UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES

MEMORANDUM

DATE: 11/20/08

SUBJECT: Mefenpyr-diethyl (HOE 107892) Safener: Revised Human Health Risk Assessment to Support the Establishment of Rotational Crop Tolerances on Soybean Seed, Hay and Forage and Canola Seed in Conjunction with Increased Application Rate.

PC Code: 811800
Decision No.: 380446
Petition No.: PP#7E7224
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: 358782
Registration No.: NA
Regulatory Action: Section 3
Case No.: NA
CAS No.: 135590-91-9
40 CFR: 180.509

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1.0 Executive Summary

Mefenpyr-diethyl, also known as HOE 107892, is a safener used with several herbicides on cereal grain crops. Tolerances for residues of mefenpyr-diethyl, and its 2,4-dichlorophenyl-pyrazoline metabolites resulting from application of the safener at a rate up to 0.0267 pounds per acre per growing season are listed in 40 CFR §180.509. This action requests an increase in the maximum allowable seasonal use rate to 0.053 lb safener/A, as well as the establishment of rotation crop tolerances on soybean seed, hay and forage and canola seed needed as a result of the higher application rate.

The toxicology database on mefenpyr-diethyl is considered adequate for selecting endpoints and uncertainty factors to support the proposed amended use of this safener. Mefenpyr-diethyl has low acute toxicity by the oral, dermal, and inhalation routes of exposure. It is not a dermal irritant but is a slight dermal sensitizer and ocular irritant. Metabolism studies indicate that mefenpyr-diethyl is rapidly metabolized, widely distributed, and primarily excreted *via* the urine. Repeated exposure *via* the dermal route did not induce any treatment-related effects at dose levels up to and including the limit dose. Repeated exposure studies *via* the oral route demonstrate that the target organs are the liver and hematopoietic system in dogs, mice, and rats. Mefenpyr-diethyl was negative for carcinogenicity in rats and mice, and it did not show any genotoxic potential. Developmental toxicity was not observed in the rat but was observed in the rabbit (abortions). Mefenpyr-diethyl did not induce any signs of reproductive toxicity or neurotoxic potential. The developmental toxicity studies in rats and rabbits, as well as the reproductive toxicity study in rats, did not demonstrate any pre- or postnatal sensitivity.

The toxicity database is considered adequate to assess the amended use. There is no evidence of increased sensitivity or susceptibility in rats or rabbits following pre- and/or post-natal exposure to mefenpyr-diethyl, no evidence of neurotoxicity in any study, and exposure values are not expected to underestimate risk. Therefore, the FQPA factor has been reduced to 1X for this chemical.

No effects were seen in the toxicity database that could be attributed to a single exposure of mefenpyr-diethyl. An endpoint and dose were selected from the dog chronic oral toxicity study for the chronic dietary risk assessment. The chronic population adjusted dose (cPAD) of 0.51 mg/kg/day was based on the study NOAEL with a 100X uncertainty factor to account for inter- and intra-species extrapolation. At the study LOAEL liver effects were observed. There are currently no residential uses of mefenpyr-diethyl; therefore endpoints for non-dietary, non-occupational risk assessments were not selected. Based on the current use patterns chronic dermal and inhalation occupational exposures are not expected. The endpoints and doses used for the short- and intermediate-term dermal and inhalation endpoints for occupational risk assessment were selected from the developmental toxicity study in the rabbit. For both durations and routes of exposure, the point of departure is the NOAEL of 100. At the study LOAEL, abortions were observed. The level of concern (LOC) for all four risk assessments is for margins of exposure (MOEs) that are less than 100.

Absorption via the dermal and inhalation routes was assumed to be equivalent to oral exposure for these assessments.

Mefenpyr-diethyl is classified as "not likely to be carcinogenic to humans".

Adequate residue chemistry data has been submitted to support the proposed amended use and establishment of requested rotational crop tolerances. An adequate GC/MSD analytical enforcement method for plants is available to enforce the proposed tolerances. The available data support the establishment of tolerances for residues of mefenpyr-diethyl in soybean and canola seed at 0.02 ppm and in soybean hay and forage at 0.10 ppm. No other new or revised primary plant or animal tolerances are required to support the requested increased application rate. HED notes that all labels which contain mefenpyr-diethyl at the rate of 0.053 lbs safener/A/growing season specify plantback intervals of: (i) 30 days for leafy, fruiting, and root vegetables; (ii) 90 days for field corn; (iii) 120 days for soybean and canola; and (iv) 12 months for all other crops other than wheat and barley, which can be planted back at any time.

No Codex, Canadian, or Mexican maximum residue limits (MRLs) are established for residues of mefenpyr-diethyl and metabolites in crop or livestock commodities; therefore, there are no issues with international harmonization raised by this action.

HED conducted a highly conservative chronic dietary risk assessment for food and drinking water for mefenpyr-diethyl using tolerance level residues, assuming 100% crop treated, and incorporating modeled water numbers reflecting an exaggerated rate application. Mefenpyr-diethyl dietary exposure from food and drinking water based on the newly proposed use pattern results in an estimated risk equivalent to <1% of the cPAD for the general population and all regulated subpopulations. No toxic effects attributable to a single exposure of mefenpyr-diethyl were seen in the database; therefore, an acute dietary risk assessment was not conducted. Mefenpyr-diethyl is not likely to be a human carcinogen; thus, a cancer dietary risk assessment is not required.

No products containing mefenpyr-diethyl are available for sale in the residential market because of the crops specified on the applicable labels. As such, a residential risk assessment was not conducted.

Since there are no residential uses for mefenpyr-diethyl, the aggregate risk assessments include the contribution of risk from dietary (food and water) sources only. HED has no concern for aggregate risks resulting from the increased application of mefenpyr-diethyl requested in this petition.

HED conducted occupational handler and post application exposure and risk assessments to support the requested amended use pattern. Mefenpyr-diethyl can be applied by aerial or ground application methods to barley, wheat, and hay. Current labels require normal work clothing (WDGs) or double layer clothing (EC) with appropriate footwear, eye protection, and chemical resistant gloves. Respirators are not required. Restricted entry intervals (REI) are 24 hours on

all labels. Risks from occupational exposures were calculated for handlers using aerial and ground-based application equipment which would be typical for herbicide applications to large field crops. For all scenarios considered, risks were not of concern at current label requirements for clothing and personal protective equipment use (i.e., calculated MOEs well exceeded the target of 100 ranging from ~5000 up to ~300,000 at the label specified PPE). Post-application worker risks were also evaluated for scouting activities which is the only likely hand labor activity which would occur relative to the use of mefenpyr-diethyl in agriculture and risks were not of concern even on the day of application when individuals scout for an 8 hour workday (i.e., MOE ~5000 and target = 100). Current labels require a 24 hour REI so actual risks would be even of less concern because residues would dissipate some between application and the REI of 1 day.

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

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

Regulatory Recommendations and Data Deficiencies

HED has no objection to the establishment of rotational crop for residues of the herbicide safener mefenpyr-diethyl (1-(2,4-dichlorophenyl)-4,5-dihydro-5-methyl-1H-pyrazole-3,5-dicarboxylic acid, diethyl ester) and its 2,4-dichlorophenyl-pyrazoline metabolites at a rate of 0.053 pound safener per acre per growing season in/on the following rotational crop commodities:

Soybean, seed	0.02 ppm
Soybean, hay	0.10 ppm
Soybean, forage	0.10 ppm
Canola, seed	0.02 ppm

HED notes that not only should the new tolerances be established, but the tolerance definition should be revised to permit use of mefenpyr-diethyl at up to 0.053 pounds safener/A per growing season.

RD should assure that all labels which contain mefenpyr-diethyl at the rate of 0.053 lbs safener/A/growing season specify plantback intervals of: (i) 30 days for leafy, fruiting, and root vegetables; (ii) 90 days for field corn; (iii) 120 days for soybean and canola; and (iv) 12 months for all other crops other than wheat and barley, which can be planted back at any time.

The petitioner is required to submit a revised Section F to reflect the commodity definitions presented in Appendix B, Table B1.

Data Gaps

The following data should be required as a condition of registration:

- Subchronic (28-day) Inhalation Study
- Immunotoxicity Study (New requirement under the Revised Part 158 Toxicology Data Requirements (2007 edition)
- Multiresidue method testing for mefenpyr-diethyl

2.0 Ingredient Profile

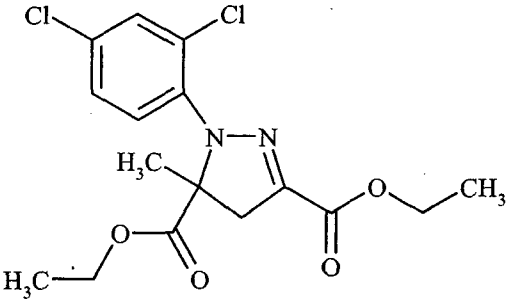
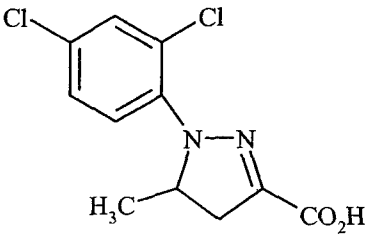
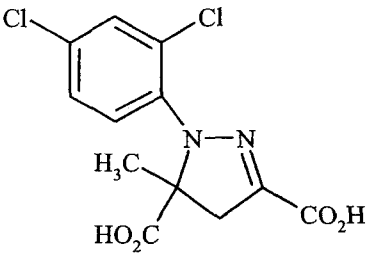
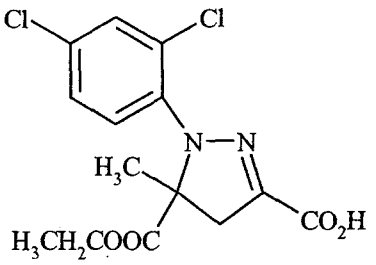
Mefenpyr-diethyl is a safener used with several herbicides. Safeners are substances added to herbicidal active ingredients in formulations to protect crops from potential adverse effects of the herbicides. Although safeners are not considered pesticidal by the Agency, they are often similar in molecular structure to active pesticides. Thus, the Agency has established some tolerances for safeners. HED notes that mefenpyr-diethyl does not appear to be structurally similar to any currently registered pesticides.

2.1 Summary of Registered/Proposed Uses

No specimen labels were provided as part of the request to increase the application rate and establish rotational crop tolerances for mefenpyr-diethyl. Mefenpyr-diethyl is used as a safener with various herbicides on cereal grain crops. HED considered the current product labels which contain mefenpyr-diethyl as part of the review to support the requested use revision. This action requests an increase in the maximum allowable seasonal use rate from the current limit of 0.026 lb safener/A to 0.053 lb safener/A.

Based on the available confined and limited field rotational crop data, all labels which permit the use of mefenpyr-diethyl at rates above 0.026 lb safener/A to the new seasonal maximum of 0.053 lb safener/A, should contain the following plantback restrictions: (i) 30 days for leafy, fruiting, and root vegetables; (ii) 90 days for field corn; (iii) 120 days for soybean and canola; and (iv) 12 months for all other crops other than wheat and barley.

2.2 Structure and Nomenclature

Table 2.2. Mefenpyr-Diethyl Nomenclature.	
Chemical structure	
Common name	Mefenpyr-diethyl
Company experimental name	AE F107892, HOE 107892
IUPAC name	Diethyl (*RS*)-1-(2-,4-dichlorophenyl)-5-methyl-2-pyrazoline-3,5-dicarboxylic acid
CAS name	1-(2,4-dichlorophenyl)-4,5-dihydro-5-methyl-1*H*-pyrazole-3,5-dicarboxylic acid, diethyl ester
CAS registry number	135590-91-9
Chemical structure of AE F094270 (HOE 094270) metabolite	
Chemical structure of AE F109453 (HOE 109453) metabolite	
Chemical structure of AE F113225 (HOE 113225) metabolite	

2.3 Physical and Chemical Properties

Table 2.3 Physicochemical Properties of Mefenpyr-Diethyl.

Parameter	Value	Reference
Melting point/range	50-52 °C 43-47 °C	MRID 43984109
pH	Was not determined, because mefenpyr-diethyl technical is practically insoluble and nondispersible in water.	MRID 43984109
Density (20 °C)	1.31 g/cm^3 at 20°C	MRID 43984109
Water solubility (20 °C)	0.017 g/L at pH 0.9 0.020 g/L at pH 6.2 pH 10 solubility not determined due to compound hydrolysis	MRID 43984109
Solvent solubility (20 °C)	Methanol >400 g/L isopropanol 151 g/L n-hexane 35 g/L toluene >400 g/L dichloromethane >500 g/L acetone >500 g/L ethyl acetate >400 g/L dimethylsulfoxide >500 g/L polyethylene glycol 151 g/L sesame oil 56 g/L	MRID 43984109
Vapor pressure (20 °C)	6.3 x 10^{-6} Pa	MRID 44024001
Dissociation constant, pK_a	Neither acidic nor basic functional groups. Dissociation, if any, is expected to be negligible.	MRID 43984109
Octanol/water partition coefficient, Log(K_{OW})	3.83 at pH 6.3 and 21 °C	MRID 43984109
UV/visible absorption spectrum (nm)	Primary λ_{max} = <200 Secondary λ_{max} = 305	MRID 43984109

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

The toxicology database on mefenpyr-diethyl is considered sufficient for selecting endpoints and uncertainty factors to support the proposed amended use of this safener. The following studies were available for consideration in this assessment. No additional information was found in a screening literature search relevant to the hazard assessment.

- Subchronic: 90-day oral toxicity (rat); 13-week oral toxicity (dog); 90-day (mouse)
- Developmental: rat (pre- and postnatal) and rabbit developmental toxicity studies
- Reproduction: 2-generation reproduction study (rat)
- Chronic: combined oral chronic toxicity/carcinogenicity (rat); carcinogenicity (mouse); chronic oral toxicity (dog)
- Other: mutagenicity battery; metabolism

3.1.2 Mode of Action, Metabolism, Toxicokinetic Data

Metabolism studies in rats showed that mefenpyr-diethyl was rapidly absorbed and metabolized, with the majority of the radiolabel excreted *via* the urine and feces within the first 24 hours. Renal excretion was the predominant route of elimination in both sexes. Three metabolites were identified in both the urine and feces (HOE 113225, HOE 109453, HOE 094270), but the parent compound was found only in the feces. The metabolic pathway consists of consecutive hydrolysis (saponification) of the two carboxylic acid ester groups, resulting in an aromatization of the pyrazoline ring (Hoe 107892→ HOE 113225 → HOE 109453 → HOE 094270). Excretion is biphasic, and metabolism appears to be influenced by sex to a minor extent; i.e., males either have a lower intestinal absorption or a higher biliary excretion compared to females.

3.1.3 Toxicological Effects

Mefenpyr-diethyl has low acute toxicity by the oral, dermal, and inhalation routes of exposure. It is not a dermal irritant but is a slight dermal sensitizer and ocular irritant. Metabolism studies indicate that mefenpyr-diethyl is rapidly metabolized, widely distributed, and primarily excreted *via* the urine. Repeated exposure *via* the dermal route did not induce any treatment-related effects at dose levels up to and including the limit dose. Repeated exposure studies *via* the oral route demonstrate that the target organs are the liver and hematopoietic system in dogs, mice, and rats. Mefenpyr-diethyl was negative for carcinogenicity in rats and mice, and it did not show any genotoxic potential. Developmental toxicity was not observed in the rat but was observed in the rabbit (abortions) at the same dose level producing maternal toxicity. Mefenpyr-diethyl did not induce any signs of reproductive toxicity or neurotoxic potential. The developmental toxicity studies in rats and rabbits, as well as the reproductive toxicity study in rats, did not demonstrate any pre- or post-natal sensitivity.

No neurotoxicity studies are available on mefenpyr-diethyl, but there was no evidence of neurotoxicity in any of the submitted studies.

The database for carcinogenicity is considered adequate for the current assessment, and mefenpyr-diethyl is classified "not likely to be carcinogenic to humans". Although the dose levels in the rat carcinogenicity study are not considered adequate to assess the carcinogenic potential of mefenpyr-diethyl, a new study is not required for the current action. However, a new study will be required if new uses result in significantly higher residues in food and/or significantly higher occupational (or future residential) exposure. The mutagenicity/genetic

toxicity database is considered complete, and there is no concern for mutagenicity. There is no evidence of endocrine disruption.

The toxicology database for mefenpyr-diethyl is complete under Part 158 (1984 edition), with the exception of a subchronic inhalation toxicity study. It is recommended that a 28-day inhalation study be required because the application of mefenpyr-diethyl will be by either aerial application or spray boom equipment, and there is no effective measure of toxicity by the inhalation route. Although mefenpyr-diethyl does not meet the criteria for a waiver of a subchronic inhalation study (not a Toxicity Category IV), its use does not result in significant inhalation exposure (MOEs > 1000).

Under the Revised Part 158 Toxicology Data Requirements (2007 edition) for registration of a pesticide (food and non-food uses), acute and subchronic neurotoxicity studies and an immunotoxicity study are new data requirements.

There is no evidence of neurotoxicity in the toxicology database on mefenpyr- diethyl, which includes subchronic, chronic, developmental toxicity, and reproduction studies performed at dose of 250 mg/kg/day and above. Therefore, based on the above considerations, HED does not believe that conducting acute and subchronic neurotoxicity studies will result in a NOAEL less than the NOAEL of 51 mg//kg/day already set for mefenpyr-diethyl; therefore additional neurotoxicity studies are not required.

Mefenpyr-diethyl was assessed in a complete battery of subchronic, chronic, carcinogenicity, developmental and reproductive studies. HED considered the entire toxicity database for mefenpyr-diethyl for potential adverse effects on the thymus and spleen as indications of potential immunotoxicity and noted enlarged spleens; more severe hematopoiesis and hemosiderin deposits and increased spleen weights were observed in mice at doses greater than the limit dose. However, these were determined to be non-specific changes not indicative of immunotoxicity. Therefore, based on the above considerations, HED does not believe that conducting a special series 870.7800 immunotoxicity study will result in a NOAEL less than the NOAEL of 51 mg//kg/day already set for mefenpyr diethyl and an additional uncertainty factor (UF_{DB}) for database uncertainties does not need to be applied.

3.1.4 FQPA Safety Factor

The database for prenatal developmental and reproductive toxicity is considered adequate. Developmental toxicity was not observed in the rat but was observed in the rabbit (abortions) at the same dose level producing maternal toxicity. Mefenpyr-diethyl is not considered a reproductive toxicant. The developmental and reproductive toxicity studies showed no evidence of increased sensitivity or susceptibility of young rats or rabbits following pre- and/or postnatal exposure to mefenpyr-diethyl. There is a lack of evidence of neurotoxicity in any study on mefenpyr-diethyl.

The Food Quality Protection Act (FQPA) safety factor has been reduced to 1X for all population

subgroups, including infants and children. There are no concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity, and estimates of exposure are not likely to underestimate risk.

3.1.4.1 Evidence of Neurotoxicity

There is no concern for neurotoxicity resulting from exposure to mefenpyr-diethyl.

3.1.4.2 Evidence of Developmental Toxicity

In the two rat developmental toxicity studies conducted at 0 and 1000 mg/kg/day, minimal fetal body-weight effects and decreased maternal body-weight gain were observed during the first week. There were no developmental effects. In the rabbit developmental toxicity study, developmental toxicity (abortion) was observed at the same dose level producing maternal toxicity. Executive summaries of the rat and rabbit developmental toxicity studies may be found in Appendix A to this assessment.

3.1.4.3 Evidence of Reproductive Toxicity

There was no evidence of reproductive toxicity following exposure *via* the diet at concentrations of 0, 200, 1000, and 5000 ppm during the pre-mating (10 weeks) period [males: 16, 82, and 428 mg/kg/day; females: 18, 94, and 482 mg/kg/day] for 2 generations. Parental toxicity consisted of decreased body weight and body-weight gain, and an increase in spleen weight and in the severity (not incidence) of splenic extramedullary hematopoiesis in females. In the pups, decreased body weight and body-weight gains were observed at the same dose levels as the parental animals. The NOAEL is 1000 ppm for both the parental animal and offspring. The executive summary of the reproductive toxicity study in rats may be found in Appendix A to this document.

3.1.4.4 Additional Information from Literature Sources

No additional information was found in the literature regarding pre- or post-natal toxicity to mefenpyr-diethyl.

3.1.4.5 Determination of Susceptibility

There is little concern for prenatal toxicity resulting from exposure to mefenpyr-diethyl. There is no evidence of increased susceptibility [qualitative and quantitative] following *in utero* exposure to mefenpyr-diethyl in either the rat or rabbit developmental toxicity study, and there is no evidence of increased susceptibility [qualitative or quantitative] following *in utero* and/or pre-/post-natal exposure in the 2-generation reproduction study in rats. Developmental toxicity was not observed in the rat at the limit dose (1000 mg/kg/day). The only effects observed in the rat developmental toxicity study were decreased body-weight gain and food efficiency during the first week of dosing and increased spleen weights in the maternal animal and a marginal decrease

in fetal body weight/body-weight gain during lactation (postnatal study). Developmental toxicity (abortions) was observed in the rabbit at a dose level of 250 mg/kg/day. In the reproduction study, decreased body weight and body-weight gain (parental animal and offspring) and an increase in spleen weight and in the severity (not incidence) of splenic extramedullary hematopoiesis were observed in females. There is no evidence of neurotoxicity, and there are no residual concerns.

3.2 Dose Response Assessment

3.2.1 Acute Reference Dose (aRfD) - Females age 13-49

HED originally concluded (HIARC Memo, HED Doc. No. 012998, 11/24/1998) that there were no effects seen in the toxicity database that could be attributed to a single exposure of mefenpyr-diethyl. However, there was no discussion regarding the findings (abortions) in the rabbit study. In connection with the uses of mefenpyr-diethyl that are the subject of this action, HED has reevaluated the acute dietary endpoint for females ages 13-49 and concurs with the previous determination that there is no endpoint attributable to a single exposure (dose) seen in the oral toxicity studies, including the developmental studies that would be appropriate for this population subgroup. HED's current policy is that decreased body weight is not an effect likely to result from a single dose of a pesticide. Further, the abortions seen in the rabbit study did not occur within a timeframe suggesting a single dose effect.

3.2.2 Acute Reference Dose (aRfD) - General Population

No appropriate endpoint attributable to a single exposure (dose) was identified from oral toxicity studies for the general population.

3.2.3 Chronic Reference Dose (cRfD)

Study Selected: chronic oral toxicity – dog (OPPTS 870.4100)
MRID No.: 44316402
Executive Summary: See Appendix A, Guideline §870.4100
Dose and Endpoint for Risk Assessment: NOAEL = 51 mg/kg/day, based on increased liver weight in both sexes, cholestasis, and increased alkaline phosphatase at the systemic LOAEL of 260 mg/kg/day.
Uncertainty Factor(s): 100X [10 interspecies; 10X intraspecies]
Comments about Study/Endpoint/Uncertainty Factors: For the current risk assessment, a re-evaluation of the endpoints used was performed. Previously, the chronic dietary endpoint was selected by HIARC from the 2-generation reproduction study in rats. However, the mg/kg/day for the NOAEL of 1000 ppm (57 mg/kg/day) was based on the intake of test material by the F1 males during the post-mating phase, since this provided the lowest dose. However, since it is more appropriate to use the intake from the premating phase of the study for the P0 generation, the NOAEL for the study is calculated to be 82 mg/kg/day for the 1000 ppm concentration. Since this no longer provides the lowest NOAEL, the mefenpyr-diethyl team re-evaluated the other long-term studies considered previously by the HIARC. Based on this re-assessment, the

chronic dog study was selected. This study is supported by the chronic rat study, which shows a similar NOAEL (48 mg/kg). A comparison of the rat and dog subchronic oral toxicity studies shows that the dog is the more sensitive species (based on LOAEL for common effects). The route and duration of exposure are appropriate for selection of the chronic dietary endpoint. The executive summary of the chronic toxicity study in dogs may be found in Appendix A to this document.

3.2.4 Dermal Absorption

No dermal absorption data have been submitted for mefenpyr-diethyl. There is a 21-day dermal toxicity study available for mefenpyr-diethyl.

3.2.5 Dermal Exposure (Short- and Intermediate-Term)

Study Selected: Developmental toxicity study – rabbit (OPPTS 870.3700)
MRID No.: 44089202
Executive Summary: See Appendix A, Guideline §870.3700
Dose and Endpoint for Risk Assessment: NOAEL = 100 mg/kg/day, based on a higher rate of abortions at the LOAEL of 250 mg/kg/day.
Uncertainty Factor(s): 100X [10 interspecies; 10X intraspecies]
Comments about Study/Endpoint/Uncertainty Factors: Previously, no endpoints were selected for short- and intermediate-term dermal risk assessment, based on the lack of effect following subchronic dermal exposure at limit dose in rats and the lack of developmental effects in the rat at the limit dose. The HIARC was silent regarding the abortions in the rabbit developmental toxicity study. For the current action, the rabbit developmental toxicity study was selected for this exposure assessment. The incidence of abortions at the highest dose tested is considered significant and treatment-related (occurred in over a third of the animals at this dose level; 6/15). The abortions first occurred following 10 days of dosing (gestation day 16-23). Since no dermal absorption data are available, toxicity by the dermal route is considered to be equivalent to toxicity by the oral route of exposure.

3.2.6 Dermal Exposure (Long-Term)

Based on the current use pattern (1 application per growing season), long-term exposure *via* the dermal route is not expected.

3.2.7 Inhalation Exposure (Short- and Intermediate-Term)

Study Selected: developmental toxicity – rabbit (OPPTS 870.3700)
MRID No.: 44089202
Executive Summary: See Appendix A, Guideline §870.3700
Dose and Endpoint for Risk Assessment: NOAEL = 100 mg/kg/day, based on a higher rate of abortions at the LOAEL of 250 mg/kg/day.
Uncertainty Factor(s): 100X [10 interspecies; 10X intraspecies]

Comments about Study/Endpoint/Uncertainty Factors: Previously, no endpoint was selected for short-term inhalation risk assessment, based on the low acute toxicity (Toxicity Category III) and the use pattern (1 application per growing season; either aerial application or spray boom equipment that is as low to the ground as possible). During the current assessment, it was determined that typical risk assessments routinely do inhalation exposures for these occupational scenarios. The same study and endpoint used for the dermal assessments have been selected for the short- and intermediate-term inhalation exposure assessments. Since no inhalation absorption data are available for mefenpyr-diethyl, toxicity by the inhalation route was considered to be equivalent to toxicity by the oral route of exposure.

3.2.8 Inhalation Exposure (Long-Term)

Based on the current use pattern (1 application per growing season; either aerial application or spray boom equipment that is as low to the ground as possible), a long-term inhalation risk assessment is not required.

3.2.9 Classification of Carcinogenic Potential

Mefenpyr-diethyl is classified as "not likely to carcinogenic to humans". Carcinogenicity studies showed no evidence of an increase in the incidence of tumors in either the rat or the mouse.

3.2.10 Summary of Toxicological Doses and Endpoints

There are no residential uses; therefore, dermal and inhalation exposure risk assessments not required.

Table 3.4.1 Summary of Toxicological Doses and Endpoints for Mefenpyr-diethyl for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	No hazard was identified in any toxicity study for this duration of exposure			
Acute Dietary (Females 13-49 years of age)	No hazard was identified in any toxicity study for this duration of exposure			

Table 3.4.1 Summary of Toxicological Doses and Endpoints for Mefenpyr-diethyl for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (All Populations)	NOAEL = 51 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Chronic RfD = 0. 51 mg/kg/day cPAD = 0. 51 mg/kg/day	**chronic oral toxicity study (dog)** LOAEL = 260 mg/kg/day, based on increased liver weight in both sexes, cholestasis, and increased alkaline phosphatase.
Cancer (oral)	Classification: Not likely to be carcinogenic to humans			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. N/A = not applicable.

Table 3.4.2 Summary of Toxicological Doses and Endpoints for Mefenpyr-diethyl for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short- and Intermediate-Term	oral[a] NOAEL= 100 mg/kg/day (dermal absorption rate = 100%)	UF_A= 10x UF_H=10x	Occupational LOC for MOE = 100	**Developmental toxicity study – rabbit** LOAEL = 250 mg/kg/day based on abortions
Dermal Long-Term	Based on the use pattern, chronic dermal exposure is not expected.			
Inhalation Short-Term (1-30 days) and Intermediate-Term (1 – 6 months)	oral[a] NOAEL= 100 mg/kg/day (inhalation absorption rate = 100%)	UF_A= 10x UF_H=10x	Occupational LOC for MOE = 100	**Developmental toxicity study – rabbit** LOAEL = 250 mg/kg/day based on abortions
Inhalation Long-Term (>6 months)	Based on the use pattern, chronic inhalation exposure is not expected.			
Cancer (oral, dermal, inhalation)	Classification: Not likely to be carcinogenic to humans.			

[a] Absorption *via* the dermal/inhalation route is assumed to be equivalent to oral absorption

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.3 Endocrine Disruption

EPA is required under the 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 recommendations of its Endocrine Disruptor 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).

4.0 Public Health and Pesticide Epidemiology Data

Since mefenpyr-diethyl is used as a safener, and not as the active ingredient in pesticide formulations, incident data is not likely to be available for mefenpyr-diethyl. Any incident reported for a formulation containing this safener, is likely to be attributed to the active ingredient in the formulation, not to this inert ingredient; therefore a discussion of public health and epidemiology data is not relevant to this action

5.0 Dietary Exposure/Risk Characterization

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Plants, Animals and Rotational Crops

Residue Chemistry Memo DP#s 238730, 271364, 264319, 276208, 11/22/02, Y. Donovan (PP# 7F04850)

The metabolism of mefenpyr-diethyl in plants (barley) and animals (goat, rat, and hen) is well understood. Identified metabolic pathways are substantially similar in plants and animals. EPA has determined that mefenpyr-diethyl parent and its three 2,4-dichlorophenyl-pyrazoline metabolites (HOE 113225, HOE 109453, and HOE 094270) are the residues of concern for risk assessment and tolerance setting purposes in plant and animal commodities as well as in rotational crops.

5.1.2 Analytical Methodology

Residue Chemistry Memo DP#D342071, D. Davis, 6/3/08 (PP# 7E7224)

An enforcement method for plants entitled "An Analytical Method for Determination of Residues of AE F107892 (mefenpyr-diethyl) and its Metabolites in Wheat and Barley by Gas Chromatography using Mass Selective Detection (Report Supplement to EPA MRID 45457401)" is available. Radiovalidation and independent laboratory validation (ILV) data have been submitted for the plant method. The Agency analytical lab has concluded that this method is suitable for food tolerance enforcement of mefenpyr-diethyl and the three metabolites HOE 094270, HOE 113225, and/or HOE 109453.

The data-collection method used in the analysis of samples from field corn and soybean field rotational crop study is similar to the enforcement method with minor modifications. Samples of rotated corn forage and stover and soybean forage and hay were analyzed for residues of mefenpyr-diethyl and its regulated metabolites. The limit of quantitation (LOQ) was 0.10 ppm for each analyte in/on these commodities. Samples of rotated corn grain and soybean seed were analyzed for residues of mefenpyr-diethyl and metabolite AE F094270 (HOE 094270); the LOQ was 0.01 ppm each for mefenpyr-diethyl and AE F094270 (HOE 094270) in/on corn grain and soybean seed.

Data are required concerning the recovery of mefenpyr-diethyl residues of concern using FDA's multiresidue method protocols (PAM Vol. I). This requirement was previously requested in a mefenpyr-diethyl petition, PP#7F04850 (DP# 238730, 11/22/02, Y. Donovan), to establish tolerances for barley and wheat RACs.

5.1.3 Environmental Degradation

EFED Memoranda, D226076, A. Clem, 3/18/97 and D262735, A. Clem, 11/26/01

Laboratory studies indicate the principal mode of dissipation of HOE-107892 to be aerobic metabolism in soil (microbially mediated hydrolysis), with secondary contribution by soil sensitized photolysis. Concentrations of HOE-107892 would decrease relatively rapidly in soil with a DT50 of approximately a few days to one week. However, in the process, by-products which are structurally very similar to parent and longer-lived are formed (HOE-094270, HOE-113225, and HOE-109453).

5.1.4 Comparative Metabolic Profile

The metabolic profile for mefenpyr-diethyl appears to be substantially similar in plants, animals and the environment. The primary identified metabolites in rats, ruminants, poultry, cereal grains and after environmental degradation are the three 2,4-dichlorophenyl-pyrazoline metabolites, HOE 094720, HOE 113225 and HOE 109453, which are included in the risk assessment and for tolerance setting purposes.

5.1.5 Pesticide Metabolites and Degradates of Concern

Table 5.1.5 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression for Mefenpyr-Diethyl

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Parent and three 2,4-dichlorophenyl-pyrazoline metabolites (HOE 113225, HOE 109453, and HOE 094270)	
	Rotational Crop	Parent and three 2,4-dichlorophenyl-pyrazoline metabolites (HOE 113225, HOE 109453, and HOE 094270)	
Livestock	Ruminant	Parent and three 2,4-dichlorophenyl-pyrazoline metabolites (HOE 113225, HOE 109453, and HOE 094270)	
	Poultry	Parent and three 2,4-dichlorophenyl-pyrazoline metabolites (HOE 113225, HOE 109453, and HOE 094270)	
Drinking Water		Parent and three 2,4-dichlorophenyl-pyrazoline metabolites (HOE 113225, HOE 109453, and HOE 094270)	Not Applicable

5.1.6 Drinking Water Residue Profile

EFED Memoranda, D226076, A. Clem, 3/18/97 and D262735, A. Clem, 11/26/01

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) in response to tolerance petitions for uses on wheat and barley. The assessment was based on use of the safener at an exaggerated rate of 0.08 lb ai/A, which is higher than the currently requested use pattern; therefore, those estimated drinking water values remain valid and were incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

Monitoring data for mefenpyr-diethyl and its metabolites are not available; therefore, surface and ground water estimated drinking water concentrations (EDWCs) were derived from models.

The chronic surface water EDWC was calculated from the EFED FIRST (Tier 1) index reservoir simulation model for a single application of HOE-107892 at an exaggerated rate of 0.090 kg/ha (0.080 lb/acre). The tabulated concentrations are the summations (in parent equivalent concentrations) of relatively short-lived parent and several longer-lived transformation products that are structurally similar to the parent compound. The chronic concentration of combined parent and metabolites computed from FIRST in parent equivalents is 3 ppb.

The chronic groundwater EDWC was calculated using the SCI-GROW2 model. The database of pesticide chemicals used to develop and update the SCI-GROW2 regression model shows that the highest pesticide concentration measured on a one pound per acre application basis for a certain mobile and persistent pesticide of similar molecular weight is roughly 55 µg/L (ppb). The current minimum value for Koc in the database used to develop SCI-GROW2 is 11 mL/g, while maximum values for aerobic soil metabolism half-life are roughly 1000 days. Since HOE-107892 has Koc and aerobic soil metabolism half-lives well within the bounds covered by the model, as do its structurally similar transformation products (from collateral laboratory evidence and reasonable inference), groundwater concentrations of HOE-107892 applied at exaggerated rate of 0.080 lb/acre/year and any associated transformation products (in equivalent molar concentrations) are not likely to exceed individually, or in combination, a concentration of 4 µg/L (ppb).

The higher value of the two, the chronic groundwater EDWC of 4 µg/L (ppb), was used for this dietary assessment.

5.1.7 Food Residue Profile

Residue Chemistry Memo DP#D342071, D. Davis, 6/3/08 (PP# 7E7224)

No new magnitude of the residue data, reflecting the new proposed seasonal rate of 0.053 lb safener/A, were submitted for the primary crop commodities. It is, however, noted that the field trial data that were previously submitted in support of the petition to establish tolerances for primary crops were conducted at an exaggerated rate of 0.089 lb safener/A. HED has determined that the established tolerances for primary crop commodities remain adequate to support the proposed higher application rate.

There are livestock feedstuffs associated with the proposed rotational crop tolerances. These feedstuffs include canola meal, soybean seed, soybean forage, soybean hay, soybean aspirated grain fractions, soybean meal, soybean hulls, and soybean silage. The residues expected in ruminant feedstuffs addressed herein are not expected to significantly alter the ruminant's dietary burden. Since no new or increased livestock commodity tolerances are needed to support the requested use pattern revision, no new animal commodity data are required with respect to feeding studies, storage stability or analytical methods to support this petition.

The submitted limited field rotational crop data for field corn and soybean are adequate and are supported by storage stability data. The field rotational crop data for field corn will support a 90-day plantback interval (PBI) with no need for rotational crop tolerances. The field rotational crop data for soybean will support the requested tolerances and a 120-day PBI. The field rotational crop data for soybean may also serve as surrogate data to establish a rotational crop tolerance and a 120-day PBI on canola seed. The Registration Division (RD) should insure that all labels which contain mefenpyr-diethyl at the higher application rate specify these plantback intervals.

Based on the available exaggerated rate data on soybean seed and canola seed, HED concludes that residues of mefenpyr-diethyl in soybean and canola processed commodities will not exceed the established tolerances for the RAC.

5.1.8 International Residue Limits

U.S. tolerances for residues of the herbicide safener, mefenpyr-diethyl, and its 2,4-dichlorophenyl-pyrazoline metabolites at the rate of 0.0267 pound safener per acre per growing season are listed in 40 CFR §180.509(a) at the following levels for various plant and animal commodities: (i) 0.05 ppm (barley and wheat grain); (ii) 0.2 ppm (barley hay and wheat forage and hay); (iii) 0.5 ppm (barley and wheat straw); and (iv) 0.1 ppm (meat byproducts of cattle, goat, hog, horse, and sheep).

No Codex, Canadian, or Mexican maximum residue limits (MRLs) are established for residues of mefenpyr-diethyl and metabolites in crop or livestock commodities; therefore, there are no issues with international harmonization raised by this action.

5.2 Dietary Exposure and Risk

Dietary Exposure and Risk Memorandum D353114, D. Davis, 6/3/08

5.2.1 Acute Dietary Exposure/Risk

No toxic effects attributable to a single exposure of mefenpyr-diethyl were seen in the database; therefore, an acute dietary endpoint was not selected and an acute dietary risk assessment was not conducted.

5.2.2 Chronic Dietary Exposure/Risk

A highly conservative chronic dietary risk assessment was conducted for food only and for food and drinking water for mefenpyr-diethyl using tolerance level residues and assuming 100% crop treated. Mefenpyr-diethyl dietary exposure from food alone based on the newly proposed use pattern results in an estimated risk equivalent to <1% of the chronic population adjusted dose (cPAD) for the general U.S. population and all regulated subpopulations. Additionally, exposure from food and drinking water based on the newly proposed use pattern results in an estimated risk equivalent to <1% of the cPAD for the general population and all regulated subpopulations. Exposure and risk estimates are shown in Table 5.2, below.

5.2.3 Cancer Dietary Risk

Mefenpyr-diethyl is classified as a "not likely to be carcinogenic to humans"; thus, a cancer dietary risk assessment is not required.

Table 5.2. Summary of Dietary (Food Only and Food and Drinking Water) Exposure and Risk for Mefenpyr-diethyl

Population Subgroup	Chronic Dietary Food Only		Chronic Dietary Food and Water	
	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	% cPAD*
General U.S. Population	0.000105	<1	0.000189	<1
All Infants (< 1 year old)	0.000067	<1	0.000343	<1
Children 1-2 years old	0.000235	<1	**0.000360**	**<1**
Children 3-5 years old	**0.000239**	**<1**	0.000356	<1
Children 6-12 years old	0.000167	<1	0.000248	<1
Youth 13-19 years old	0.000101	<1	0.000162	<1
Adults 20-49 years old	0.000089	<1	0.000167	<1
Adults 50+ years old	0.000070	<1	0.000153	<1
Females 13-49 years old	0.000080	<1	0.000158	<1

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

No products containing mefenpyr-diethyl are available for sale in the residential market because of the crops specified on the applicable labels. As such, a residential risk assessment was not conducted.

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 ground application method employed for mefenpyr-diethyl. The Agency 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. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency 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 with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessments and Risk Characterization

There are no residential uses for mefenpyr-diethyl; therefore, the aggregate risk assessments include the contribution of risk from dietary (food and water) sources only. No toxic effects attributable to a single exposure of mefenpyr-diethyl were seen in the database; therefore, an acute aggregate risk assessment was not conducted. The chronic (long-term) aggregate risk is equivalent to the chronic dietary risk from food and water detailed above. Mefenpyr-diethyl is classified as "not likely to be carcinogenic to humans"; thus, a cancer aggregate risk assessment was not conducted. HED has no concern for aggregate risks resulting from the increased application of mefenpyr-diethyl requested in this petition.

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 mefenpyr-diethyl and any other substances and mefenpyr-diethyl 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 mefenpyr-diethyl 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

A separate occupational risk assessment document has not been completed for mefenpyr-diethyl. Risks were calculated according to the labels identified which are the products in which mefenpyr-diethyl is used as a safener.

Mefenpyr-diethyl can be applied by aerial or ground application methods to barley, wheat, and hay. The current petition also requests that soybeans and canola be added as crops. The labels specify maximum application rates but there is no differentiation between the seasonal rates and what is allowable in a single application event so all occupational exposures were evaluated using the range described above with 0.053 lb mefenpyr-diethyl per acre being considered the maximum allowable in a single application. Current labels require normal work clothing (WDGs) or double layer clothing (EC) with appropriate footwear, eye protection, and chemical resistant gloves. Respirators are not required. Restricted entry intervals (REI) are 24 hours on all labels. Risks from occupational exposures were calculated for handlers using aerial and ground-based application equipment which would be typical for herbicide applications to large field crops. For all scenarios considered, risks were not of concern at current label requirements for clothing and personal protective equipment use (i.e., calculated MOEs well exceeded the target of 100 ranging from ~5000 up to ~300,000 at the label specified PPE). Post-application

worker risks were also evaluated for scouting activities which is the only likely hand labor activity which would occur relative to the use of mefenpyr-diethyl in agriculture and risks were not of concern even on the day of application when individuals scout for an 8 hour workday (i.e., MOE =5000 and target = 100). Current labels require a 24 hour REI so actual risks would be even of less concern because residues would dissipate some between application and the REI of 1 day.

9.1 Occupational Handler Risk

The following occupational handler scenarios were assessed based on the proposed use directions, the available labels where mefenpyr-diethyl is used as a safener and information on actual field practices:

- 1a) mixer/loader-dry flowable formulation for aerial applications (i.e., 350 and 1200 acres per day treatments were considered for typical and large scale growers);
- 1b) mixer/loader-dry flowable formulation for groundboom applications (i.e., 80 & 200 acre treatments for typical and large-scale equipment/growers);
- 2a) mixer/loader-liquid formulation for aerial applications (i.e., 350 and 1200 acres per day treatments were considered for typical and large scale growers);
- 2b) mixer/loader-liquid formulation for groundboom applications (i.e., 80 & 200 acre treatments for typical and large-scale equipment/growers); 2a) mixer/loader-liquid formulation for aerial applications (i.e., 350 and 1200 acres per day treatments were considered for typical and large scale growers);
- 3) aerial applications using fixed wing aircraft (i.e., 350 and 1200 acres per day treatments were considered for typical and large scale growers); and
- 4) groundboom applications (i.e., 80 & 200 acre treatments for typical and large-scale equipment/growers).

[Note: For exposure analysis water dispersible granules and dry flowable formulations are considered similar and as such, exposure data based on dry flowable formulations have been used in this assessment.]

No chemical-specific exposure monitoring data were submitted in support of this evaluation of mefenpyr-diethyl. The Pesticide Handlers Exposure Database V1.1 (Surrogate Guide of August 1998) was used for determining the unit exposure values. Additionally, standard Agency values for acres treated per day for field crops (HED ExpoSAC policy 9.1) for the various scenarios evaluated in this assessment. Application rates and the applicable product requirements for personal protective clothing/equipment were defined based on the labels referenced in Section 2 and Table 2.2 above. All applicable toxicological points of departure and associated uncertainty factors were defined based on the information presented above in Section 3.5. All calculated occupational handler risks are presented in Table 9.1 below. As indicated above, risk estimates based on current labels for the product that include mefenpyr-diethyl are not of concern (i.e., all MOEs exceed 100 for all scenarios).

Table 9.1: Combined Short-/Intermediate-Term Margins of Exposure For Mefenpyr-diethyl Occupational Handlers

Number	Scenario	Representative Application Targets/Crops	Application Parameters		Short-/Intermediate-Term Margins Of Exposure		
			Application Rate	Area Treated	WDG Label PPE Requirements	EC Label PPE Requirements	If Engineering Controls Are Used
Mixer/loaders							
1a	Dry Flowable: Aerial/Chemigation	Soybeans/Canola	0.026	1200	NA	4697	10563
		Soybeans/Canola	0.053	1200	NA	2304	5182
		Soybeans/Canola	0.026	350	NA	16103	36216
		Soybeans/Canola	0.053	350	NA	7899	17766
1b	Dry Flowable: Groundboom	Soybeans/Canola	0.026	200	20161	NA	63378
		Soybeans/Canola	0.053	200	9890	NA	31091
		Soybeans/Canola	0.026	80	50403	NA	158446
		Soybeans/Canola	0.053	80	24726	NA	77728
2a	Liquids: Aerial / Chemigation	Soybeans/Canola	0.026	1200	9271	NA	25839
		Soybeans/Canola	0.053	1200	4548	NA	12676
		Soybeans/Canola	0.026	350	31786	NA	88590
		Soybeans/Canola	0.053	350	15593	NA	43459
2b	Liquids: Groundboom	Soybeans/Canola	0.026	200	55626	NA	155033
		Soybeans/Canola	0.053	200	27288	NA	76054
		Soybeans/Canola	0.026	80	139065	NA	387583
		Soybeans/Canola	0.026	80	139065	NA	387583
Applicators							
3	Aerial Liquid Application	Soybeans/Canola	0.026	1200	NA	NA	44270
		Soybeans/Canola	0.053	1200	NA	NA	21717
		Soybeans/Canola	0.026	350	NA	NA	151782
		Soybeans/Canola	0.053	350	NA	NA	74459
4	Groundboom	Soybeans/Canola	0.026	200	91327	114664	266935
		Soybeans/Canola	0.053	200	44802	56250	130949
		Soybeans/Canola	0.026	80	228316	286660	667338
		Soybeans/Canola	0.053	80	112004	140626	327373

Notes:
WDG label requirements for PPE: single layer clothing, gloves, no respirator, appropriate footwear and eye protection
EC label requirements for PPE: coveralls over shorts/short-sleeved shirt, gloves, no respirator, appropriate footwear and eye protection
Dermal or Inhalation Absorbed Dose = (((Acres treated/day)*(Unit Exposure)*(Application Rate)*(Abs. Rate %/100))/Body Weight 70 kg)
Margins of Exposure = (NOAEL (mg/kg/day)/Absorbed dose (mg/kg/day)); target uncertainty factor = 100
[Note: Corrections for units are required for inhalation dose estimates of ug to mg/lb ai; all unit exposure estimates from PHED Surrogate Guide (August 1998) & acres treated per day from standard Agency values for these types of equipment and applications found in HED Exposac Policy 9.1.]

9.2 Occupational Postapplication Risk

Hand labor activities for the crops considered in this assessment are very limited to essentially scouting which would be thought to occur only sporadically after applications. Most other

activities which would routinely occur such as harvest and, in some cases limited cultivation activities, would be mechanized and not be expected to result in occupational exposures.

No chemical-specific data (e.g., dislodgeable foliar residue or DFR) data were available for mefenpyr-diethyl with which to calculate risks so the Agency criterion for situations when no monitoring data are available (i.e., initial DFR = 20% of the application rate) was used as the basis for this assessment. Additionally, a transfer coefficient of 1500 cm^2/hour referenced from HED ExpoSAC policy 3.1 for scouting in field crops has been used as the exposure metric in the calculations coupled with an 8 hour workday. All other factors such as the point of departure and target uncertainty factors are similar to those used above for the occupational handler calculations.

Post application risks are calculated by determining exposures by the following formula:

DFR ($\mu g/cm^2$) * Transfer coefficient (cm^2/hour) * 8 hour workday * (Dermal abs. factor)/Body Weight (kg)

Based on the application rate of 0.053 lb ai/acre coupled with 20 percent of the application rate being equivalent to the dislodgeable foliar residue fraction the DFR concentration on the day of application at the maximum application rate is [0.12 $\mu g/cm^2$]. This value coupled with the other factors described above results in an absorbed dose of [0.02 mg/kg/day] on the day of application with a resulting MOE of 5000 which is well above the Agency's level of concern. As indicated above, current labels require a 24 hour REI so actual risks would be even of less concern because residues would dissipate some between application and the REI of 1 day.

10.0 Data Needs and Label Recommendations

10.1 Toxicology

The following toxicology studies are required:

- Subchronic (28-day) Inhalation Study

New requirement under the Revised Part 158 Toxicology Data Requirements (2007 edition):

- Immunotoxicity Study

10.2 Residue Chemistry

860.1200 Directions for Use

RD should assure that all labels which contain mefenpyr-diethyl at the rate of 0.053 lbs safener/A/growing season should specify plantback intervals of: (i) 30 days for leafy, fruiting, and root vegetables; (ii) 90 days for field corn; (iii) 120 days for soybean and canola; and (iv) 12 months for all other crops other than wheat and barley, which can be planted back at any time.

860.1360 Multiresidue Methods

No data have been submitted concerning recovery of residues of mefenpyr-diethyl using FDA multiresidue method protocols (PAM Vol. I). This previously identified deficiency remains outstanding.

860.1550 Proposed Tolerances
The petitioner is required to submit a revised Section F to reflect the commodity definitions presented in Appendix B, Table B1.

10.3 Occupational and Residential Exposure

None required at this time

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500; 2007) for a food use chemical for mefenpyr-diethyl are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	no
870.3465	90-Day Inhalation	yes	no
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	no	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes[A]
870.5100	Bacterial Reverse Mutation Assay	yes	yes
870.5300	*In Vivo* Mammalian Cell Assay	yes	yes
870.5xxx	*In Vitro* Cytogenetics Chromosomal Aberrations	yes	yes
870.6100a	Acute Delayed Neurotoxicity (hen)	no	no
870.6100b	90-Day Neurotoxicity (hen)	no	no
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	no
870.6200b	90-Day Neuro. Screening Battery (rat)	yes	no
870.6300	Developmental Neurotoxicity	CR	no
870.7200	Companion Animal Safety	CR	no
870.7485	Metabolism & Pharmacokinetics	yes	yes
870.7600	Dermal Penetration	CR	no
870.7800	Immunotoxicity	Yes	no

[A]rat carcinogenicity study is not adequate to assess the carcinogenic potential of mefenpyr-diethyl; although not required for the current action, a new study will be required if new uses result in significantly higher residues in food and/or significantly higher occupational (or future residential) exposure; CR conditionally required

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile – Mefenpyr-diethyl				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral [rat]	43972211	[A]LD_{50} = >5000 mg/kg	IV
870.1200	Acute dermal [rat]	43972213	[B]LD_{50} = >4000 mg/kg	III
870.1300	Acute inhalation [rat]	43972214	[C]LC_{50} = >1.32 mg/L	III
870.2400	Acute eye irritation [rabbit]	43972215	slight ocular irritant PIS 12.8	III
870.2500	Acute dermal irritation [rabbit]	43972216	not a dermal irritant PII 0.17.	IV
870.2600	Skin sensitization [guinea pig]	43972217 44280001	Slight dermal sensitizer	N/A

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Mefenpyr-diethyl		
Guideline No./ Study Type	**MRID No. (year) Classification /Doses**	**Results**
870.3100 90-Day oral toxicity [Wistar rat IBM-Han outbred, SPF]	MRID 43972219 (1992) (purity 94.5%) 0, 100, 500, 2500, 7500 ppm [males 0, 8.1, 42.1, 206.7, 660.6 mg/kg/day] [females 0, 8.6, 44 .3, 223, 708.9 mg/kg/day] (4-week recovery phase) acceptable/guideline	NOAEL = males 207/females 223 mg/kg/day (2500 ppm) LOAEL = males 661/female 709 mg/kg/day (7500 ppm), based on decreased body-weight gains (≈10%), decreased erythrocyte counts, hemoglobin, and hematocrit values, increased reticulocyte counts (+29%-39%), mean corpuscular volume, and gamma glutamyl transferase (GGT) activities (+55%).
870.3100 4-week oral toxicity [Wistar rat IBM-Han outbred, SPF]	MRID 44364401 (1992) (purity 98.9%) 0, 100, 500, 1000, 2500, 5000, 7500 ppm [males: 0, 10.1, 52.3, 102, 258.3, 518.7, 773.6 mg/kg/day] [females: 0, 10, 52.3, 101.4, 249, 488.2, 744.3 mg/kg/day] acceptable/non-guideline (*study used to set dose levels for 90-day study)*	NOAEL = 7500 ppm (744 mg/kg/day) assessment of several enzyme/biochemical parameters were performed (liver and kidney) Liver: induction of drug-metabolizing enzymes: *statistically-significant (n=5/sex/group) increases in GSH, DEM, PROD, TCCR, GGT in one or both sexes(mainly dose-related)*

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Mefenpyr-diethyl

Guideline No./ Study Type	MRID No. (year) Classification /Doses	Results
870.3150 13-week oral toxicity in nonrodent (beagle dog)	MRID 43972220 (1992) (purity 94.5% a.i.) 0, 400, 2000, 10000 ppm [males 0, 14.9, 80.5, 341 mg/kg/day] [females 0, 15.6, 81.2, 336.1 mg/kg/day] acceptable/guideline	NOAEL = 2000 ppm (80.5 mg/kg/day) LOAEL = 10000 ppm (336 mg/kg/day), based on increased absolute and relative liver weight and alkaline phosphatase activity (both sexes); focal liver lesions (hemorrhage, necrosis, inflammation; females); slight anemia (both sexes); decreased mean body weight and body-weight gain (females); and decreased food consumption (both sexes) *other findings include decreases in RBC, hemoglobin, hematocrit, increased reticulocyte counts that are consistent with findings in other studies/species*
870.3150 **30-day** oral toxicity in nonrodent (beagle dog)	MRID not assigned (1990) (purity 98.9%) 0, 1250, 2500, 5000, 10000 ppm (males: 0, 48, 92, 174, 375 mg/kg/day) (females: 0, 53, 98, 184, 308 mg/kg/day) acceptable/non-guideline	NOAEL = 10000 ppm (375/308 mg/kg/day), HDT *(increased alkaline phosphatase in females at HDT)*
870.3100 90-Day oral toxicity [Hanover-derived out-bred NMRI mice]	MRID 43972218 (1991) 0, 100, 500, 2500, 7500 ppm [males 0, 17.83, 89.27, 449.01, 1492.76 mg/kg/day] [females 0, 20.77, 105.39, 523.5, 1743.13 mg/kg/day] acceptable/guideline	NOAEL = 500 pp (89 mg/kg/day) LOAEL = 2500 ppm (449 mg/kg/day), based on decreased body weight, kidney weight, increased liver weight, and hepatocyte hypertrophy in males; decreased bilirubin and increased lactic acid dehydrogenase values in females At 7500 ppm, enlarged livers, increased liver weight (50% greater than control), hepatocyte hypertrophy, enlarged spleens; more severe hematopoiesis and hemosiderin deposits than controls, increased spleen weight (both sexes), decreased kidney weight (males), decreased bilirubin (females), increased lactic acid dehydrogenase values (both sexes), slightly elevated ALAT and ASAT (females)
870.3200 21/28-Day dermal toxicity (Wistar rat)	MRID 44089201 (1992) (purity 94.3% a.i.) 0, 100, 300, 1000 mg/kg/day acceptable/guideline	NOAEL = 1000 mg/kg/day
870.3250 90-Day dermal toxicity	no study located/not required	
870.3465 90-day inhalation toxicity	Datagap	

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Mefenpyr-diethyl

Guideline No./ Study Type	MRID No. (year) Classification /Doses	Results
870.3700a Prenatal developmental in rodent [Wistar rat]	MRID 43972221(1992) 94.5% a.i. 0, 1000 mg/kg/day gestation days 7-16 acceptable/guideline	**Maternal** NOAEL = <1000 mg/kg/day **Maternal** LOAEL = 1000 mg/kg/day, based on decreased body-weight gain (76% of control) and food efficiency during first week of dosing; increases in absolute and relative spleen weights **Developmental** NOAEL = 1000 mg/kg/day (HDT) **Developmental** LOAEL = no effects observed
870.3700a Prenatal developmental in rodent [Wistar rat]	MRID 44654201 (1992) 94.3% a.i. 0, 1000 mg/kg/day gestation days 7-16 *Includes post-natal development* acceptable/guideline	**Maternal** NOAEL = <1000 mg/kg/day **Maternal** LOAEL = 1000 mg/kg/day, based on decreased body-weight gain and food efficiency during first week of dosing **Developmental** NOAEL <1000 mg/kg/day **Developmental** LOAEL = 1000 mg/kg/day, there was a marginal decrease in fetal body weight (95% of control at birth; 91% of control at PND 21) and body-weight gain (90% of control overall) during lactation
870.3700b Prenatal developmental in nonrodent (Himalayan rabbit)	MRID 44089202 (1992) (purity 94.5% a.i.) 0, 40, 100, 250 mg/kg/day gestation days 6-18 acceptable/guideline	**Maternal toxicity NOAEL** = 100 mg/kg/day **Maternal toxicity LOAEL** = 250 mg/kg/day, based on abortions *(5 abortions between GD 16-23; premature delivery of 1 control (GD 28) and 1 HDT (GD 27)* **Developmental toxicity NOAEL** = 100 mg/kg/day **Developmental toxicity LOAEL** = 250 mg//kg/day, based on abortions
870.3800 Reproduction and fertility effects (WIST Han Ibm:WIST ISPF rat)	MRID 44661601/44654202 (1994/1995) (purity 94.3% a.i.) 0, 200, 1000, 5000 ppm [P0 males: 0, 16.4, 82.8, 428.3 mg/kg/day] [P0 females: 0, 18.6, 94.4, 482.7 mg/kg/day] *NOTE: mg/kg/day changed to reflect P0 pre-mating intake; doses of F1 males postmating used in original DER/HIARC* acceptable/guideline	**Parental toxicity NOAEL** = 1000 ppm (82 mg/kg/day) **Parental toxicity LOAEL** = 5000 ppm (428 mg/kg/day), based on decreased mean body weight and body-weight gain in parental animals and offspring and an increase in spleen weight and severity (but not incidence; all rats displayed this finding; both generations) of splenic extramedullary hematopoiesis in females (increased spleen weight in F1 females) **Reproductive NOAEL** = 5000 ppm (males 428/females 482 mg/kg/day), highest dose tested **Reproductive LOAEL** = > 5000 ppm **Offspring NOAEL** = 1000 ppm (82 mg/kg/day) **Offspring LOAEL** = 5000 ppm (428 mg/kg/day), based on decreased body weight [LD 14 (90% of control) and LD 21 (85% of control)]

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Mefenpyr-diethyl

Guideline No./ Study Type	MRID No. (year) Classification /Doses	Results
870.4100a Chronic toxicity rodents (Wistar rat)	MRID 43972222/43972223 (1994) (purity 94.3% a.i.) 0, 40, 200, 1000, 5000 ppm M 0, 1.92, 9.8, 48.5, 251.6 mg/kg/day F 0, 2.38, 12.1, 60, 318 mg/kg/day acceptable/guideline	**Systemic toxicity NOAEL** = males 48.5/females 60 mg/kg/day **Systemic toxicity LOAEL** = males 252/females 318 mg/kg/day, based on significant increases in reticulocyte counts
870.4100b Chronic toxicity nonrodent (beagle dog)	MRID 44316402 (1992) 0, 60, 300, 1500, 7500 ppm (purity 94.3% a.i.) males 0, 2.3, 10.1, 51.4, 260.2 mg/kg/day females 0, 2.1, 11.1, 57.6, 282.2 mg/kg/day acceptable/guideline	**Systemic toxicity NOAEL** = 1500 ppm (51 mg/kg/day) **Systemic toxicity LOAEL** = 7500 ppm (260 mg/kg/day, based on adverse findings in the liver (cholestasis, increased alkaline phosphatase, and increased liver weight in both sexes)
870.4200 Carcinogenicity (Wistar rat)	MRID 43972222/43972223 (1994) (purity 94.3%) 0, 40, 200, 1000, 5000 ppm M 0, 1.92, 9.8, 48.5, 251.6 mg/kg/day F 0, 2.38, 12.1, 60, 318 mg/kg/day acceptable/guideline	see above under 870.4100a **new study will be required if new uses result in significantly higher residues in food and/or significantly higher occupational (or future residential) exposure** dose levels not adequate to assess carcinogenic potential (90-day study concluded that 7500 ppm should be tested in this study)
870.4300 Carcinogenicity (Hanover-derived out-bred NMRI mouse)	MRID 43972224/43972225 (1994/1995) (purity 94.3% a.i.) 0, 20, 100, 500, 2500 ppm [males 0, 2.76, 14.1, 70.6, 350.8 mg/kg/day] [females 0, 3.78, 18.3, 92, 463 mg/kg/day] acceptable/guideline	**Systemic toxicity NOAEL** = 2500 ppm (males 351 mg/kg/day /females 463 mg/kg/day **Systemic toxicity LOAEL** = not determined **No treatment related tumors** Doses considered adequate (based on subchronic study)
870.6200a Acute neurotoxicity screening battery	No study available. Not required.	
870.6200b Subchronic neurotoxicity screening battery	No study available. Not required	

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Mefenpyr-diethyl

Guideline No./ Study Type	MRID No. (year) Classification /Doses	Results
870.6300 Developmental neurotoxicity	No study available. Not required.	
870.7485 Metabolism and pharmacokinetics (Wistar Hoe WISKf, SPF 71 rat)	MRID 44654203 (1996) (purity 99%) 1 mg/kg for 14 days + 1 mg/kg [phenyl- ^{14}C] labeled compound (gavage) acceptable/guideline	Urine primary elimination route; accounted for 83% (males)/ 92% (females) of administered dose; fecal excretion accounted for 22%/11%, respectively; most of [^{14}C] recovered during first 24 hours; tissue/organ residual activity at 168 hours ≤0.6%; biphasic elimination pattern was identified: initial rapid $T_{1/2}$: males 4.2/females 3.7 hours (urine) and males 7.8/females 10.4 hours (feces); longer $T_{1/2}$: males 24.9/females 28.8 hours (urine); males 33.6/females 56.6 hours (feces); sex-specific differences in metabolic disposition found: males principal metabolite in urine was dicarboxylic acid HOE 109453 (89.3%) with only minor amounts of the pyrazolyl carboxylic acid HOE 094270 (7.5%) and the monocarboxylic acid HOE 113225 (3.2%); females excreted similar amounts of HOE 109453 (50.7%) and HOE 113225 (41.5%), with minor amounts of HOE 094270 (6.2%). Fecal excretion: HOE 113225 (males 54.1%/females 40.6%); HOE 109453 (males 34.1%/females 48.3%), HOE 094270 (<7%); no parent recovered in excreta; absorption and metabolic pathways did not become saturated at dose used (no accumulation in tissues/organs)
870.7485 Metabolism and pharmacokinetics (Wistar WISK SPF 71 rat)	MRID 44654204 (1992) (purity 99%) 1 or 100 mg/kg acceptable/guideline	Renal excretion was predominant route of elimination (males 68% and 65%/females 72% and 65% by 48 hours) following 1 and 100 mg/kg, respectively; test material not found in urine; 3 metabolites identified: HOE 109453 (males 63% and 62%/females 42% and 48%); HOE 113225 (males 2% and 0.2%/females 28% and 14%); HOE 094270 (males 2.9$ and 2.4%/females 2.3% and 2.1%) following 1 and 100 mg/kg, respectively. Parent compound was found in the feces (males 7.9% and 8.1%/females 2.9% and 0.95%), respectively in addition to the 3 metabolites found in the urine; metabolic pathway: consecutive hydrolysis (saponification) of the 2 carboxylic acid ester groups and a decarboxylation of one of the carboxylic groups, resulting in an aromatization of the pyrazoline ring (Hoe 107892→ HOE 113225 → HOE 109453 → HOE 094270). HOE 109453 was found in the plasma. Metabolism appears to be influenced by sex to minor extent; males either have a lower intestinal absorption or a higher biliary excretion compared to females.
870.5265 Ames assay	MRID 43972226 4-5000 ug/plate Classification: acceptable/guideline	no indication that test material induced a mutagenic effect in any tester strain +/-S9 activation; no clear evidence of cytotoxicity; compound insolubility seen at ≥2500 ug/plate -S9, 10000 ug/plate +S9
870.5375 mammalian cell gene mutation assay	MRID 43972230 10-100 ug/mL; -S9; 25-100 ug/mL +S9 Classification: acceptable/guideline	no evidence that test material was mutagenic under conditions of assay; cytotoxicity at 100 ug/mL -S9 only.

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Mefenpyr-diethyl		
Guideline No./ Study Type	**MRID No. (year) Classification /Doses**	**Results**
870.5375 *in vitro* mammalian cytogenetic assay (Chinese hamster lung fibroblasts)	MRID 43972227 5-25 ug/mL (-S9) and 5-100 ug/mL (+S9) Classification: acceptable/guideline	no indication that test material induced a clastogenic response at any dose level or harvest time in either presence or absence of S9 activition
870.5385 *in vivo* mammalian cytogenetic assay (mouse)	MRID 43972227 Classification: acceptable/guideline	no evidence that test material induced a clastogenic or aneugenic effect in either sex at any sacrifice time at 5000 mg/kg.
Guideline 5550, unscheduled DNA synthesis in mammalian cells in culture	MRID 439722229 doses up to 100 ug/mL (+/-S9); cytotoxic/insoluble without S9; +S9 not cytotoxic at 100 ug/mL Classification: unacceptable/non-guideline	no clear evidence that test material was genotoxic under assay conditions. overall assay sensitivity compromised because high levels of radioactive label, indicating that replicative DNA synthesis was not successfully blocked in all experimental groups.
870.7485 Metabolism and pharmacokinetics (Wistar WISK SPF 71 rat)	MRID 44661602/44661603 (1992/1993) 1 and 100 mg/kg	main route of excretion is urine: males 76%/68%; females 88%/79% of administered dose (1 mg/kg and 100 mg/kg, respectively); feces: 30%/32%; females 14%/24%, respectively. most eliminated within first 24 hours; excretion biphasic: biological half-life for excretion *via* urine for males and females at low and high dose were between 4 and 7 hrs (rapid phase I) and 23 and 31 hrs (terminal phase II); concentrations in organ/tissue and blood/plasma at study termination (7 days post dose) were 2-3 times higher in females than males (both doses); no [^{14}C] was detected in CNS; plasma showed highest concentrations in both sexes and dose levels (males 0.021 and 0.59 µg equivalents/g; females 0.063 and 1.96 µg equivalents/g), respectively; plasma levels ≈60%-80% higher than in blood (erythrocyte concentration of 7%-8% of plasma concentration at 1 mg/kg and 14%-22% at 100 mg/kg.
870.7600 Dermal penetration	no study available	

A.3 Executive Summaries

(Note: see HIARC document TXR 012998 for all other Executive Summaries)

A.3.1 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

EXECUTIVE SUMMARY: HOE 107892 (purity: 94.3% w/w) was administered by oral gavage, once daily from day 7 to 16 of gravidity to a group of 20 mated female Wistar rats at a dose of 1000 mg/kg bw and a control group received the vehicle (2% w/v starch mucilage) without the test substance (MRID 44654201). The animals delivered normally and reared their offspring for 21 days. There were no maternal mortalities, no treatment-related clinical signs of toxicity and no treatment-related gross pathological observations. Mean maternal body weight was comparable between the control and treated group throughout gestation and lactation. Mean maternal body-weight gain was significantly lower (14%) during treatment (days 7 to 17 of gestation) due to a significant difference (decreased 24%) during the first week of treatment (days 7 to 14 of gestation) and was accompanied by a significant reduction in food efficiency and food consumption, therefore suggesting the decrease in maternal body- weight gain was treatment-related. There was a possible treatment-related reduction in the absolute and relative spleen weights of the treated dams, but the biological and toxicological significance was uncertain. There was a marginal treatment-related impairment in fetal body weight (5-9% less than controls) and body-weight gain (10% less than controls), and a treatment-related decrease in the mean absolute spleen and heart weights of the pups in the treated group, which could be due to maternal stress and/or the toxicity of the test substance. The biological and toxicological significance of the reduced absolute spleen and heart weights was uncertain. There were no treatment-related effects on the litter data parameters examined (with the exception of body weight), and no impairment in the physical, functional or behavioral development of the neonates which suggests that the test substance was not teratogenic under the conditions of the study.

Based on the results of the study, the NOAEL for maternal toxicity is < 1000 mg/kg/ bw/day and the maternal LOAEL is 1000 mg/kg bw/day based on decreases in body weight gain and food efficiency during the first week of treatment. The NOAEL for developmental toxicity is < 1000 mg/kg bw/day and the developmental LOAEL is 1000 mg/kg bw/day based on marginal decreases in fetal body weight and body weight gain during lactation.

The post-natal development study in the rat is classified as acceptable/nonguideline. There is no guideline requirement for a post-natal developmental toxicity study.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 43972221) Hoe 107892 (94.5% a.i.) in starch mucilage was administered orally by gavage to 20 Wistar rats at the limit dose (1,000 mg/kg/day) from days 7 through 16 of gestation.

At 1000 mg/kg/day, mean body weight gain for days 7-14 was significantly lower (24.2%) than the control group during the same time period. There was a slight, although

not statistically significant increase in body weight gain during the latter part of treatment (days 14- 17) and during the post-treatment period. The food efficiency index was also significantly lower during the first week of treatment. In addition to the decrease in body weight gain during treatment, absolute and relative spleen weights were significantly increased in the treated animals when compared to the control group (anemia, enlarged spleens and increased hematopoiesis has been observed in other studies across species).

The LOAEL for maternal toxicity is 1000 mg/kg/day and the NOAEL is < 1000 mg/kg/day based on decreases in body weight gain and food efficiency during the first week of treatment and on increases in absolute and relative spleen weights.

There were no treatment-related effects in developmental parameters. A developmental LOAEL was not achieved. The developmental NOAEL is the limit dose, 1,000 mg/kg/day.

The developmental toxicity study in the rat is classified Acceptable/Guideline and it satisfies the guideline requirement for a developmental toxicity study [OPPTS 870.3700; §83-3(a)] in rats. Although a maternal NOAEL was not defined, there was no developmental toxicity at the limit dose.

There are two rat developmental toxicity which were both performed at the limit dose only. Both show only minimal fetal body-weight effects and decreased maternal body-weight gain during the first week. Although a NOAEL was not defines in either study, no developmental toxicity was observed at the limit dose. Therefore, sensitivity to infants and children as defined by FQPA can be addressed.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

EXECUTIVE SUMMARY: HOE 107892 (purity: 94.5% w/w) was administered by oral gavage once daily from days 6 to 18 of gravidity to groups of 15 to 16 mated female Himalayan rabbits at a dose of 0 (vehicle only), 40, 100 or 250 mg/kg bw (MRID 44089202). The test substance was suspended in 2% (w/v) starch mucilage. All surviving does were sacrificed and delivered by caesarian section on day 29 of gravidity after which the fetuses were kept for 24 horns in an incubator. There were no mortalities, no treatment-related adverse clinical observations and no treatment-related effects on gross pathology or organ weights observed in the does. Mean maternal body weight was comparable between the control group and the treated groups thoughout the study. At 100 mg/kg bw, there was a reduced mean absolute food consumption which was not considered adverse since there were no other treatment-related effects observed at this dose (8 1-85% of control during treatment period, p ł 0.05). At 250 mg/kg bw, there was a significant decrease (p ł 0.05) in body-weight gain during the first week of treatment (days 6 to 13) which was accompanied by a significantly reduced (p ł 0.05) food efficiency index and food consumption. There was also a higher rate of abortions. There

were no other treatment-related effects at any dose level on delivery or on litter data parameters examined, including those found dead due to abortions or premature delivery.

The NOAEL for maternal toxicity is 100 mg/kg bw/day and the LOAEL is 250 mg/kg bw/day based on a higher rate of abortions. The decreases in body- weight gain, food efficiency index and food consumption may also be an indication of maternal toxicity as well; however, due to the fact there was no effect on mean body weights in the treated groups and that the percent increase in mean bodyweight over the entire gestation period, when compared to the total bodyweight is only 10% (11% for the control group and 9% for the high dose group), this effect is considered to be marginal. **The NOAEL for developmental toxicity is 100 mg/kg bw and the LOAEL for developmental toxicity is 250 mg/kg bw based on a higher rate of abortions.** Examination of the individual animal data does not indicate that the abortions were solely due to maternal toxicity.

The developmental toxicity study in the rabbit is classified as Acceptable guideline and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(b)) in the rabbit.

A.3.2 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects - Rat

EXECUTIVE SUMMARY: A two-generation reproduction study was conducted using WIST Han Ibm: WIST ISPF) rats, fed test diets containing CGA 107892, purity 94.3%, at dietary concentrations of 0, 200, 1000 or 5000 ppm, continuously throughout the study period, 25 rats/sex/group (MRID 44661601/44654202). This is equivalent to ranges of 0, 11.2-16.4, 57.3 -82.8 and 306-428 mg/kg/day for males during the pre- and postmating periods for 2 generations and ranges of 0, 15.3-32.1, 76.0-161.2 and 392.0-779.6 mg/kg/day for females during the premating, gestation and lactation periods for 2 generations. The lowest dose levels were selected for the NOAELs and LOAELs. Each female in each generation was mated to produce one litter only. Parental systemic toxicity was observed at 5000 ppm (306 mg/kg/day) based on decreased mean body weight and mean body weight gain in parents during the premating period (P generation, both sexes, and Fl generation, males only). There were no treatment-related effects on mean food consumption. Decreases in mean body weight and body weight gain were also evident in the offspring at this dose level (Fl pups on days 7, 14 and 21 postpartum, and F2 pups on days 14 and 21 postpartum). The only other findings considered to be treatment-related were an increase in mean spleen weight and an increase in the severity (but not in the incidence) of splenic extramedullary hematopoiesis in females in the 5000 ppm group. It was considered equivocal whether a similar, but less pronounced, increase in the severity of splenic extramedullary hematopoiesis noted for males in the 5000 ppm group was related to treatment.

The parental/offspring systemic toxicity NOAEL is set at 1000 ppm (82 mg/kg bw/day for males and 94 mg/kg bw/day for females) and the LOAEL is set at 5000 ppm (428 mg/kg bw/day for males and 482 mg/kg bw/day for females) based on decreased mean body weight and mean body weight gain in parents and offspring and on an increase in mean spleen weight and an increase in the severity (but not in the incidence) of splenic extramedullary hematopoiesis in females. The reproductive NOAEL is set at 5000 ppm (428 mg/kg bw/day for males and 482 mg/kg bw/day for females, the highest dose tested), since there were no adverse, treatment-related effects on reproductive parameters evident at any dose level tested.

The reproductive study in the rat is classified as Acceptable guideline and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800, §83-4) in the rat.

A.3.3 Chronic Toxicity

870.4100b Chronic Toxicity - Dog

EXECUTIVE SUMMARY: HOE 107892, purity 94.3%, was evaluated for chronic oral toxicity in pure bred beagle dogs (6 animals/sex/dose) (MMD 44316402). Animals were dosed in the diet for a period of 52 weeks and 4-6 days at concentrations of 0, 60, 300, 1500 or 7500 ppm (equal to 0, 2.3, 10.1, 51.4 and 260.2 mg/kg bw/day, respectively, in males and 0,2.1, 11.1, 57.6 and 282.2 mg/kg bw/day, respectively, in females). There were no treatment-related mortalities, changes in body weight or food consumption. Liver findings included high ALP enzyme levels in males and females treated at 7500 ppm (13/14 and 52/53 weeks for males (178% ($p < 0.05$), 213% ($p < 0.01$)) and 13/14, 26/27 and 52/53 weeks for females (350 - 412%, $p < 0.01$)); high absolute and relative liver weights in males ($p < 0.05$) and females ($p < 0.01$) treated at 7500 ppm and a high liver/body weight ratio in females ($p < 0.05$) treated at 1500 ppm; and grade 1 (minimal) intrahepatic cholestasis in the liver of 2 males and 2 females of the high-dose group. Along with the other findings in the liver (high ALP and high liver weights), cholestasis is considered to be toxicologically significant. For this study, the NOAEL is 1500 ppm (51.4 mg/kg bw/day) and the LOAEL is 7500 ppm (260.2 mg/kg/day) based on adverse findings in the liver in the high-dose group and treatment-related, non-adverse findings in animals treated at 1500 ppm (high liver/body weight ratio in females treated at 1500 ppm).

This chronic toxicity study in the dog is Acceptable guideline and satisfies the guideline requirement for a chronic oral study (870.4100) in dogs.

A.4 References (in MRID order)

43972211 Ehling, G.; Leist, K. (1990) (Inert ingredient): Testing for Acute Oral Toxicity in the Male and Female Wistar Rat: Lab Project Number: 90.0420: A43614: 90.0608. Unpublished .

43972212 Ehling, G.; Leist, K. (1990) (Inert ingredient): Testing for Acute Oral Toxicity in the Male and Female NMRI Mouse: Lab Project Number: 90.0422: A43378: 90.0450. Unpublished.

43972213 Ehling, G.; Leist, K. (1990) (Inert ingredient): Testing for Acute Dermal Toxicity in the Male and Female Wistar Rat: Lab Project Number: 90.0427: A43325: 90.0451. Unpublished.

43972214 Hofmann, T.; Jung, R. (1990) (Inert ingredient): Testing for Acute Aerosol Inhalation Toxicity in the Male and Female Wistar Rat, 4-Hour LC50: Lab Project Number: 90.0984: A44883: 90.1423. Unpublished

43972215 Leist, K.; Hack, R. (1990) (Inert ingredient): Testing for Primary Eye Irritation in the Rabbit: Lab Project Number: 90.0426: A43537: 90.0531. Unpublished.

43972216 Leist, K.; Hack, R. (1990) (Inert ingredient): Testing for Primary Dermal Irritation in the Rabbit: Lab Project Number: 90.0425: A43416: 90.0510. Unpublished

43972217 Hack, R.; Leist, K. (1991) (Inert ingredient): Testing for Sensitizing Properties in the Pirbright-White Guinea Pig in a Maximization Test: Lab Project Number: 90.0990: A45698: 91.0254. Unpublished

43972218 Tennekes, H.; Janiak, D.; Probst, H.; et al. (1991) (Inert ingredient): Substance Technical Sub-Chronic Oral Toxicity: 13-Week Feeding Study in Mice: Lab Project Number: 284894: A48481. Unpublished

43972219 Tennekes, H.; Janiak, T.; Probst, D. et al. (1990) (Inert ingredient): Substance Technical Sub-Chronic Oral Toxicity: 13-Week Feeding Study in Rats: RCC, Research and Consulting Co.; RCC Umweltchemie Ag; and EPS Ag Lab Project Number: 285028: A47873. Unpublished.

43972220 Allen, T.; Braunhofer, P.; Frei, T. et al. (1992) (Inert ingredient): 13-Week Oral Toxicity (Feeding) Study with (inert ingredient) Substance Technical in the Dog: RCC, Research and Consulting Co.; RCC Umweltchemie Ag; and RCC Lab Project Number: 285120: A47753. Unpublished.

43972221 Albrecht, M.; Baeder, C. (1992) (Inert ingredient): Testing for Embryotoxicity in the Wistar Rat After Oral Administration (Limit Test): Lab Project Number: RR0620: 90.0988: A48150. Unpublished.

43972222 Dotti, A.; Keller, B.; Luetkemeier, H. et al. (1994) (Inert ingredient): Combined Chronic Toxicity/Oncogenicity (Feeding) Study with (inert ingredient) Substance Technical in the Rat: RCC, Research and Consulting Co. AG. Lab Project Number: 293490: A53310. Unpublished.

43972223 Dotti, A. (1995) (Inert ingredient): Combined Chronic Toxicity/Oncogenicity (Feeding) Study with (inert ingredient) Substance Technical in the Rat--First Amendment to Report: RCC, Research and Consulting Co., Ltd., Lab Project Number: 293490: A56020. Unpublished.

43972224 Dotti, A.; Keller, B.; Luetkemeier, H.; et al. (1994) (Inert ingredient): Oncogenicity (Feeding) Study with (inert ingredient) Substance Technical in the Mouse: RCC, Research and Consulting Co. AG. Lab Project Number: 94101 JMA: 291137: A53241. Unpublished.

43972225 Dotti, A. (1995) (Inert ingredient): Oncogenicity (Feeding) Study with (inert ingredient) Substance Technical in the Mouse--First Amendment to Report: RCC, Research and Consulting Co., Ltd., Lab Project Number: A56021: 291137. Unpublished.

43972226 Mueller, W. (1990) (Inert ingredient): Study of the Mutagenic Potential in Strains of Salmonella typhimurium (Ames Test) and Escherichia coli: Lab Project Number: 90.0421: A44259: 90.0783. Unpublished.

43972227 Mueller, W. (1990) (Inert ingredient): Chromosome Aberrations in vitro in V79 Chinese Hamster Cells: Lab Project Number: 90.0430: A44267: 90.0884. Unpublished.

43972228 Mueller, W. (1990) (Inert ingredient): Micronucleus Test in Male and Female NMRI Mice after Oral Administration: Lab Project Number: 90.0419: A44264: 90.0808. Unpublished

43972229 Mueller, W. (1990) Evaluation of (inert ingredient)--Substance, Technical in the Unscheduled DNA Synthesis Test in Mammalian Cells in Vitro: Lab Project Number: 90.0418: A44405: 90.0685. Unpublished

43972230 Mueller, W. (1990) (Inert ingredient): Detection of Gene Mutations in Somatic Cells in Culture HGPRT-Test with V79 Cells: Lab Project Number: 90.0429: A44823: 90.0611. Unpublished

44654202 Dotti, A. (1995) (Inert Ingredient) Substance Technical: Two-Generation Reproduction Study in Rat: Amendment to Report A52643: Lab Project Number: 293433: A56022. Unpublished

44654203 Burkle, W.; Maas, J. (1996) (Inert Ingredient-(carbon 14): Investigation of the Kinetics and Metabolism in Male and Female Rats Following 14 Daily Non-Labelled Doses and Radiolabelled Oral Dose of 1mg/kg/day: Lab Project Number: 172/4: H012/K114D: A56423. Unpublished

44654204 Burkle, W. (1992) (Inert Ingredient)-(carbon 14): Metabolism in the Rat Following a Single Dose of 1 and 100mg/kg Body Weight p. o: Lab Project Number: CM92/113: 172/2: A49252. Unpublished

44661601 Dotti, A.; Springall, C.; Biedermann, K. (1994) (Inert Ingredient) Substance Technical (... ZC94 0001) Two-Generation Reproduction Study in the Rat: Lab Project Number: 293433: A522643. Unpublished

44661602 Eckert, H.; Kellner, H.; Puttkamer, G. (1992) (Inert Ingredient)-(carbon-14) Pharmacokinetics in the Rat After Oral Administration of 1 and 100 mg/kg Body Weight: Lab Project Number: 172/1: CM90/103. Unpublished

44661603 Eckert, H.; Kellner, H.; Puttkamer, G. (1993) (Inert Ingredient)-(carbon-14) Pharmacokinetics in the Rat after Oral Administration of 1 and 100 mg/kg Body Weight: Amendment to Report Number A49005: Lab Project Number: 172/1: CM90/103: A51777. Unpublished

44089201 Ebert, E.; Leist, K. (1992) (Inert ingredient): Repeated-Dose Dermal Toxicity (21 Treatments in 29 Days) in the Wistar Rat: Hoechst Aktiengesellschaft . Lab Project Number: 91.0450: CR0103: A48666. Unpublished.

44089202 Horstmann, G.; Baeder, C. (1992) (Inert ingredient): Testing for Embryotoxicity in the Himalayan Rabbit After Oral Administration: Lab Project Number: RK0621: 90.0989: A49620. Unpublished.

44280001 Stammberger, I.; Jung, R. (1991) Sensitivity Check of the Guinea Pig Strain (Pirbright-White Guinea Pig) for Sensitisation Tests on the Skin with Nickel-II-Sulphate in a Maximisation Test: (Positive Control Test for MRID 43972217): Lab Project Number: 91.0298: A47419: 92.0097. Unpublished

44316401 Allen, T.; Corney, S.; Frei, T.; et al. (1990) (Inert ingredient): 30-Day Oral Toxicity (Feeding) Study with (inert ingredient) in the Dog: RCC Research and Consulting Co., Ltd; RCC Umweltchemie AG; and RCC (UK) Ltd. Lab Project Number: A45830: RCC 271754: 271754. Unpublished

44316402 Allen, T.; Braunhofer, P.; Frei, T.; et al. (1992) (Inert ingredient): 52-Week Oral Toxicity (Feeding) Study with (inert ingredient) in the Dog: Lab Project Number: A49032: RCC 291115: 291115. RCC Research and Consulting Co., Ltd; RCC Umweltchemie AG; and BRL Biological Research Labs, Ltd. Unpublished

44316403 Ebert, E. (1992) (Inert ingredient): Repeated Dose Oral Toxicity (4-Week Feeding Study) in the NMRI Mouse--Plus Addendum: Hoechst Aktiengesellschaft. Lab Project Number: A47423: A48480: 90.0424. Unpublished.

44364401 Ebert, E.; Leist, K. (1997) (Inert Ingredient): Repeated--Dose Oral Toxicity (4-Week Feeding Study) in the Wister Rat--Plus Addendum: Hoechst Aktiengesellschaft Lab Project Number: A47872: A49720: 91-1152. Unpublished

44654201 Albrecht, M.; Baeder, C. (1992) (Inert Ingredient) Substance Technical: Testing for Embryotoxicity and Effects on Post-Natal Development in Wistar Rats After Oral Administration (Limit Test): Lab Project Number: P2R0636/RR0636: A48786: 92.0559. Unpublished

Appendix B: Tolerance Summary and Table

Table B1. New Tolerance Summary for Mefenpyr-diethyl			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Soybean seed	0.02	0.02	*Soybean, seed*
Soybean hay	0.10	0.1	*Soybean, hay*
Soybean forage	0.10	0.1	*Soybean, forage*
Canola seed	0.02	0.02	*Canola, seed*

HED notes that not only should the new tolerances be established, but the **tolerance definition** should be revised to permit use of mefenpyr-diethyl at up to 0.053 pounds safener/A per growing season.

Appendix C: Combined Short-Term MOEs for Occupational Handler Risk Assessment

Number	Scenario	Representative Application Targets/Crops	Application Parameters: Application Rate	Application Parameters: Area Treated	Baseline	Single Layer, Gloves & No Respirator	Single Layer, Gloves & PF5 Respirator	Single Layer, Gloves & PF10 Respirator	Double Layer, Gloves & No Respirator	Double Layer, Gloves & PF5 Respirator	Double Layer, Gloves & PF10 Respirator	Eng. Controls
					Mixer/Loaders							
1a	Dry Flowable: Aerial/Chemigation	Soybeans/Canola	0.026	1200	3360	3360	3391	3395	4697	4758	4766	10563
		Soybeans/Canola	0.053	1200	1648	1648	1664	1666	2304	2334	2338	5182
		Soybeans/Canola	0.026	350	11521	11521	11628	11641	16103	16313	16340	36216
		Soybeans/Canola	0.053	350	5652	5652	5704	5711	7899	8003	8016	17766
1b	Dry Flowable: Groundboom	Soybeans/Canola	0.026	200	20161	20161	20349	20373	28180	28548	28595	63378
		Soybeans/Canola	0.053	200	9890	9890	9982	9994	13824	14005	14028	31091
		Soybeans/Canola	0.026	80	50403	50403	50872	50931	70450	71370	71487	158446
		Soybeans/Canola	0.053	80	24726	24726	24956	24985	34560	35012	35069	77728
2a	Liquids: Aerial / Chemigation	Soybeans/Canola	0.026	1200	77	9271	9654	9704	12327	13014	13105	25839
		Soybeans/Canola	0.053	1200	38	4548	4736	4761	6047	6384	6429	12676
		Soybeans/Canola	0.026	350	265	31786	33099	33271	42265	44619	44932	88590
		Soybeans/Canola	0.053	350	130	15593	16237	16322	20734	21889	22042	43459
2b	Liquids: Groundboom	Soybeans/Canola	0.026	200	464	55626	57924	58225	73964	78083	78630	155033
		Soybeans/Canola	0.053	200	228	27288	28416	28563	36284	38305	38573	76054
		Soybeans/Canola	0.026	80	1160	139065	144810	145562	184911	195208	196576	387583
		Soybeans/Canola	0.026	80	1160	139065	144810	145562	184911	195208	196576	387583
					Applicators							
3	Aerial Liquid Application	Soybeans/Canola	0.026	1200	NA	NA	NA	NA	NA	NA	NA	44270
		Soybeans/Canola	0.053	1200	NA	NA	NA	NA	NA	NA	NA	21717
		Soybeans/Canola	0.026	350	NA	NA	NA	NA	NA	NA	NA	151782
		Soybeans/Canola	0.053	350	NA	NA	NA	NA	NA	NA	NA	74459
4	Groundboom	Soybeans/Canola	0.026	200	91327	91327	95148	95648	114664	120753	121560	266935
		Soybeans/Canola	0.053	200	44802	44802	46676	46922	56250	59237	59633	130949
		Soybeans/Canola	0.026	80	228316	228316	237870	239121	286660	301882	303900	667338
		Soybeans/Canola	0.053	80	112004	112004	116691	117304	140626	148093	149083	327373

Appendix D: Review of Human Research

Studies reviewed for ethical conduct:

No MRID - PHED Surrogate Exposure Guide

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

Studies reviewed by the Human Studies Review Board:

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

13544

R164460

Chemical Name: Diethyl-1-(2,4-dichlorophenyl)-5-methyl-2-pyrazolin-3,5-dicarboxylate (Mefenpyr-diethyl)

PC Code: 811800
HED File Code: *11000* Chemistry Reviews
Memo Date: 11/20/2008
File ID: DPD358782
Accession #: 000-00-0127

HED Records Reference Center
12/10/2008