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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Date: May 31, 2007

MEMORANDUM

SUBJECT: Mefenoxam: Human Health Risk Assessment for Proposed Uses on Succulent Shelled Beans and Turnip Greens. PC Code: 113502, Petition Nos. 5F7018 and 9E6057, DP Barcode: 325137.

FROM: Myron S. Ottley, Risk Assessor/ Senior Toxicologist
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The HED Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will results from the proposed use of mefenoxam on succulent shelled beans and turnip greens. In conjunction with this action, RD also requested that HED evaluate, analytical method validation, storage stability, and papaya/kiwifruit field trial data submitted to satisfy deficiencies identified in previous HED reviews.

A summary of the findings and an assessment of human risk resulting from the proposed uses of mefenoxam are provided in this document. Bonnie Cropp-Kolligian performed the residue chemistry review, Becky Daiss conducted the dietary exposure assessment, Jack Arthur performed the occupational and residential exposure assessment, Myron S. Ottley performed the toxicology review and the risk assessment, and the drinking water assessment was performed by James Hetrick of the Environmental Fate and Effects Division (EFED).

Recommendation for Tolerances and Registration:

HED recommends the mefenoxam/metalaxyl tolerance expressions be modified. The metalaxyl/mefenoxam residue to be regulated in plant and livestock commodities should be parent only ((R)- and (S)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester). The multiresidue method PAM, Vol. I Section 302 (Protocol D), which completely recovers metalaxyl/mefenoxam *per se* (>80% according to FDA PESTDATA) is an adequate enforcement method for the determination of metalaxyl/mefenoxam *per se* in plant and livestock commodities. All future metalaxyl/mefenoxam magnitude of the residue data should include (1) analysis for residues of parent only using the multiresidue method PAM, Vol. I Section 302 (Protocol D) in order to establish more appropriate tolerance levels and (2) analysis with a 2,6-DMA common moiety method and recovery data for parent, CGA-62826, and CGA-94689 in order to refine dietary risk assessments.

Provided that the tolerance expressions are modified and pending submission of a revised Section B (see requirements in Appendix B), there are no residue chemistry issues that would preclude granting a registration for the requested foliar uses of mefenoxam on succulent shelled beans and turnip greens. Residues of mefenoxam in/on succulent shelled beans and turnip greens resulting from the proposed maximum uses of mefenoxam are not expected to exceed the currently established crop group tolerances for residues of metalaxyl (40 CFR 180.408(a)) in/on legume vegetables (0.2 ppm) and leaves of roots and tubers (15.0 ppm), respectively. Hence, HED recommends in favor of granting the proposed uses but against the registrant's request to establish new tolerances for residues of mefenoxam in/on succulent shelled beans and turnip greens under 40 CFR 180.546(a).

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Introduction

Syngenta Crop Protection, Inc. has requested a new use for mefenoxam formulated as Ridomil Gold® EC (emulsifiable concentrate) on succulent shelled beans, Ridomil Gold® Copper EC and Ridomil Gold® SL on turnip greens. In this document, human health risks are characterized and estimated based on the proposed uses. Bonnie Cropp-Kolligian performed the residue chemistry review, Becky Daiss conducted the dietary exposure assessment, Jack Arthur performed the occupational and residential exposure assessment, Myron S. Ottley performed the toxicology review and risk assessment, and the drinking water assessment was performed by James Hetrick of the Environmental Fate and Effects Division (EFED).

1.0 Executive Summary

General Information

Mefenoxam is the enriched R-enantiomer of the fungicide metalaxyl, which is a racemic mixture of R- and S-enantiomers. The basic producer, Syngenta (formerly Novartis Crop Protection, Inc. and formerly Ciba Crop Protection), has replaced metalaxyl with mefenoxam because it is the most fungicidally active component of the mixture, and has therefore reduced the use rates by half. Mefenoxam is registered for use as a seed treatment, soil application, and/or foliar application on a variety of food and feed crops, as well as turf, and is formulated as an emulsifiable concentrate, a flowable concentrate, a granular, and a wettable powder.

Mefenoxam is a systemic fungicide which is absorbed through the leaves, stems, and roots of plants. Mefenoxam inhibits protein synthesis in fungi. Mefenoxam belongs to the phenylamide class of systemic fungicides. Other phenylamides are metalaxyl, furalaxyl, benalaxyl, and oxadixyl. Phenylamides are effective against soil-borne diseases caused by *Pythium* and *Phytophthora* and foliar diseases caused by the *Phycomycetes* (downy mildews). Mefenoxam and other phenylamides may enter the environment through use as foliar, soil, or seed treatments for agricultural crops or as a treatment in the residential environment.

Mefenoxam and metalaxyl have the same empirical formula. Metalaxyl merely includes a near equal amount of both enantiomers (optical isomers whose molecular structures have a mirror-image relationship to each other), whereas, mefenoxam includes mainly the R-enantiomer. Due to this relationship between mefenoxam and metalaxyl, toxicology and residue chemistry data for metalaxyl have been used to better understand the toxicity and chemistry of mefenoxam.

Toxicology

Mefenoxam has moderate acute toxicity (classified as Toxicity Category II for acute oral toxicity). It is classified in Toxicity Categories III and IV for acute dermal and acute inhalation toxicity, respectively. Mefenoxam is considered a slight dermal irritant and a severe to corrosive eye irritant.

The database for mefenoxam indicates that the major target organ is the liver. Liver effects observed in oral studies in rat, mouse, and dog include increased liver enzymes, increased incidence of pathological observations in the liver and increased liver weights. The dog appears to be the most sensitive species.

In developmental toxicity studies with mefenoxam in rats, no developmental toxicity was observed. The database does not indicate any reproductive toxicity, and the level of concern for neurotoxicity is low based on the available studies. Based on these data, the FQPA 10X Safety Factor was not retained.

Mefenoxam technical and metalaxyl technical are not mutagenic. Metalaxyl has been classified as "not likely to be a human carcinogen." Based on the classification of metalaxyl, mefenoxam is also considered "not likely to be a human carcinogen."

Endpoints have been identified for the following exposures: chronic dietary; short- and intermediate-term incidental ingestion; long-term dermal; and short-, intermediate- and long-term inhalation. An acute dietary endpoint was not identified.

For the purposes of this risk assessment the toxicology database for mefenoxam is considered complete. However, a data gap was identified by the Hazard Identification Assessment Review Committee (HIARC), requiring a **28-Day inhalation study** (TXR. No 014492, M. Bonner, 03/06/01) for mefenoxam use on grapes. This data gap needs to be addressed by the Registrant.

Exposure and Aggregate Risk

Dietary Exposure

Acute dietary (food only) exposure was not assessed because an acute dietary endpoint was not identified. Chronic dietary (food) exposure was somewhat refined by the use of average % crop treated data for some crops and the incorporation of processing factors for cereal grain flour and fruit juice The 1 in 10 year annual estimated surface water concentration from the Tier II PRZM-EXAMS model was used to assess contributions from drinking water. The analysis modeled chronic dietary exposure for different age groups and compared exposure to the chronic population-adjusted dose (cPAD; the exposure at which no adverse effects are expected, including sensitive subgroups). The population subgroup with the highest exposure was children aged 1-2 years; their exposure (food + drinking water) occupies 66% of the cPAD. The exposure for the US population occupies 28% (food + drinking water) of the cPAD. These risks do not exceed the Health Effects Division's (HED's) level of concern (i.e., exposure comprises less than 100% of the cPAD)

Residential Exposure

Residential exposures and risks were calculated for adult handlers and children who may be exposed. Adult handler inhalation exposure was assessed for the short-term exposure scenario (1-30 days) for homeowners who mix/load and apply mefenoxam for use on turf. The scenario with the highest exposure is based on the "belly grinder" application method and results in a Margin of Exposure (MOE) of 150,000 (an MOE of 100 or greater is considered below HED's

level of concern). Intermediate-term inhalation exposure is not expected. Dermal exposure was not assessed since dermal endpoints for short- or intermediate-term time periods were not identified. Children's incidental oral exposure was also assessed for both short-term and intermediate-term time periods. Three scenarios were evaluated: hand-to-mouth exposure, object-to-mouth exposure and ingestion of soil. Since these three activities could, theoretically, take place over the same time period, total exposure for all three was calculated. The combined short-term MOE is 4,200 and the combined intermediate-term MOE is 1,000. Thus, all residential risks are below HED's level of concern (i.e., results in an MOE of at least 100). Residential long-term exposure is not expected.

Drinking Water Exposure
The drinking water assessment, calculated by EFED, was conducted using registrant submitted data for metalaxyl and mefenoxam. It provides Tier II (PRZM-EXAMS) surface water modeling and Tier 1 (SCI-GROW) groundwater modeling. The modeling was conducted for total metalaxyl and mefenoxam residues including metalaxyl, mefenoxam, *N*-(2,6-dimethylphenyl)-*N*-(methylacetyl-L-alanine) (CGA-62826), and *N*-(3_hydroxy-2,6-dimethylphenyl)-*N*-(methoxyacetyl)-L-alanine (CGA 119857). The metalaxyl /mefenoxam residue concentrations from Tier II surface water modeling are not expected to exceed 108.9 µg/L for the 1 in 10 year daily peak concentration, 36.7 µg/L for the 1 in 10 year annual concentration, and 25.9 µg/L for the 30 year annual average concentration. Metalaxyl /mefenoxam residue concentrations from Tier I ground water modeling are not expected to exceed 1.72 µg/L. However, it should be mentioned that the maximum metalaxyl concentration in registrant-sponsored ground water monitoring studies was 3.0 µg/L.

Aggregate Risk

HED conducted a somewhat refined chronic dietary and drinking water exposure assessment for all existing and proposed new food uses of metalaxyl/mefenoxam and drinking water. In this assessment, it was assumed that residues were present at tolerance levels in plant commodities for both direct use tolerances for metalaxyl/mefenoxam and indirect or inadvertent tolerances for metalaxyl. Additional factors were applied to certain plant commodities to address concerns regarding the adequacy of the residue analytical method to determine metalaxyl/mefenoxam residues of concern in plant and livestock commodities. This concern was raised during the review of method validation data required for reregistration which were submitted with this petition. Data from metabolism studies on goats and hens were used to estimate conservative levels of metalaxyl/mefenoxam in livestock commodities. Processing data for cereal grain flour and fruit juice were also used in the assessment. Estimated average % crop treated data for mefenoxam was used when available. The 1 in 10 year annual estimated surface water concentration from the Tier II PRZM-EXAMS model was used to assess contributions from drinking water.

An acute dietary endpoint was not identified. Therefore an acute aggregate risk assessment was not needed. Results of the chronic dietary assessment indicate that the general U.S. population and all other population subgroups have exposure and risk estimates below HED's level of concern. The chronic dietary exposure estimate for the highest exposed population subgroup,

children 1-2 years of age, is 66% of the cPAD (general population = 28% of the cPAD).

All short-term and intermediate-term margins of exposure (MOEs) were greater than 100; therefore, short- and intermediate term risk estimates to do exceed HED's level of concern for adults or children. Similarly, results of the chronic aggregate risk assessment indicate that risk estimates do not exceed HED's level of concern.

Occupational Exposure and Risk

The Health Effects Division (HED) has identified toxicity endpoints for use in the mefenoxam ORE assessment. Short- and intermediate-term dermal endpoints were not identified because no systemic toxicity was seen at the limit dose in a 21-day dermal toxicity study in rabbits. However, short- and intermediate-term inhalation endpoints were identified for use in assessing mefenoxam exposure to both occupational and non-occupational handlers. Short- and intermediate-term oral endpoints were identified for use in assessing toddler's incidental ingestion of residues following mefenoxam use on residential turf. However, because no acute oral endpoint was identified, an assessment of episodic granular ingestion by toddlers was not performed. Chronic exposure is not expected for any mefenoxam use pattern.

Occupational handlers may be exposed during mixing, loading and application of mefenoxam using aerial, chemigation and groundboom equipment. MOEs for inhalation exposure from all occupational handler scenarios were above 100, and do not trigger HED concern. Inhalation exposure is considered negligible for postapplication activities with treated crops, and dermal exposure was not considered because dermal toxicity was not observed; thus an occupational postapplication assessment was not required.

It should be noted that, for postapplication activities with mefenoxam-treated crops, a 48-hour restricted entry interval (REI) is required under the Worker Protection Standard (WPS) because eye irritation test results place mefenoxam in Toxicity Category I.

HED Recommendations

The Mefenoxam Risk Assessment Team in consultation with HED's RARC (02/14/2007) recommends the residues to be regulated for the tolerance expression be modified to include residues of metalaxyl/mefenoxam per se and the residues of concern for dietary risk assessments are metalaxyl/mefenoxam per se, its metabolites containing the 2,6-dimethylaniline (2,6-DMA) moiety, its metabolites containing the 2-hydroxymethyl-6-methylaniline (HMMA) moiety, its metabolites containing the ring hydroxylated dimethylaniline (Ring-OH) moiety, and its metabolites containing the benzoic acid moiety.

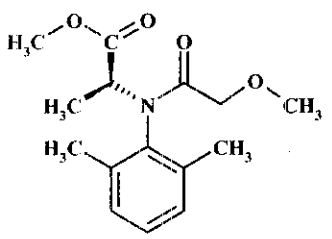
Upon re-evaluation of the available radiovalidation and method validation data, it was determined that the common moiety residue analytical methods used to collect magnitude of the residue data for the purposes of setting tolerance levels will not adequately recover all of the metalaxyl/mefenoxam residues of concern. While these methods are adequate to recover residues of metalaxyl/mefenoxam per se, they are not likely to recover metalaxyl/mefenoxam metabolites containing the Ring-OH moiety or the benzoic acid moiety and available radiovalidation and method validation data indicate that the methods will not adequately recover metabolites containing the HMMA moiety and may not adequately recover all metabolites containing the 2,6-DMA moiety with the certainty needed to set legal limits. However, for the purposes of estimating the combined residues of metalaxyl/mefenoxam and its metabolites containing the 2,6-DMA moiety in/on plant and livestock commodities in chronic dietary risk assessments, these common moiety methods are deemed adequate for data collection and therefore, current/reassessed tolerance levels are adequate to account for these residues in the risk analysis.

HED evaluated Syngenta's requests and concluded that there is a reasonable certainty that no harm will result to the general population and to infants and children from aggregate exposure to mefenoxam. Furthermore, based on the occupational assessment included in this document, HED concludes that risks to occupational workers from exposure to mefenoxam are minimal and are not cause for concern. The findings of this human health risk assessment support the proposed use of mefenoxam on succulent shelled beans and turnip greens under the established metalaxyl tolerances for legume vegetables and leaves of root and tuber vegetables. No new tolerances need to be established.

Residues of mefenoxam in/on succulent shelled beans and turnip greens resulting from the proposed maximum uses of mefenoxam are not expected to exceed the currently established crop group tolerances for residues of metalaxyl (40 CFR 180.408(a)) in/on legume vegetables (0.2 ppm) and leaves of root and tuber vegetables (15.0 ppm), respectively. Hence, HED recommends in favor of granting the proposed uses but against the registrant's request to establish new tolerances for residues of mefenoxam in/on succulent shelled beans and turnip greens under 40 CFR 180.546(a).

2.0 Ingredient Profile

Table 2.0 Mefenoxam Nomenclature

Compound	 (R)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester Empirical Formula: $C_{15}H_{21}NO_4$
Common name	Mefenoxam
Company experimental name	CGA-329351
IUPAC name	methyl *N*-(methoxyacetyl)-N-(2,6-xylyl)-D-alaninate
CAS name	methyl *N*-(2,6-dimethylphenyl)-N-(methoxyacetyl)-D-alaninate
CAS #	70630-17-0

2.1 Summary of Proposed Uses

Table 2.1 Summary of Directions for Use of Mefenoxam.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Proposed Uses						
Bean, succulent shelled						
Foliar spray; Ground	4.8% WP [100-804]	0.1	4	0.4	3	Begin applications at the onset of disease and continue on a seven day schedule (7-day RTI).[1]
Turnip, greens						
Foliar spray; Ground or Aerial	4 lb/gal EC [100-801] 4 lb/gal SL [100-1202]	0.0625-0.125	2	0.250 (implied)	7	Tank mix use with other fungicides. Applications to be made in a minimum of 25 gal/A (ground) or 5 gal/A (aerial), with a 14-day RTI.[1]

[1] Planting of rotational crops other than those on the label is restricted to 12 months following the last application.

The enantiomeric relationship between mefenoxam and metalaxyl is the basis for bridging residue chemistry data between the two active ingredients: mefenoxam and metalaxyl have the same empirical formula, yet mefenoxam primarily consists of one optical isomer, whereas metalaxyl includes approximately equal amounts of both optical isomers.

2.2 Physical and Chemical Properties

Table 2.2 Physicochemical Properties of Mefenoxam.		
Parameter	Value[1]	Reference
Boiling point/range	>270 °C (PAI)	DP #223261, L. Kutney, 4/24/96
pH	5-6 at 25 °C (1% aqueous dispersion; TGAI)	
Density	1.125 g/cm^3 (20 °C; TGAI)	
Water solubility	26 g/L (25 °C; PAI)	
Solvent solubility	Completely miscible in acetone, dichloromethane, ethyl acetate, methanol, n-octanol, and toluene; 59 g/L in n-hexane at 25 °C (TGAI).	
Vapor pressure	3.3 x 10^{-3} (25 °C; PAI)	
Dissociation constant, pK_a	None in 1-10 pH range (PAI)	
Octanol/water partition coefficient, Log(K_{OW})	1.71 at 25 °C (TGAI)	
UV/visible absorption spectrum	Not available	

[1] TGAI = Technical grade of the active ingredient; PAI = Purified active ingredient.

A detailed explanation of the physical and chemical properties of mefenoxam are provided in "HED Risk Assessment: Human Health Risk Assessment for Mefenoxam on the Herb Subgroup, Globe Artichoke, and Minor/Tropical Fruits" (DP Number 274784, C. Christensen, 06/14/01).

3.0 Hazard Characterization/Assessment

On March 6, 2001, the HIARC reevaluated the toxicology database for mefenoxam, and reaffirmed the previous HIARC conclusions for mefenoxam (TXR. No 014492, M. Bonner, 03/06/01). The RAB3 Risk Assessment Team reaffirms the conclusions of the HIARC.

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

3.1.1.1 Studies available and considered (animal, human, general literature)

Acute- oral, dermal, inhalation, eye irritation, skin irritation, dermal sensitization
Subchronic- Dermal 21-day rat; oral 90-day rat, oral 28-day rat, oral 90-day dog;
Chronic- Oral rat and dog;
Reproductive/developmental- Oral developmental rabbit and rat; 2-generation reproductive rat;
Other- Oral mouse cancer study, mutagenicity screens, rat metabolism and

pharmacokinetic; dermal penetration

3.1.1.2 Mode of action, metabolism, toxicokinetic data

Mefenoxam belongs to the phenylamide class of systemic fungicides (Group 4), and is absorbed through the leaves, stems, and roots of plants; it inhibits protein synthesis in fungi. Phenylamides are effective against soil-borne diseases caused by *Pythium* and *Phytophthora* and foliar diseases caused by *Phycomycetes* (downy mildews). Mefenoxam is registered for seed treatment, soil application, and/or foliar application on a variety of food and feed crops.

3.1.1.3 Sufficiency of studies/data

The toxicity database for mefenoxam/metalaxyl is deemed adequate for endpoint selection for exposure risk assessment scenarios and for FQPA evaluation.

HED has concluded that the available toxicity databases on mefenoxam/metalaxyl are sufficient to characterize toxicity and to identify endpoints that will be protective of populations evaluated in the risk assessment.

3.1.2 Toxicological Effects

NOAEL and LOAEL: The NOAEL (No Observed Adverse Effect Level) is the dose level, in a given study, at which no adverse effects were noted. Similarly, the LOAEL (Lowest Observed Adverse Effect Level) is the dose level at which effects of toxicological significance were observed. NOAELs/LOAELs derived from the toxicity database are well characterized (with the exception of certain endpoints in the developmental neurotoxicity study) and are used as endpoints for appropriate risk assessments.

Acute Toxicity

The acute toxicity of mefenoxam is presented in Table 3.1.2 below. All acute toxicity studies were conducted using mefenoxam as the test substance. Mefenoxam has moderate acute toxicity (classified as Toxicity Category II for acute oral toxicity). It is classified in Toxicity Categories III and IV for acute dermal and acute inhalation toxicity, respectively. Mefenoxam is considered a slight dermal irritant and a severe to corrosive eye irritant.

Table 3.1.2. Acute Toxicity of Mefenoxam

Guideline No./Study Type	MRID #(S)	Results	Toxicity Category
870.1100 Acute oral toxicity	43800383	LD_{50}(M)=1671 (1380-2024) mg/kg LD_{50}(F)=490 (360-666) mg/kg LD_{50}(both)=1269 (737-2187) mg/kg	II
870.1200 Acute dermal toxicity	43800384	LD_{50} > 2000 mg/kg	III
870.1300 Acute inhalation toxicity	43800385	LC_{50} > 2.29 mg/L	IV
870.2400 Acute eye irritation	43800386	severe to corrosive ocular irritant	I
870.2500 Acute dermal irritation	43800387	slight dermal irritant	IV
870.2600 Skin sensitization	43800388 43800389	maximization test - not a sensitizer Buehler test - not a sensitizer	NA

Due to the similarities in the toxicological data between mefenoxam and metalaxyl, the toxicity data submitted for metalaxyl can be used to support the registration of mefenoxam: the mefenoxam toxicity database is based on studies using mefenoxam where available, and metalaxyl as needed, and is considered complete for risk assessment purposes (TXR No. 0012380, W. Sette, 11/04/97). However, the HIARC determined that to be consistent with current evaluation requirements, **a 28-Day inhalation study is required** (the inhalation endpoint is currently based on a developmental toxicity study by gavage in the rat) (TXR. No 014492, M. Bonner, 03/06/01).

Systemic Toxicity

The database for mefenoxam indicates that the major target organ is the liver. Liver effects observed in oral studies in the rat, mouse, and dog include increased liver enzymes, increased incidence of pathological observations in the liver and increased liver weights. The dog appears to be the most sensitive species.

Metabolism

In a metabolism study in rats, 96.3% of the administered dose was excreted in the urine or feces within 48 hours following treatment.

Developmental and Reproductive Toxicity

In developmental toxicity studies with metalaxyl in rats, developmental toxicity was observed only at maternally toxic dose levels. In rabbits no developmental toxicity was observed up to the highest dose tested. In developmental toxicity studies with mefenoxam in rats, no developmental toxicity was observed up to the highest dose tested. Concerning reproductive or developmental toxicity, there were no toxicological differences in reproductive performance, fetal viability, body weight, or development.

Neurotoxicity
No neurotoxicity studies were conducted, but there were clinical signs of hypoactivity and convulsions seen in two studies. Post-dosing hypoactivity was noted in the 28-day rat gavage study at a dose of 150 mg/kg/day with mefenoxam, but this observation was not seen in the 28-day study with metalaxyl. Post-dosing convulsions in dams given 250 mg/kg/day of metalaxyl were noted in the rat developmental study, also a gavage study, yet not noted in the developmental study with mefenoxam. Evidence of neurotoxicity was not observed in studies other than these two gavage studies. Thus, clinical signs of hypoactivity and convulsions seen in one subchronic gavage study with mefenoxam and in the one developmental study with metalaxyl were considered a low level of concern.

Mutagenicity
Metalaxyl is not considered mutagenic, and mutagenicity studies do not indicate increased mutagenic potential following exposure to metalaxyl and mefenoxam.

Carcinogenicity
Metalaxyl has been classified as "not likely to be a human carcinogen" based on the results of a carcinogenicity study in mice and a combined chronic toxicity and carcinogenicity study in rats. As part of the bridging process, these studies were used for the registration of mefenoxam. Based on the classification of metalaxyl, mefenoxam is also considered "not likely to be a human carcinogen."

3.1.3 Dose-response

The mefenoxam/metalaxyl risk assessment team selected the most sensitive and protective endpoints from the database to employ in the risk assessment. An appropriate endpoint was identified for the chronic dietary exposure scenario but not for acute dietary exposure, and appropriate endpoints were selected for occupational scenarios following inhalation exposures. Dermal occupational exposures are not anticipated. Short- and intermediate-term residential exposure scenarios are anticipated, and appropriate endpoints were selected.

3.1.4 FQPA

There are adequate data in the mefenoxam/metalaxyl database to characterize the potential for pre-natal or post-natal risks to infants and children: two-generation reproduction studies in rats and developmental studies in rats and rabbits. The available data support the reduction of the FQPA factor to 1X.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Metalaxyl was rapidly absorbed, distributed, metabolized, and eliminated in rats under all dosing regimens. Within 24 hours most radioactivity was recovered in urine and feces (69.92 - 82.5%);

recovery after 7 days was essentially complete. Urine was primary elimination route in females (65.5 - 74.1%) and fecal elimination dominated in males (54.19 - 63.60%

3.3 FQPA Considerations

The FQPA Safety Factor Committee evaluated the available hazard and exposure data for mefenoxam on October 23, 2000 to determine the FQPA safety factor to be used in human health risk assessments (as required by the FQPA of August 3, 1996). The Committee concluded that the FQPA safety factor could be removed (*i.e.*, reduced to 1X) in assessing the risk posed by this chemical. The mefenoxam risk assessment team evaluated the hazard and exposure data base for mefenoxam according to the 2002 OPP 10X Guidance Document and confirmed that the safety factor could be removed for mefenoxam because:

- There is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure;
- The level of concern for neurotoxicity is low based on the available studies because: (1) acute observations noted in the gavage studies are inconsistent with the rest of the database; (2) convulsions and hypoactivity are gavage-specific and not seen with other routes of exposure; (3) convulsions are not reproducible within or between studies; (4) no convulsions or hypoactivity were seen in the 28-day feeding study with mefenoxam at higher doses or in the 28-day gavage study with metalaxyl.
- A developmental neurotoxicity study is **not** required at this time; and
- The dietary (food and drinking water) and non-dietary exposure assessments will not underestimate the potential exposures for infants and children

3.3 Dose Response Assessment

Table 3.3 Summary of Toxicological Doses and Endpoints for Mefenoxam for Use in Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/ Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary	None. No appropriate endpoint attributable to a single dose was identified.			
Chronic Dietary (All populations)	NOAEL= 7.41 mg/kg/day	UF_A=10x UF_H=10x FQPA SF=1x	Chronic RfD = 0.074 mg/kg/day cPAD = 0.074 mg/kg/day	6 Month Feeding (Metalaxyl) Study in Dog MRID no. 00071598 LOAEL = 39 mg/kg/day, based on increased liver weights and clinical chemistry (alkaline phosphatase).
Incidental Ingestion, Short-Term (1 - 30 days)	NOAEL = 50 mg/kg/day	UF_A=10x UF_H=10x	MOE = 100 (Residential) MOE = NA (Occupational)	Developmental Toxicity in Rat (Mefenoxam) MRID no. 43800393 LOAEL = 250 mg/kg/day, based on clinical signs of toxicity including post-dosing convulsions.
Incidental Ingestion, Intermediate-Term (1 - 6 months)	NOAEL = 7.41 mg/kg/day	UF_A=10x UF_H=10x	MOE = 100 (Residential) MOE = NA (Occupational)	6 Month Feeding (Metalaxyl) Study in Dog MRID no. 00071598 LOAEL = 39 mg/kg/day, based on increased liver weights and clinical chemistry (alkaline phosphatase).
Dermal, Short-and Intermediate Term	NA		MOE = NA (Residential) MOE = NA (Occupational)	No endpoint was identified. No systemic toxicity was seen at the limit dose (1000 mg/kg/day) in a 21-day dermal rabbit toxicity study (Metalaxyl). MRID no.00072394
Dermal, Long-Term	NOAEL = 7.41 mg/kg/day	UF_A=10x UF_H=10x	MOE = NA (Residential) MOE = NA (Occupational)	6 Month Feeding (Metalaxyl) Study in Dog MRID no. 00071598 LOAEL = 39 mg/kg/day, based on increased liver weights and clinical chemistry (alkaline phosphatase).
Inhalation, Short-Term	NOAEL = 50 mg/kg/day [b]	UF_A=10x UF_H=10x	MOE = 100 (Residential) MOE = 100 (Occupational)	Developmental Toxicity in Rat (Mefenoxam) MRID no. 43800393 LOAEL = 250 mg/kg/day, based on clinical signs of toxicity including post-dosing convulsions.
Inhalation, Intermediate-Term	NOAEL = 7.41 mg/kg/day [b]	UF_A=10x UF_H=10x	MOE = 100 (Residential) MOE = 100 (Occupational)	6 Month Feeding (Metalaxyl) Study in Dog MRID no. 00071598 LOAEL = 39 mg/kg/day, based on increased liver weights and clinical chemistry (alkaline phosphatase).
Inhalation, Long-Term	NOAEL = 7.41 mg/kg/day [b]	UF_A=10x UF_H=10x	MOE = NA (Residential) MOE = NA (Occupational)	6 Month Feeding (Metalaxyl) Study in Dog MRID no. 00071598 LOAEL = 39 mg/kg/day, based on increased liver weights and clinical chemistry (alkaline phosphatase).
Cancer (oral, dermal, inhalation)	Classification: "not likely to be carcinogenic to humans"			

[c] UF = 100 (10X for interspecies and 10X for intraspecies differences), FQPA SF = 1X, MOE = margin of exposure, NA = not applicable
[a] Dermal absorption factor of 35% will be used for conversion from oral to dermal route (TXR. No. 014165, A. Lowit, 05/17/00)
[b] Absorption of 100% will be assumed in route to route conversion

3.4 Endocrine Disruption

The EPA is required under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, mefenoxam may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

No data are available at this time.

5.0 Dietary Exposure/Risk Characterization

5.1 Summary of Proposed Uses

Section 2.1 provides a use profile table, along with a summary of directions for proposed used of mefenoxam.

5.2 Dietary Exposure/Risk Pathway

Mefenoxam. Memo: Summary of Analytical Chemistry and Residue Data. D325127, B.Cropp-Kohlligian, June 2007
Mefenoxam. HED MARC Issues Memo: D268454, N. Dodd, 10/17/00
Mefenoxam. HED MARC Decision Memo: D269910, N. Dodd, 10/27/00

5.2.1 Metabolism in Primary Crops

The nature of the residue in plants is adequately understood for mefenoxam, based on metalaxyl metabolism studies. The metalaxyl metabolism studies on potato, grape, and lettuce indicate that metalaxyl is taken up, translocated, and extensively metabolized by plants. Metabolism involves oxidation of a ring-methyl group to the alcohol and then the carboxylic acid, hydroxylation of the

phenyl group, hydrolysis of the methyl ester and methyl ester bonds, and N-dealkylation. The major residues were: metalaxyl in potato tubers and grapes; metalaxyl, CGA-94689 (free and conjugated), and possibly CGA-100255, CGA-62826, and CGA-108905 in potato foliage; and metalaxyl and CGA-94689 (free and conjugated) in grape leaves and lettuce. Glucose conjugates of CGA-94689, CGA-100255, CGA-62826, CGA-107955, CGA-37734, and CGA-67869 have been found. [For the chemical names and structures of identified metabolites, see Appendix A.]

Metalaxyl metabolites can be separated into four classes: (i) those containing a 2,6-DMA moiety; (ii) those containing a HMMA moiety; (iii) those containing a Ring-OH moiety; and (iv) those containing a benzoic acid moiety. The only HMMA metabolite found in primary plant commodities is CGA-94689 (free and conjugated).

5.2.2 Metabolism in Livestock

The nature of the residue in livestock is adequately understood for mefenoxam, based on metalaxyl goat and hen metabolism studies. Metalaxyl in ruminants may be hydrolyzed to the ester alcohol and the acid alcohol which may in turn be N-dealkylated. Alternatively, oxidation can lead to either benzylic alcohol or phenolic compounds. The major residues in milk were fatty acid conjugates of CGA-67869, and the major residues in tissues were CGA-107955, CGA-94689, and CGA-67869; some metabolites may have been conjugated with glucuronic acid.

In poultry, metalaxyl is hydrolyzed to either the benzylic alcohol CGA-94689 or the ester alcohol CGA-67869; subsequently, the hydroxy metabolite CGA-94689 is converted to the sulfate P4 and CGA-67869 is converted to the fatty acid conjugate U3 or the acid alcohol CGA-107955; and CGA-107955 is subsequently hydrolyzed to the benzylic alcohol. The predominant metalaxyl metabolites in poultry are the disubstituted free acid form (P1) of CGA-94689 (isomer B), the sulfuric acid conjugate of CGA-94689 (isomer B), the disubstituted free acid form (P2) of CGA-94689 (isomer A), CGA-107955, and a fatty acid conjugate of P1 and P2. Metalaxyl was isolated only in whole egg. [For the chemical names and structures of identified metabolites, see Appendix A.]

As for plants, metalaxyl metabolites in livestock can be separated into four classes: (i) those containing a 2,6-DMA moiety; (ii) those containing a HMMA moiety; (iii) those containing a Ring-OH moiety; and (iv) those containing a benzoic acid moiety. Residues containing the 2,6-DMA moiety accounted for up to approximately 50% of the residues in ruminant tissues. Residues containing the HMMA moiety accounted for 34% of the residues in goat kidney and 12-14% of the residues in goat muscle and fat.

5.2.3 Analytical Methodology

Method I in PAM, Vol. II (Method AG-348) and Method AG-395 (sent to FDA for inclusion in PAM, Vol. II as Method III), are available for tolerance enforcement and have been used to collect data; however, after evaluation of the available radiovalidation and method validation data, HED concludes that these common moiety methods are not adequate to determine

metalaxyl/mefenoxam residues of concern in the current tolerance expressions.

The petitioner has not responded to the data requirements specified in a previous review to attempt to improve the recoveries of CGA-94689 and CGA-62826 in Method AG-395 and to submit a copy of the improved method developed by Enviro-Text Laboratories for determination of mefenoxam residues in canola seed. If the recent recommendations of the HED RARC are adopted, these data are no longer needed.

HED notes that method validation data and concurrent method recovery data that have been submitted for crop field trials in support of mefenoxam uses, including those associated with this petition, have reflected fortification of samples with mefenoxam only. Validation data for regulated metabolite CGA-94689 or for any metabolite containing the 2,6-DMA metabolite have not been submitted.

Neither enforcement method can distinguish between the R and S isomers; however, a confirmatory method (LC/MS/MS Method 456-98) for the enantioselective determination of metalaxyl or mefenoxam in crops has been adequately validated by ACB/BEAD and a revised version of the method has been submitted for inclusion in PAM, Vol. II.

Given concerns regarding the adequacy of the residue analytical methods to determine metalaxyl/mefenoxam residues of concern in plant and animal commodities, HED's RARC recommended the use of factors, as appropriate, derived from available residue chemistry data, to estimate total metalaxyl/mefenoxam residues of concern for dietary risk assessments.

Furthermore, the HED RARC concurred with the Risk Assessment Team's proposal that the metalaxyl/mefenoxam residues of concern in plant and livestock commodities for dietary risk assessments are metalaxyl/mefenoxam *per se*, its metabolites containing the 2,6-dimethylaniline (2,6-DMA) moiety, its metabolites containing the 2-hydroxymethyl-6-methylaniline (HMMA) moiety, its metabolites containing the ring hydroxylated dimethylaniline (Ring-OH) moiety, and its metabolites containing the benzoic acid moiety. It was determined that all residues identified in plant and livestock commodities from the available metabolism studies are of concern since none can be excluded for toxicological reasons.

Upon re-evaluation of the available radiovalidation and method validation data, it was determined that the common moiety residue analytical methods used to collect magnitude of the residue data for the purposes of setting tolerance levels will not adequately recover all of the metalaxyl/mefenoxam residues of concern. While these methods are adequate to recover residues of metalaxyl/mefenoxam *per se*, they are not likely to recover metalaxyl/mefenoxam metabolites containing the Ring-OH moiety or the benzoic acid moiety and available radiovalidation and method validation data indicate that the methods will not adequately recover metabolites containing the HMMA moiety and may not adequately recover all metabolites containing the 2,6-DMA moiety with the certainty needed to set legal limits. However, for the purposes of estimating the combined residues of metalaxyl/mefenoxam and its metabolites containing the 2,6-DMA moiety in/on plant and livestock commodities in chronic dietary risk

assessments, these common moiety methods are deemed adequate for data collection and therefore, current/reassessed tolerance levels are adequate to account for these residues in the risk analysis.

5.2.5 Pesticide Metabolites and Degradates of Concern

Previously, the HED Metabolism Assessment Review Committee (HED MARC Decision Memo, 10/27/00) concluded that the mefenoxam residues to be regulated for the tolerance expression and for dietary assessments would be as follows:

> In plants: (R)- and (S)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester, its metabolites containing the 2,6-DMA moiety, and one metabolite containing the HMMA moiety, N-(2-hydroxymethyl-6-methylphenyl)-N-(methoxyacetyl)alanine methyl ester (CGA-94689), each expressed as mefenoxam equivalents.
> In livestock: (R)- and (S)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester, its metabolites containing the 2,6-DMA moiety, and its metabolites containing the HMMA moiety, each expressed as mefenoxam equivalents.
> In rotational crops: (R)- and (S)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester, its metabolites containing the 2,6-DMA moiety, and one metabolite containing the HMMA moiety, N-2-hydroxymethyl-6-methylphenyl)-N-(methoxyacetyl)alanine methyl ester (CGA-94689), each expressed as mefenoxam equivalents, except that 2-[(methoxyacetyl)(2-methoxy-1-methyl-2-oxoethyl)amino]-3-methylbenzoic acid (CGA-108905, which contains the HMMA moiety) would also be included in the risk assessment for cereal grain rotational crops and N-(3-hydroxy-2,6-dimethylphenyl)-N-(methoxyacetyl)alanine methyl ester (CGA-100255, which contains the Ring-OH moiety) would be included in the risk assessment for leafy vegetables (Brassica and non-Brassica).

The Mefenoxam Risk Assessment Team in consultation with HED's RARC (14-Feb-2007) recommends the residues to be regulated for the tolerance expression be modified to include residues of metalaxyl/mefenoxam *per se* and the residues of concern for dietary risk assessments are metalaxyl/mefenoxam *per se*, its metabolites containing the 2,6-dimethylaniline (2,6-DMA) moiety, its metabolites containing the 2-hydroxymethyl-6-methylaniline (HMMA) moiety, its metabolites containing the ring hydroxylated dimethylaniline (Ring-OH) moiety, and its metabolites containing the benzoic acid moiety.

Table 5.1.8 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix	Residues included in Risk Assessment	Residues included in Tolerance Expression

Table 5.1.8 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary and Rotational Crops	Metalaxyl/mefenoxam *per se* Metabolites containing the 2,6-DMA (2,6-dimethylalanine) moiety Metabolites containing the HMMA (2-hydroxymethyl-6-methylaniline) moiety Metabolites containing the Ring-OH (ring hydroxylated dimethylaniline) moiety	Metalaxyl/mefenoxam *per se*
Livestock	Ruminant and Poultry	Metalaxyl/mefenoxam *per se* Metabolites containing the 2,6-DMA (2,6-dimethylalanine) moiety Metabolites containing the HMMA (2-hydroxymethyl-6-methylaniline) moiety Metabolites containing the Ring-OH (ring hydroxylated dimethylaniline) moiety	Metalaxyl/mefenoxam *per se*
Drinking Water		Metalaxyl/mefenoxam *per se* N-(2, 6-dimethylphenyl)-N-(methylacetyl-L-alanine) (CGA-62826), and N-(3_hydroxy-2, 6-dimethylphenyl)-N-(methoxyacetyl)-L-alanine (CGA 119857).	Not Applicable

5.2.6 Drinking Water Profile

The drinking water assessment was conducted using registrant submitted data for metalaxyl and mefenoxam. It provides Tier II (PRZM-EXAMS) surface water modeling and Tier 1 (SCI-GROW) groundwater modeling. The modeling was conducted for total metalaxyl and mefenoxam residues including metalaxyl, mefenoxam, N-(2, 6-dimethylphenyl)-*N*-(methylacetyl-L-alanine) (CGA-62826), and *N*-(3_hydroxy-2, 6-dimethylphenyl)-*N*-(methoxyacetyl)-L-alanine (CGA 119857). The metalaxyl/mefenoxam residue concentrations from Tier II surface water modeling are not expected to exceed 108.9 µg/L for the 1 in 10 year daily peak concentration, 36.7 µg/L for the 1 in 10 year annual concentration, and 25.9 µg/L for the 30 year annual average concentration. Metalaxyl/mefenoxam residue concentrations from Tier I ground water modeling is not expected to exceed 1.72 µg/L. However, it should be mentioned that the maximum metalaxyl concentration in registrant-sponsored ground water monitoring studies was 3.0 µg/L.

Table 5.2.1 Summary of Estimated Surface Water and Groundwater Concentrations for Metalaxyl/Mefenoxam.

	Metalaxyl/Mefenoxam	
	Surface Water Conc., ppb [a]	**Groundwater Conc., ppb [b]**
Acute	108.9	1.72
Chronic (*non-cancer*)	36.7	1.72
Chronic (cancer)	25.9	1.72

[a] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on the scenario for Florida citrus crops.

[b] From the SCI-GROW model assuming a maximum seasonal use rate of 6 lb ai/A, a K_{oc} of 409, and a half-life of 400 days.

5.2.7 Food Residue Profile

Lima Beans

The submitted lima bean crop field trial data are adequate to support the proposed use of the WP formulation on succulent shelled beans. In consideration of the petitioner's proposed restriction to limit use to succulent shelled beans grown east of the Mississippi River, the number and locations of the field trials are in accordance with OPPTS Guideline 860.1500 for green lima bean. The available data support the proposed use pattern of a maximum of 4 foliar applications of a WP formulation at 0.1 lb ai/A/application, with a 7-day minimum retreatment interval and a 3-day PHI. The data will support a tolerance in/on succulent shelled beans at 0.05 ppm. A legume vegetable crop group tolerance for residues of metalaxyl at 0.2 ppm already exists (40 CFR 180.408(a)).

Turnip Greens

A tolerance for metalaxyl residues of concern in/on mustard greens has been established at 5.0 ppm. The petitioner is currently proposing use of the 4 lb/gal EC formulation of mefenoxam (EPA Reg. No. 100-801) on turnip greens up to two foliar sprays at 0.125 lb ai/A/application

with a 14-day retreatment interval and a 7-day PHI. This use pattern is identical to the currently registered foliar use pattern of the 4 lb/gal EC formulation of mefenoxam on mustard greens. The registered uses on mustard greens were approved in a previous HED memo (DP Number 324493, L. Cheng, 3/17/06).

HED has concluded previously that residue data for mustard greens may be used to support use on turnip greens (in conjunction with the decision to move turnip greens to the Brassica leafy vegetables crop group; see memo dated 6/20/06 from B. Schneider to B. Madden). , The available mustard greens data support a tolerance for mefenoxam residues in/on turnip greens at 5.0 ppm. A leaves of roots and tubers crop group tolerance for residues of metalaxyl at 15.0 ppm already exists (40 CFR 180.408(a))

Bean, succulent seed without pod

The submitted lima bean crop field trial data are adequate to support the proposed use of the WP formulation on succulent shelled beans. In consideration of the petitioner's proposed restriction to limit use to succulent shelled beans grown east of the Mississippi River, the number and locations of the field trials are in accordance with OPPTS Guideline 860.1500 for green lima bean. The available data support the proposed use pattern of a maximum of 4 foliar applications of a WP formulation at 0.1 lb ai/A/application, with a 7-day minimum retreatment interval and a 3-day PHI. The data will support a tolerance in/on succulent shelled beans at 0.05 ppm. A legume vegetable crop group tolerance for residues of metalaxyl at 0.2 ppm already exists (40 CFR 180.408(a)).

Kiwifruit

In a previous review of the kiwifruit petition (PP#9E6057; DP Barcodes D260093 and D266900, N. Dodd, 3/13/01), HED had concluded that additional crop field trial data for kiwifruit were needed to satisfy geographic representation requirements; one additional crop field trial in CA was required. The registrant has now satisfied this data requirement. The number and location of the current crop field trials, conducted using mefenoxam, are in accordance with OPPTS Guideline 860.1500 for kiwifruit.

In the previous petition, HED had concluded that the available data were adequate to support conditional registration on kiwifruit. The data in the previous petition reflected two applications of a 2 lb/gal EC formulation of metalaxyl as a soil drench to the base of kiwifruit vines at a rate equivalent to 0.7 lb ai/A/application (assuming a plant density of 160 vines per acre). Applications were made in early December and 112 or 117 days later in spring at leaf emergence; kiwifruit samples were harvested 194 or 198 days after the second application. Residues were <0.05-0.057 ppm. The application rate used in these studies would correspond to 0.35 lb ai/A/application for mefenoxam, in consideration of the fact that mefenoxam products contain twice as much pesticidally active isomer as metalaxyl products.

The available crop field trial data also support the proposed new use pattern to kiwifruit. The data support a maximum of five soil surface applications of an EC formulation at 0.35 lb ai/A/application, for a total rate of 1.75 lb ai/A, with a 7-day PHI; up to three applications may be

made in the spring with 28-day minimum retreatment intervals, followed by up to two applications in the fall, with 28-day minimum retreatment intervals.

The current and previous crop field trial data support the established tolerance for residues of mefenoxam in/on kiwifruit at 0.10 ppm.

Papaya:
In a previous review of the papaya petition (PP#9E6057; DP Barcodes D260093 and D266900, N. Dodd, 3/13/01), HED had concluded that additional crop field trial data for papaya were needed to satisfy geographic representation requirements; additional crop field trials in FL and HI were required such that a total of either 3 trials with two treated samples per trial or 2 trials with four treated samples per trial were available for each use (soil drench and trunk/foliar). The registrant has now satisfied this data requirement. The number and location of the current crop field trials, conducted using mefenoxam and reflecting both soil drench and trunk/foliar applications in each trial, are in accordance with OPPTS Guideline 860.1500 for papaya.

In the previous petition, HED had concluded that the available data were adequate to support conditional registration on papaya. The data in the previous petition reflected two applications of a 2 lb/gal EC formulation of metalaxyl as a soil drench at 3.0 lb ai/A/application. The first application was made 12-13 days after transplanting and the second application was made 140 days later. Papaya samples were harvested 26 days after the second application; residues were 0.29-0.38 ppm in/on four samples. In a separate test, a 10% WP formulation of metalaxyl was applied four times as a trunk (fruit column) and foliage spray at 0.30 lb ai/A/application, with a 21-day retreatment interval. Papaya samples were collected 1 day after the last treatment; residues were 0.16-0.20 ppm in/on four samples. The application rates used in these studies (in consideration of the fact that mefenoxam products contain twice as much pesticidally active isomer as metalaxyl products) would correspond to 1.5 lb ai/A/application for mefenoxam soil drench applications and 0.15 lb ai/A/application for trunk/foliar applications. The data for papaya were translated to support the proposed uses on star apple, black sapote, mango, sapodilla, canistel, and mamey sapote.

The available crop field trial data also support the proposed new use pattern to canistel, mango, papaya, sapodilla, black sapote, mamey sapote, and star apple. The data would support a maximum of two soil surface applications of a 4 lb/gal EC or SL formulations at 1.5 lb ai/A/application and a maximum of four trunk/foliar spray applications of a 4.8% WP formulation of mefenoxam at 1.95 lb ai/A/application, for a total seasonal rate of 10.8 lb ai/A, with a 1-day PHI. The soil surface applications are to be made on the same day as the first and last trunk/foliar applications, and the trunk/foliar applications are to be made with a 14-day retreatment interval.

The current and previous crop field trial data support the established tolerance for residues of mefenoxam in/on the following crops at 0.40 ppm: canistel, mango, papaya, sapodilla, black sapote, mamey sapote, and star apple.

Table 5.2.2. Summary of Residue Data from Crop Field Trials with Mefenoxam.									
Crop matrix	Total Applic. Rate (lb ai/A)	PHI (days)	Residue Levels (ppm) [1]						
			n	Min.	Max.	HAFT [2]	Median	Mean	Std. Dev.
Lima bean, green	0.395-0.601	2-4	14	<0.05	<0.05	<0.05	0.025	0.025	0.0
Kiwifruit	1.746-1.776	7	6	<0.05	<0.05	<0.05	0.025	0.025	0.0
Papaya, fruit	10.98-11.24	1	6	<0.05	0.081	0.077	0.065	0.056	0.025

[1] For calculation of the minimum, maximum, and HAFT, the LLMV (0.05 ppm) was used for residues reported below the LLMV. In the calculation of the median, mean, and standard deviation, 0.025 ppm (half the LLMV) was used for residues reported as less than the LLMV.
[2] HAFT = Highest Average Field Trial.

5.2.8 International Residue Limits

There are no Codex, Canadian, or Mexican Maximum Residue Limits or tolerances for the proposed uses of mefenoxam on beans, succulent shelled and turnip, greens.

There are Codex MRLs for Metalaxyl M (mefenoxam) for plant commodities expressed as metalaxyl. Although there are no Codex MRLs for animal commodities the definition for animal commodities is metalaxyl + metabolites containing the 2,6-dimethylaniline moiety. The Codex MRLs for Metalaxyl M have not been advanced to final status, pending revocation of metalaxyl MRLs.

5.3 Dietary Exposure and Risk

Metalaxyl/Mefenoxam Chronic Aggregate Dietary and Drinking Water Exposure and Risk Assessment for the Petitions PP#5F7018 and PP#9E6057 and Associated Section 3 Registration Action DP Number 337966,04/19/2007 , Becky Daiss

5.3.1 Acute Dietary

An endpoint for acute dietary risk assessment was not identified and corresponding risk assessments are not required (acute dietary and acute aggregate risk assessment).

5.3.2 Chronic Dietary

HED conducted a somewhat refined chronic dietary and drinking water exposure assessment for all existing and proposed new food uses of metalaxyl/mefenoxam and drinking water. In this assessment, it was first assumed that residues were present at tolerance levels in plant commodities for both direct use tolerances for metalaxyl/mefenoxam and indirect or inadvertent tolerances for metalaxyl. Additional factors derived from metabolism data were applied to certain plant commodities to address concerns regarding the adequacy of the residue analytical method to determine metalaxyl/mefenoxam residues of concern in plant and livestock

commodities. This concern was raised during the review of method validation data required for reregistration which were submitted with this petition. Data from metabolism studies on goats and hens were used to estimate conservative levels of metalaxyl/mefenoxam in livestock commodities. Processing data for cereal grain flour and fruit juice were also used in the assessment. Estimated average % crop treated data for mefenoxam was used when available. The 1 in 10 year annual estimated surface water concentration from the Tier 1 PRZM-EXAMS model was used to assess contributions from drinking water.

Results of the chronic dietary assessment indicate that the general U.S. population and all other population subgroups have exposure and risk estimates below HED's level of concern. The DEEM chronic dietary exposure estimate for the highest exposed population subgroup, children 1-2 years of age, is 66% of the cPAD.

Table 5.3. Summary of Dietary and Drinking Water Exposure and Risk for Metalaxyl/Mefenoxam

Population Subgroup	cPAD (mg/kg/day)	Dietary/Drinking Water Exposure (mg/kg/day)	%cPAD
General U.S. Population	0.074	0.0206	28
All Infants (< 1 year old)	0.074	0.0226	31
Children 1-2 years old	**0.074**	**0.0488**	**66**
Children 3-5 years old	0.074	0.0464	63
Children 6-12 years old	0.074	0.0315	43
Youth 13-19 years old	0.074	0.0203	28
Adults 20-49 years old	0.074	0.0168	23
Adults 50+ years old	0.074	0.0146	20
Females 13-49 years old	0.074	0.0161	22

5.3.3 Cancer Dietary

Metalaxyl has been classified as "not likely to be a human carcinogen" based on the results of a carcinogenicity study in mice and the combined chronic toxicity and carcinogenicity study in rats. Based on the classification of metalaxyl, mefenoxam is also considered "not likely to be a human carcinogen," and an assessment of cancer risk was not conducted.

6.0 Residential Exposure

Mefenoxam: Occupational Exposure/Risk Assessment for New Uses on Lima Beans and Turnip Greens (DP#:335092. PC# 113502) 03/16/2007 Jack Arthur

There are residential uses currently registered for mefenoxam. While no residential uses are subject to this current petition, the Food Quality Protection Act requires that all existing non-occupational exposures be considered for aggregate risk to the general population. The products registered for residential uses that could result in non-occupational exposure include the following:

EPA Reg No	Product name	(% ai)	Formulation
100-793	Subdue®MAXX® EC	(46.6%)	Emulsifiable Concentrate
100-794	Subdue®MAXX® GR	(0.97%)	Granular
100-795	Subdue®MAXX® WSP	(43.6%)	WP in Water-soluble Packets
100-795	Subdue®MAXX® EC	(21.3%)	Emulsifiable Concentrate

Registered residential uses may result in short-term to intermediate-term exposures; however, based on current use patterns, chronic exposure (6 or more months of continuous exposure) to mefenoxam is not expected. Exposure may occur to adults from handling the pesticide, and to both adults and children from contact with treated areas following application. Toxicity endpoints have been identified for use in assessing risks from short- and intermediate-term inhalation exposure to residential handlers, and short- and intermediate-term incidental ingestion exposure to toddlers. Non-occupational (i.e., residential) handler and postapplication exposures are assessed below for the two major mefenoxam products on turf which are considered to represent the reasonable upper-bound residential exposure potential: Subdue® MAXX® EC (46.6%), and Subdue® MAXX® GR (0.97%).

6.1 Residential Handler Exposure

Residential handler exposure has been assessed for two formulations of mefenoxam: an emulsifiable concentrate, Subdue®MAXX® EC, which is used at a maximum rate of 0.015 lb ai/1000 ft^2; and, a granular, Subdue®MAXX® GR, which also is used at a maximum rate of 0.015 lb ai/1000 ft^2. Exposure and risk for residential applicators are summarized in Table 5.

The five scenarios used were: (1) Granular Bait Dispersed by Hand, (2) Belly Grinder-Granular Open Pour- Mixer/Loader/Applicator (MLAP), (3) Push Type Granular Spreader (MLAP), (4) Mixer/loader/applicator Liquid - Low-pressure handwand, and (5) garden hose-end sprayer.

Residential handlers may be exposed on a short-term basis. Intermediate-term handler exposure (more than 30 days of continuous exposure) is not expected. **All exposure scenarios for short-term inhalation result in MOEs that do not trigger HED's level of concern** (i.e., MOEs are larger than the target MOE of 100, which includes an FQPA factor of 1X). See Table 6.1

The method used for estimating residential applicator exposure is believed to produce a central tendency to high-end estimate of exposure.

Table 6.1. Inhalation Exposure and Risk Estimates for Non-Occupational Lawn Applicators

PHED Scenario Selected from Draft SOP for Residential Exposure Assessments	Application Rate	Area Treated per day	Unit Exposure (mg/lb ai)	PHED Data Confidence	Short-term Daily Inhalation Dose[1] (mg/kg/day)	Short-Term MOE[2]
1. Granular Bait Dispersed by Hand	0.015 lb ai/1000 ft^2	1000 ft^2	0.47[3]	Medium	0.00012	430,000
2. Belly Grinder Granular Open Pour (Mix, Load, Apply)	0.65 lb ai/acre	0.5 acres	0.062[3]	High	0.00033	150,000
3. Push Type Granular (Mix Load, and Apply)	0.65 lb ai/acre	0.5 acres	0.00091[4]	High	0.0000049	10,000,000
4. Mixer/loader/applicator Liquid/Low-pressure Handwand	0.015 lb ai/1000 ft^2	1000 ft^2	0.03[3]	Medium	0.0000075	6,700,000
5. Garden hose-end sprayer	0.65 lb ai/acre	0.5 acres	0.016[4]	Low	0.000087	570,000

[1] Daily Dose = [Application Rate (lb ai/A) x Acres Treated (A/day) x Unit Exposure(mg/lb ai handled) x Absorption Factor (100%)]/Body Weight (60 kg).
[2] MOE = NOAEL/ Daily Dose. Short-term Inhalation NOAEL=50 mg/kg/day.
[3] PHED unit exposure value from Draft SOPs for Residential Exposure Assessments (December 18, 1997).
[4] Data from Outdoor Residential Exposure Taskforce (MRID 449722-01).

6.2. Residential Postapplication Exposure

Registered residential uses may result in short-term to intermediate-term exposures, however, based on current use patterns, chronic exposure (6 or more months of continuous exposure) to mefenoxam is not expected. Exposure may occur to adults from handling the pesticide, and to both adults and children from contact with treated areas following application. Toxicity endpoints have been identified for use in assessing risks from short- and intermediate-term inhalation exposure to residential handlers, and short- and intermediate-term incidental ingestion

exposure to toddlers. Non-occupational (i.e., residential) handler and postapplication exposures are assessed below for the two major mefenoxam products on turf which are considered to represent the reasonable upper-bound residential exposure potential: Subdue® MAXX® EC (46.6%), and Subdue® MAXX® GR (0.97%).

Residential handler exposure has been assessed for two formulations of mefenoxam: an emulsifiable concentrate, Subdue®MAXX® EC, which is used at a maximum rate of 0.015 lb ai/1000 ft^2; and, a granular, Subdue®MAXX® GR, which also is used at a maximum rate of 0.015 lb ai/1000 ft^2. Exposure and risk for residential applicators are summarized in Table 5.

The five scenarios used were: (1) Granular Bait Dispersed by Hand, (2) Belly Grinder-Granular Open Pour- Mixer/Loader/Applicator (MLAP), (3) Push Type Granular Spreader (MLAP), (4) Mixer/loader/applicator Liquid - Low-pressure handwand, and (5) garden hose-end sprayer.

Residential handlers may be exposed on a short-term basis. Intermediate-term handler exposure (more than 30 days of continuous exposure) is not expected. **All exposure scenarios for short-term inhalation result in *MOEs that do not trigger* HED's level of concern** (i.e., MOEs are larger than the target MOE of 100, which includes an FQPA factor of 1X).

The method used for estimating residential applicator exposure is believed to produce a central tendency to high-end estimate of exposure.

Table 6.2.1 Oral Hand-to-mouth Exposure and Risk for Children from Treated Lawns

Application Rate (lb ai/A)	Fraction of ai Available	Turf Transferable Residue[1] (ug/cm^2)	Exposure Time (hrs/day)	Extraction by saliva	Hand Surface Area (cm^2/event)	Frequency (events/ hr)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	Short-Term MOE[3]	Intermediate-Term MOE[3]
0.65	0.35	0.36	2	0.5	20	20 (ST) 9.5 (IT)	15	0.010 (ST) 0.0046 (IT)	5200	1600

1 Turf Transferable Residue (ug/cm2) = Application rate (lb ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm2
2 Daily Dose = (Turf Transferable Residue (ug/cm2) x Extraction by Saliva x Hand Surface Area (cm2/event) x Frequency (events/hr) x 1E-3 mg/ ug x ET (hrs/day)] / [Body Weight (kg)]
3 Short & Intermediate-Term Oral MOE = Short- (50 mg/kg/day) & Intermediate-Term (7.4 mg/kg/day) Oral NOAEL/Daily Dose

Table 6.2.2. Exposure and Risk for Children from Object-to-mouth (Turfgrass) from Treated Lawns

Application Rate (lb ai/A)	Fraction of ai Available	Grass Residue[1] (ug/cm^2)	Mouthing Rate (cm^2/day)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	Short--Term MOE[3]	Intermediate--Term MOE[3]
0.65	0.2	1.4	25	15	0.0023	22,000	3200

1Grass residue (ug/cm2) = [Application Rate (lbs ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm2]
2 Daily Dose = [Grass reside (ug/cm2) x mouthing rate (cm2/day) x 1E-3 mg/ug] / [Body Weight (kg)]
3 Short & Intermediate-Term Oral MOE = Short- (50 mg/kg/day) & Intermediate-Term (7.4 mg/kg/day) Oral NOAEL/Daily Dose

Table 6.2.3. Exposure and Risk for Children from Ingestion of Soil from Treated Lawns

Application Rate (lb ai/A)	Fraction of ai Available	Soil Residue[1] (ug/g)	Ingestion Rate (g/day)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	Short--Term MOE[3]	Intermediate--Term MOE[3]
0.65	1.0	4.5	100	15	0.000033	1.5E+6	230,000

1 Soil residue (ug/g) = [Application Rate (lbs ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm^2 x 0.67 cm^3/g soil]
2 Daily Dose = [Soil reside (ug/g) x Ingestion rate (mg/day) x 1E-6 g/ug] / [Body Weight (kg)]
3 Short & Intermediate-Term Oral MOE = Short- (50 mg/kg/day) & Intermediate-Term (7.4 mg/kg/day) Oral NOAEL/Daily Dose

Combined Exposure: FQPA requires that residential exposures that could reasonably be expected to occur on the same day be combined and compared to the appropriate toxicity endpoint. For non-occupational scenarios, the three scenarios that would reasonably be expected to occur on the same day are children incidental ingestion of residues on turf from hand-to-mouth activities, object-to-mouth (turfgrass) activities and ingestion of soil. Daily incidental oral exposures, when combined, total 0.012 mg/kg/day for the short-term scenario and 0.0071 mg/kg/day for the intermediate-term scenario. When the combined short-term exposure is compared to the short-term NOAEL (50 mg/kg/day), the MOE equals 4,200. When the combined intermediate-term exposure is compared to the intermediate-term NOAEL (7.41 mg/kg/day), the MOE equals 1,000. Therefore, the combined exposures anticipated for residential scenarios do not trigger HED concern.

6.3 Recreational

Mefenoxam may be used on turf at recreational use sites and, therefore, may result in postapplication exposure to adults and children involved in recreational activities. Exposures to adults and children from the use of mefenoxam at recreational use sites are assumed to be the same as those assessed for residential use sites and, therefore, a separate recreational exposure assessment was not included. Also, it is not expected that the upper bound residential exposure scenario would occur on the same day as an upper bound recreational exposure scenario; therefore, the residential risk estimate should serve as an upper bound for both residential and recreational exposure.

6.4 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a

potential source of exposure from the groundboom application. The EPA has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The EPA is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The EPA has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

7.0 Aggregate Risk Assessments and Risk Characterization

Aggregate risk considers total exposure to mefenoxam through different pathways of exposure. Risk estimates are aggregated because it is assumed that these exposures may occur over the same time period. The identification of the same endpoint for exposures that may occur over the same time period (although via different routes) enables risk via different routes to be aggregated.

The same endpoint and NOAEL for short-term inhalation and incidental oral exposure was identified from a developmental toxicity study in rats with mefenoxam (clinical signs of toxicity including post-dosing convulsions, NOAEL=50 mg/kg/day). Likewise, the same endpoint and NOAEL for intermediate-term inhalation and incidental oral exposure and chronic dietary exposure (increased liver weight and clinical chemistry changes, NOAEL=7.41 mg/kg/day) was identified from a 6-month dog study. Therefore, short-term, intermediate-term and chronic risk estimates can be aggregated in this risk assessment.

7.1 Acute Aggregate Risk

No acute dietary endpoint was identified. Therefore, an acute aggregate risk assessment is not needed.

7.2 Short-Term Aggregate Risk

Short-term exposure occurs over 1-30 days. Short-term aggregate risk is made up of the combined exposure from inhalation, incidental oral, dietary food and water risk estimates.

Risk from dermal exposure was not included because no dermal hazard was identified. For adult residential short-term exposure (males and females), the inhalation exposure estimate for the belly grinder application scenario was used because it was the scenario resulting in the highest handler exposure (0.00033 mg/kg/day). For an estimate of children's residential exposure, the

postapplication incidental oral exposure scenario was used. Children's combined exposure from all incidental oral sources is 0.01233 mg/kg/day.

Because the short-term aggregate MOEs are all greater than 100, risk estimates do not exceed HED's level of concern for adults or children. Results are presented in Table 6.

Table 7.2. Short-Term Aggregate Risk Calculations

Population	Short-Term Scenario				
	NOAEL mg/kg/day	LOC[1]	Average Food & Water Exposure mg/kg/day	Residential Exposure[2] mg/kg/day	Aggregate MOE (food and residential)[3]
Adult Males	50	100	0.0206	0.00033	2389
Adult Females	50	100	0.0206	0.00033	2389
Children 1-2 years	50	100	0.0488	0.01233	818
Children 3-5 years	50	100	0.0464	0.01233	851
Children 6-12 years	50	100	0.0315	0.01233	1141

[1] 100x = 10x interspecies and 10x intraspecies uncertainty factors
[2] Residential Exposure = [Oral exposure + Inhalation Exposure]. Mefenoxam Exposure/Risk Assessment for New Uses on Lima Beans and Turnip Greens Jack Arthur 16-Mar-2007 (Tables 5, 6a, 6b, 6c).
[3] Aggregate MOE = [NOAEL) (Avg Food & Water Exposure + Residential Exposure)]

7.3 Intermediate-Term Aggregate Risk

Intermediate-term exposure occurs from 30 days to six months. Intermediate-term aggregate risks are made up of the combined exposure from incidental oral, dietary and drinking water risk estimates.

Risk from dermal exposure is not considered because no dermal hazard was identified. Intermediate-term residential handler (adult) exposure is not expected because of the intermittent and seasonal use pattern. Postapplication inhalation exposure for adults is considered negligible and was also not assessed. For an estimate of children's residential exposure, the postapplication oral exposure scenario was used. Children's combined exposure from all residential incidental oral sources is 0.006933 mg/kg/day.

Because the short-term aggregate MOEs are all greater than 100, risk estimates do not exceed HED's level of concern for adults or children. Results are presented in Table 7.

Table 7.3. Intermediate-Term Aggregate Risk Calculations					
Population	**Intermediate-Term Scenario**				
	NOAEL mg/kg/day	**LOC[1]**	**Average Food & Water Exposure mg/kg/day**	**Residential Exposure[2] mg/kg/day**	**Aggregate MOE (food and residential)[3]**
Children 1-2 years	7.4	100	0.0488	0.006933	133
Children 3-5 years	7.4	100	0.0464	0.006933	139
Children 6-12 years	7.4	100	0.0315	0.006933	195

[1] 100x = 10x interspecies and 10x intraspecies uncertainty factors

[2] Residential Exposure = [Oral exposure + Inhalation Exposure]. Mefenoxam Exposure/Risk Assessment for New Uses on Lima Beans and Turnip Greens Jack Arthur 16-Mar-2007 (Tables 5, 6a, 6b, 6c.)

[3] Aggregate MOE = [NOAEL) (Avg Food & Water Exposure + Residential Exposure)]

7.4 Chronic Aggregate Risk

Chronic exposure occurs continuously for more than six months. Chronic aggregate risk is made up of the combined exposure from dietary and drinking water risk estimates. Incidental oral exposure was not included as it is not expected to occur over the long-term duration.

Chronic residential handler (adult) exposure is not expected based on the use pattern. Postapplication inhalation exposure for adults is considered negligible and was also not assessed. Finally, postapplication oral exposure to children is not expected over the chronic time period. Chronic aggregate risk estimates are based on food and drinking water exposures only.

Results of the chronic aggregate risk assessment indicate that risk estimates do not exceed HED's level of concern for adults or children. Please refer to results are presented in Table 5.3.

7.5 Cancer Risk

Based on the classification of metalaxyl, mefenoxam is considered "not likely to be a human carcinogen." Therefore, an aggregate cancer risk assessment is not 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 mefenoxam and any other substances and mefenoxam does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that mefenoxam 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

For this registration, populations of concern include occupational handlers who may be exposed during mixing, loading, and application of mefenoxam using aerial, airblast, chemigation and groundboom equipment.

9.1 Occupational Handler

There is a potential for exposure to mefenoxam during mixing, loading, and application activities. An exposure/risk assessment was performed using applicable endpoints selected by the HIARC (4/11/00) and affirmed by the risk assessment team. Handler's exposure and risk were estimated for the following scenarios: (1) mixer/loader: open mixing liquid for aerial; (2) mixer/loader: open mixing wettable powder in water-soluble bag for aerial and chemigation; (3) aerial application of liquid: closed cockpit; (4) flagging for aerial applications; (5) mixer/loader: open mixing liquid for groundboom; (6) mixer/loader: open mixing wettable powder in water-soluble bag for groundboom; and (7) groundboom application of liquid: open cab.

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. In accordance with HED's Exposure Science Advisory Council (SAC) policy, exposure data from the Pesticide Handlers Exposure Database (PHED) Version 1.1, as presented in PHED Surrogate Exposure Guide (8/98), were used with other HED standard values for areas treated per day, body weight, and the level of personal protective equipment, to assess handler exposures.

Short- and intermediate-term dermal toxicity endpoints were not identified. Although a long-term dermal endpoint was identified, long-term exposure ($\geq$ 180 days) is not expected. Therefore, a dermal risk assessment was not conducted. Inhalation toxicity endpoints of concern were identified for all durations of exposure. However, because long-term exposures are not anticipated, only short- and intermediate-term inhalation risks were assessed.

Daily inhalation exposures (assuming 100% absorption) were compared to the NOAEL of 50

mg/kg/day from a developmental study in rats (endpoint: clinical signs including post-dosing convulsions) to determine the risk for short-term inhalation exposures. The MOEs range from 21,000 (mixer/loader: open mixing liquid for groundboom) to 1,000,000 (aerial application, liquid). **These risks DO NOT exceed HED's level of concern.** For intermediate-term risks, daily inhalation exposures (assuming 100% absorption) were compared to the NOAEL of 7.4 mg/kg/day from a six-month oral study in dogs (endpoint: increased liver weights and clinical chemistry). The MOEs range from 3500 (mixer/loader: open mixing liquid for groundboom) to 170,000 (aerial application, liquid). **These risks DO NOT exceed HED's level of concern.**

The minimum level of PPE for handlers is based on acute toxicity for the end-use product. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the Worker Protection Standard (WPS).

Exposure assumptions and estimates for occupational handlers are summarized in Table 4.

Table 4. Inhalation Exposure and Risk for Occupational Handlers

PHED Exposure Scenario	Maximum Application Rate (lb ai/A)	PHED Unit Exposure (mg/lb ai)	PHED Data Confidence	Area Treated per Day (acres)	Body Weight (kg)	Daily Inhalation Dose[1] (mg/kg/day)	Short-term MOE[2]	Interm.-term MOE[2]
1.mixer/loader: open mixing liquid for aerial	0.125	0.0012	High	350	70 (60)	0.00075 (0.00088)	57,000	9900
2.mixer/loader: mixing wettable powder in water-soluble bag for aerial and chemigation.	0.1	0.00024	Low	350	70 (60)	0.00012 (0.00014)	420,000	53,000
3.aerial application of liquid: closed cockpit	0.125	0.000068	Medium	350	70 (60)	0.000043 (0.00005)	1,000,000	170,000
4.flagging for aerial applications	0.125	0.00035	High	350	70 (60)	0.00022 (0.00026)	190,000	34,000
5. mixer/loader: open mixing liquid for groundboom	1.5	0.0012	High	80	70 (60)	0.0021 (0.0024)	21,000	3500
6. mixer/loader: mixing wettable powder in water-soluble bag for groundboom	1.3	0.00024	Low	80	70 (60)	0.00036 (0.00042)	120,000	21,000
7. groundboom application of liquid: open cab	1.5	0.00074	High	80	70 (60)	0.0013 (0.0015)	33,000	4900

[1] Daily Dose =[Application Rate x Area Treated (A/day) x Unit Exposure x Absorption Factor (100%) /Body Weight:70 kg male BW used for intermediate-term; 60 kg female BW (in parentheses) used for short-term because of maternal toxicity in a developmental study.

[2] MOE = NOAEL/ Daily Dose. Short-term Inhalation NOAEL=50 mg/kg/day; Intermediate-term Inhalation NOAEL=7.4 mg/kg/day.

9.2 Postapplication

Occupational exposure can occur via the dermal and/or inhalation route. Inhalation exposure during postapplication activities is considered negligible for all mefenoxam use scenarios. Dermal exposure during postapplication activities is not considered because applicable dermal endpoints were not identified. Therefore, a risk assessment for postapplication activities with mefenoxam-treated crops is not necessary. However, because primary eye irritation testing has placed mefenoxam in Toxicity Category I, an interim 48-hour restricted entry interval (REI) is required under the Worker Protection Standard.

10.0 Data Needs and Label Recommendations

10.1 Toxicology

The toxicology database for mefenoxam is considered complete for risk assessment purposes; however, a 28-day inhalation study in rats is required.

10.2 Residue Chemistry

HED has examined the residue chemistry database for mefenoxam. If the recent recommendations of the HED RARC are adopted and pending submission of a revised Section B (see requirements under Directions for Use), there are no residue chemistry issues that would preclude granting a registration for the requested foliar uses of mefenoxam on succulent shelled beans and turnip greens. Residues of mefenoxam in/on succulent shelled beans and turnip greens resulting from the proposed maximum uses of mefenoxam are not expected to exceed the currently established crop group tolerances for residues of metalaxyl (40 CFR 180.408(a)) in/on legume vegetables (0.2 ppm) and leaves of roots and tubers (15.0 ppm), respectively. Hence, HED recommends in favor of granting the proposed uses but against the registrant's request to establish new tolerances for residues of mefenoxam in/on succulent shelled beans and turnip greens under 40 CFR 180.546(a).

If the recent recommendations of the HED RARC are adopted, then all mefenoxam data deficiencies identified in the previous review for PP#9E6057, concerning the use of mefenoxam on canistel, kiwifruit, mango, papaya, sapodilla, black sapote, mamey sapote, and star apple (DP Barcodes D260093 and D266900, N. Dodd, 3/13/01), are now resolved.

If the recent recommendations of the HED RARC are adopted, then outstanding metalaxyl/mefenoxam data requirements pertaining to residue analytical methods, storage stability for metabolites P1 and P2 in livestock commodities, and field accumulation in rotational crops are no longer required. See requirements under Residue Analytical Methods, Storage Stability, and Field Accumulation in Rotational Crops.

If the recent recommendations of the HED RARC, as outlined above, are NOT adopted, then significant residue chemistry database deficiencies exist. These deficiencies are detailed in

Appendix B

10.3 Occupational and Residential Exposure

The occupational and residential databases for mefenoxam are considered complete for risk assessment purposes.

Appendix A: Toxicity Profile

Guideline No.	Study Type, Test Substance	Results
870.3100	90-day Oral Toxicity-rodent (Rat), Mefenoxam	NOAEL = 44.8 mg/kg/day; LOAEL = 90.5 mg/kg/day based on increased hepatocyte hypertrophy, increased lymphocytic infiltration of liver.
870.3100	28-day Oral Toxicity-rodents (Rat, Gavage), Mefenoxam and Metalaxyl	Mefenoxam: NOAEL = 50 mg/kg/day; LOAEL = 150 mg/kg/day based on histopathology of the liver and clinical signs, including hypoactivity post-dosing Metalaxyl: NOAEL = 10 mg/kg/day; LOAEL = 50 mg/kg/day based on extramedullary hematopoiesis of the spleen (females) and hepatocellular hypertrophy
870.3100	28-day Oral Toxicity Rodents (Rat), Mefenoxam	NOAEL = < 42.68 mg/kg/day in males and < 47.47 mg/kg/day in females LOAEL = 42.68 mg/kg/day in males and 47.47 mg/kg/day in females based onincreased hepatocyte hypertrophy, increased absolute and relative liver weights
870.3150	90-day Oral Toxicity in Nonrodents (Dog), Mefenoxam	NOAEL = 250 ppm (M: 7.25 mg/kg/day; F: 7.93 mg/kg/day); LOAEL = 1250 ppm (M: 38.60 mg/kg/day, F: 39.46 mg/kg/day) based on increased alkaline phosphatase activity and increased absolute and relative liver weights for both sexes
870.3200	21-day Dermal Toxicity, Mefenoxam	NOAEL = 1000 mg/kg/day; LOAEL > 1000 mg/kg/day
870.3700	Prenatal Developmental in Rodents (Rat), Mefenoxam	**Maternal** NOAEL = 50 mg/kg/day; LOAEL = 250 mg/kg/day based on decreased body weight gains and food consumption. **Developmental** NOAEL = 250 mg/kg/day; LOAEL > 250 mg/kg/day.
870.3700	Prenatal Developmental in Rodents (Rat), Metalaxyl	**Maternal** NOAEL = 50 mg/kg/day; LOAEL = 250 mg/kg/day based on clinical signs, including post-dose convulsions. **Developmental** NOAEL = 250 mg/kg/day; LOAEL = 400 mg/kg/day based on increased incidence of skeletal variations.
870.3700	Prenatal Developmental in Nonrodents (Rabbit), Metalaxyl	**Maternal** NOAEL = 150 mg/kg/day; LOAEL = 300 mg/kg/day based on decreased body weight gain. **Developmental** NOAEL = 300 mg/kg/day; LOAEL > 300 mg/kg/day.

Guideline No.	Study Type, Test Substance	Results
870.3800	Reproduction and Fertility Effects (Rat), Metalaxyl	**Parental/Systemic** NOAEL = 62.5 mg/kg/day (M), 12.5 mg/kg/day (F) LOAEL > 62.5 mg/kg/day (M), = 62.5 mg/kg/day (F) based on increased relative liver weights **Reproductive** NOAEL = 62.5 mg/kg/day; LOAEL > 62.5 mg/kg/day. **Offspring** NOAEL = 12.5 mg/kg/day; LOAEL = 62.5 mg/kg/day based on histopathological changes in the livers of female pups.
870.4100	Chronic Toxicity (Dog), Metalaxyl	NOAEL = 7.80 mg/kg/day (M), 7.41 mg/kg/day (F) LOAEL = 30.63 mg/kg/day (M), 32.36 mg/kg/day (F) based on increased alkaline phosphatase, increased relative and absolute liver weights.
870.4300	Chronic Toxicity/ Carcinogenicity (Rat), Metalaxyl	NOAEL = M: 9.43 mg/kg/day (M), 9.95 mg/kg/day (F) LOAEL = 46.6 mg/kg/day (M), 55.0 mg/kg/day (F) based on increased serum alanine amino-transferase and serum aspartate amino-transferase, increased periacinar vacuolation of hepatocytes, increased absolute and relative liver weights. **No evidence of carcinogenicity**
870.4300	Carcinogenicity (Mouse), Metalaxyl	NOAEL = 24.85 mg/kg/day (M), 29.59 mg/kg/day (F) LOAEL = 128.89 mg/kg/day (M), 148.16 mg/kg/day (F) based on increased fatty infiltration of the liver. **No evidence of carcinogenicity**
870.511 870.5265	Gene Mutation , Mefenoxam	There was no concentration related positive response of induced mutant colonies over background in Salmonella or E. coli strains.
870.511 870.5265	Gene Mutation , Mefenoxam	No concentration related positive response of induced mutant colonies over background for Salmonella or E. coli strains.
870. 5375	Chromosome Aberration , Mefenoxam	Mefenoxam up to 2030 ug/mL is considered negative for inducing chromosome aberrations in CHO cell cultures +/- S9.
870. 5375	Chromosome Aberration , Mefenoxam	Mefenoxam in the presence of CA 2331 at 2000 ppm is considered positive for inducing chromosome aberrations in CHO cell cultures.
870. 5375	Chromosome Aberration , Mefenoxam	In the absence and presence of S9, statistically significant and dose dependant increases in % of cells with specific chromosome aberrations were obtained at 18 hour harvest, beginning at relatively non-toxic doses of 39.06 ug/mL/-S9 and 156.25 ug/mL/+S9
870. 5375	Chromosome Aberration Mefenoxam	CA 2331 is considered positive for inducing chromosome aberrations in CHO cells at concentrations > 10 ug/mL without activation
870.5385	In Vivo Cytogenetics, Metalaxyl	Metalaxyl had no effect on the incidence of nuclear anomalies.

Guideline No.	Study Type, Test Substance	Results
870.5550	Unscheduled DNA Synthesis, Metalaxyl	Concentrations of metalaxyl up to cytotoxic concentrations did not increase unscheduled DNA synthesis above control levels in three different assays.
870.7485	Metabolism and Pharmacokinetics (Rat), Metalaxyl	In the first 8 hours of treatment, approximately 30% of the dose was absorbed with 1% of the test substance in the skin at the application site.
870 7600	Dermal Penetration, Metalaxyl	At 24 hours after dosing, approximately 35% was absorbed.

Appendix B: Residue Chemistry Database Issues

860.1200 Directions for Use - Based on Proposed Labels: (i) Ridomil Gold® Copper (EPA Reg. No. 100-804), (2) Ridomil Gold® EC (EPA Reg. No. 100-801), and (3) Ridomil Gold® SL (EPA Reg. No. 100-1202) which should be resubmitted as Section B of the petition with the following amendments:

- Label use rates should be provided in terms of lb ai/A.

- The proposed use on succulent shelled beans must be modified to specify that foliar applications may not be made if preplant or at-planting applications were made and foliar use must be limited to states east of the Mississippi River.

- If the petitioner intends to rely on mustard greens crop field trial data to support the requested use on turnip greens, the proposed use must be amended to specify that foliar applications to turnip plants may not be made to dual purpose turnip cultivars or varieties which produce a harvestable root.

- HED had previously concluded that the established tolerances for metalaxyl [40 CFR 180.408] will be adequate to support the use of mefenoxam on the same crops provided that (i) the use rates for mefenoxam are one-half the rate of metalaxyl; (ii) mefenoxam applications are made in the same way as for metalaxyl; and (iii) the labels restrict the use of both pesticides concurrently on the same crop. The first two conditions have been met. However, it does not appear that current labels restrict the use of both pesticides concurrently on the same crop. **All mefenoxam product labels with uses on food/feed crops must be modified to specify that applications of mefenoxam may not be made to a crop if application of any product containing metalaxyl was made to the same crop in the same season.**

860.1340 Residue Analytical Methods

- Plant commodity methods: The petitioner has not responded to the data requirements specified in a previous review (DP Barcode D276001, N. Dodd, 9/13/01) to attempt to

improve the recoveries of CGA-94689 and CGA-62826 in Method AG-395 and to submit a copy of the improved method developed by Enviro-Text Laboratories for determination of mefenoxam residues in canola seed. If the recent recommendations of the HED RARC are adopted, these data are no longer needed.

- Livestock commodity methods: The petitioner has not responded to the data requirements specified in a previous review (DP Barcode D275477, N. Dodd, 9/13/01) to attempt to improve the recoveries of CGA-94689 and CGA-62826 in Method AG-576 or to conduct an independent laboratory validation of the improved method. If the recent recommendations of the HED RARC are adopted, these data are no longer needed.

860.1380 Storage Stability Data - Livestock

- The petitioner has not provided the storage stability data for metabolites P1 and P2 in livestock commodities required in a previous review (DP Barcode D248748, N. Dodd, 6/11/01). If the recent recommendations of the HED RARC are adopted, these data are no longer needed.

860.1900 Field Accumulation in Rotational Crops

- The HED Metabolism Assessment Review Committee (HED MARC Decision Memo; DP Barcode D269910, N. Dodd, 10/27/00) has previously recommended that in order to determine whether the metabolites CGA-108905 and CGA-100255 need to be included in the tolerance expression for rotational crops, the petitioner must conduct limited field rotational trials in which residues of CGA-108905 and CGA-100255 are determined . If the recent recommendations of the HED RARC are adopted, these data are no longer needed.

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R148832

Chemical: D-Alanine, N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-, methyl ester

PC Code: 113502
HED File Code: 11500 Petition Files Chemistry
Memo Date: 5/31/2007
File ID: 00000000
Accession #: 000-00-0120

HED Records Reference Center
6/20/2007