direct, all sources	0.010000	1.000	1.000	
86020000	O	Water, indirect, all sources	0.010000	1.000	1.000	

U.S. Environmental Protection Agency Ver. 2.00
DEEM-FCID Chronic analysis for MEFLUIDIDE AND SALTS (1994-98 data)
Residue file name: C:\Documents and Settings\ydonovan\DEEM Files\Mefluidide\Mefluidide-Chronic.R98
Adjustment factor #2 NOT used.
Analysis Date 03-22-2007/10:15:37 Residue file dated: 03-22-2007/10:14:22/8
Reference dose (RfD, Chronic) = .015 mg/kg bw/day
COMMENT 1: Chronic Exposure from drinking water only

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Population (total)	0.000211	1.4%
U.S. Population (spring season)	0.000209	1.4%
U.S. Population (summer season)	0.000226	1.5%
U.S. Population (autumn season)	0.000204	1.4%
U.S. Population (winter season)	0.000204	1.4%
Northeast region	0.000192	1.3%
Midwest region	0.000213	1.4%
Southern region	0.000200	1.3%
Western region	0.000241	1.6%
Hispanics	0.000239	1.6%
Non-hispanic whites	0.000206	1.4%
Non-hispanic blacks	0.000200	1.3%
Non-hisp/non-white/non-black	0.000258	1.7%
All infants (< 1 year)	0.000691	4.6%
Nursing infants	0.000256	1.7%
Non-nursing infants	0.000856	5.7%
Children 1-6 yrs	0.000294	2.0%
Children 7-12 yrs	0.000191	1.3%
Females 13-19 (not preg or nursing)	0.000148	1.0%
Females 20+ (not preg or nursing)	0.000210	1.4%
Females 13-50 yrs	0.000204	1.4%
Females 13+ (preg/not nursing)	0.000205	1.4%
Females 13+ (nursing)	0.000292	1.9%
Males 13-19 yrs	0.000155	1.0%
Males 20+ yrs	0.000189	1.3%
Seniors 55+	0.000207	1.4%
Children 1-2 yrs	0.000313	2.1%
Children 3-5 yrs	0.000293	2.0%
Children 6-12 yrs	0.000202	1.3%
Youth 13-19 yrs	0.000152	1.0%
Adults 20-49 yrs	0.000197	1.3%
Adults 50+ yrs	0.000207	1.4%
Females 13-49 yrs	0.000196	1.3%

Appendix B: Review of Human Research

Studies reviewed for ethical conduct:

No MRID - PHED Surrogate Exposure Guide

00031050 Feldman, R.J., Maibach, H.I. (1974) Percutaneous penetration of some pesticides and herbicides in man. Toxicology and Applied Pharmacology 28(?):126-132. (Also In unpublished submission received Apr 23, 1980 under 10279-7; submitted by Purdue Frederick Co., Norwalk, Conn.; CLD:242321-R)

Studies reviewed by the Human Studies Review Board:

44416201 Gledhill, A. (1997) Dichlorvos: A Study to Investigate Erythrocyte Cholinesterase Inhibition Following Oral Administration to Healthy Male Volunteers: Lab Project Number: XH5170: Y09341: C05743. Unpublished study prepared by Zeneca Central Toxicology Lab. 104 p.