UNITED STAES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: December 31, 2007

SUBJECT: **Fenhexamid. Human Health Risk Assessment for a Proposed Section 3 Registration for Use on Asparagus.**

Petition #	7E7187	PC Code:	090209
DP #:	340304	Class:	Fungicide
Decision #:	375841	40 CFR:	§180.553

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RIMUERB/RD (7505P)

ARIA/RIMUERB of RD of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. RD of OPP has requested that ARIA evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed and currently registered uses of the active ingredient fenhexamid.

In this document, ARIA has conducted an assessment of the human exposure and health risks resulting from these proposed uses and all currently registered uses. The overall risk assessment and dietary risk assessment were provided by Breann Hanson, the residue chemistry assessment by Debra Rate (ARIA), the water exposure assessment by Cheryl Sutton (Environmental Fate and Effects Division (EFED)) and the occupational exposure assessment by Mark Dow (ARIA).

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1.0 EXECUTIVE SUMMARY

The Interregional Research Project No. 4 (IR-4) has submitted a petition for use of fenhexamid [N-(2,3-dichloro-4-hydroxyphenyl)-1-methyl-cyclohexanecarboxamide], a hydroxyanilide class fungicide, on asparagus (PP# 7E7187). Fenhexamid prevents fungi from infecting plants by inhibiting germ tube elongation, mycelial growth and spore germination. Fenhexamid is absorbed into the waxy layer of the cuticle and is protected from being washed off. Fenhexamid is effective in controlling *Botrytis cinerea*, *Monolinia* (brown rot /blossom blight /twig blight) and has been shown to suppress *Uncinula necator* (powdery mildew). It also provides post-infection activity when applied early in the disease life cycle.

The most recent human health risk assessment for fenhexamid was conducted in conjunction with a request for the establishment of tolerances for residues on cilantro, non-bell pepper and pomegranate (DP #: 329137, J. Redden, 6/14/2006).

Use Profile

Fenhexamid is currently registered to Bayer CropScience and Arvesta LifeScience North America Corporation for use on a variety of food/feed crops. IR-4 is proposing a new use for fenhexamid on asparagus. The product proposed for use is Elevate® 50 WDG Fungicide (Reg. No. 66330-35), a water dispersible granule which contains 50% by weight, fenhexamid active ingredient (ai). The target pest is *Botrytis cinerea*, the plant disease organism that causes gray mold. The proposed use is for multiple broadcast foliar applications to mature ferns late in the season with a minimum retreatment interval (RTI) of 7 days. Applications are restricted to the use of ground equipment in a minimum volume of water. The minimum preharvest interval (PHI) is 90 days for asparagus grown in CA and 180 days for all other states.

Current Tolerances

There are existing permanent tolerances (40 CFR §180.553(a)) for fenhexamid in/on a variety of commodities ranging from 0.02 ppm (almond) to 30 ppm (cilantro; leafy greens, subgroup 4A, except spinach).

Proposed Tolerances

Under PP# 7E7187, IR-4 requests the establishment of a tolerance for fenhexamid in/on asparagus at 0.02 ppm.

Human Health Risk Assessment

Toxicology/Hazard

In general, the toxicology studies conducted on fenhexamid demonstrated that it has few or no biologically significant toxic effects at relatively low dose levels in many animal studies and only mild or no toxic effects at high dose levels which often approach or exceed the limit dose. It was classified as Toxicity Category IV in all acute studies and was not a dermal sensitizer. In subchronic and chronic oral studies, the most toxicologically significant effects were anemia in dogs, and

decreased body weights, increased food consumption and mild liver and/or kidney effects in rats and mice. Fenhexamid is not acutely toxic, neurotoxic, carcinogenic or mutagenic and is not a developmental or reproductive toxicant. Although no increased susceptibility of fetuses was demonstrated in developmental toxicity studies in rats and rabbits, equivocal results, with respect to evaluating potentially increased sensitivity of pups, were observed in the reproduction study in rats. On the basis of No Observed Adverse Effect Levels (NOAELs)/Lowest Observed Adverse Effect Levels (LOAELs), no increased susceptibility of pups to fenhexamid was demonstrated in this study. However, the severity of the effects observed in the pups may have been greater than that observed in the adults at the same dose levels. In addition, several other toxicological considerations, including possibly increased intake of test material in pups resulting from intake in both milk and diet during the lactation period and possibly decreased levels of UDP-glucuronyltransferase enzyme in pups resulting in decreased metabolism or "detoxification" of test material, contributed to the uncertainty of the determination. The toxicological and regulatory significance of the equivocal findings in the reproduction study are discussed more fully in section 3.3.6.2. There is low concern for pre- and/or postnatal toxicity resulting from exposure to fenhexamid. No Food Quality Protection Act Safety Factor (FQPA SF) is needed (i.e. 1X) since there are no residual uncertainties for pre and/or post natal toxicity.

Minimal or no toxic effects were observed in studies in which fenhexamid was administered by the dermal or inhalation routes of exposure. In an acute neurotoxicity study in rats, the only possibly treatment-related effect was a marginally decreased mean body temperature in male rats. This effect is not considered to be biologically significant.

In a battery of five mutagenicity studies (with and without metabolic activation, as appropriate for the specific study), technical grade fenhexamid was negative for genotoxicity in all five studies.

In a dermal absorption study in rats using a 50% wettable powder formulation as the test material, the potential cumulative dermal absorption of test material after a 10 hour dermal exposure was determined to be 20%.

No acute dietary endpoint was selected since no appropriate toxicological endpoint attributable to a single exposure was identified in the available toxicology studies. The short- and intermediate-term dermal endpoints are based on decreased body weight gain and food consumption. No other short- and intermediate-term endpoints were selected. Chronic dietary and long-term endpoints are based on decreased red blood cell (RBC) hemoglobin and hematocrit and increased Heinz bodies in males and females; increased adrenal weights and intracytoplasmic vacuoles in adrenal cortex in females.

No cancer risk assessment is required. HED classified fenhexamid as a "not likely" human carcinogen.

Dietary Exposure and Risk

Product chemistry data, residue chemistry data relevant to food use, and environmental fate data relevant to drinking water are adequate to assess human exposure to fenhexamid. Adequate residue data are available to support the proposed use pattern and tolerance. Residues of fenhexamid were <0.02 ppm in the submitted field trials.

The nature of fenhexamid residues in plants is understood based on adequate metabolism studies on grapes, tomatoes, and apples. Fenhexamid residues are non-systemic and primarily surface residues. HED's Metabolism Assessment Review Committee (MARC) concluded that only residues of parent fenhexamid need to be included in the tolerance expression and considered for risk assessment.

As the crop use being proposed in this petition does not include any regulated livestock feedstuffs, issues pertaining to livestock metabolism, analytical methods and storage stability data for livestock commodities, and residues in livestock commodities are not relevant to the current petition.

An adequate high performance liquid chromatography (HPLC) method using electrochemical detection (ECD) is available for enforcing tolerances for fenhexamid in/on plant commodities. In submitted asparagus field trials, residues of fenhexamid were determined using an LC mass spectrometry method (LC/MS).

As there are no regulated processed commodities associated with asparagus, no processing studies are required for this petition. Data pertaining to rotational crops are also not required for this petition as asparagus is not rotated.

Canadian, Mexican and Codex Maximum Residue Limits (MRLs) are established for fenhexamid on various fruit and vegetable crops. As there are no established or proposed Canadian, Mexican or Codex MRLs for fenhexamid on asparagus, there are no issues for international harmonization for the current petition.

Water Exposure and Risk

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) and incorporated directly into the chronic dietary assessment. Considering all currently registered uses as well as the proposed new uses, the highest chronic estimated drinking water concentration (EDWC) is 1.1 ppb.

Acute and Chronic Dietary Exposure Results and Characterization

No toxic effects attributable to a single (i.e., acute) exposure to fenhexamid have been identified; therefore, an acute reference dose (RfD) has not been established for fenhexamid and an acute dietary exposure assessment has not been conducted.

Chronic dietary exposure and risk was calculated assuming tolerance level residues for all commodities with existing and proposed tolerances, DEEM™ default processing factors (PFs), and assumed 100% crop treated (CT). The only exceptions to these assumptions were EPA processing adjustment factors for grapes destined for wine and sherry production and for currants, dried. The highest chronic EDWC of 1.1 ppb was used in the analysis.

The results of the analysis indicate that chronic risk from dietary (food + drinking water) exposure to fenhexamid does not exceed ARIA's level of concern (i.e. <100% chronic population adjusted doses (cPAD)) for the general U.S. population, and all population subgroups. For the U.S. population the exposure for food and water utilized 10% of the chronic Population Adjusted Dose (cPAD). The

chronic dietary risk estimate for the highest reported exposed population subgroup, children 1-2 years old, is 27% of the cPAD.

Non-Occupational and Residential Exposure/Risks

Currently, there are no residential or other non-agricultural uses of fenhexamid. For these reasons, a non-occupational/residential assessment has not been conducted.

Aggregate Exposure/Risks

No acute, short/long-term or cancer aggregate exposure is expected.

Chronic aggregate risk estimates do not exceed ARIA's level of concern. Since the chronic aggregate risk exposure includes only food and water, and the chronic dietary analysis included both, no further calculations are necessary. Since chronic dietary risk does not exceed ARIA's level of concern, chronic aggregate risk does not exceed ARIA's level of concern.

Occupational Exposure/Risks

An occupational risk assessment was completed for fenhexamid for its use on asparagus. Based upon the proposed use patterns ARIA expects the most highly exposed occupational pesticide handlers to be 1) mixer/loaders using open pour loading of granules and 2) applicators using open-cab, ground-boom spray equipment. Due to the volume of spray recommended per acre, ARIA believes aerial application is not a practical option.

A MOE of 100 is adequate to protect occupational pesticide handlers. Since all estimated MOEs are >100, the proposed use does not exceed ARIA's level of concern.

There typically is the possibility for agricultural workers to experience post-application exposure to pesticide residues. A MOE of 100 is adequate to protect agricultural workers from post-application exposures to fenhexamid. The estimated MOE is based upon conservative assumptions and is >100; therefore, risks from estimated post-application exposures do not exceed ARIA's level of concern.

A restricted entry interval (REI) of 12 hours is adequate to protect agricultural workers from post-application exposures (i.e., field treatment) to fenhexamid under these circumstances.

Environmental Justice Consideration

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

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a

residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intakes by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

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

Additional Data Needs

No deficiencies were noted in the subject petition that would preclude establishing a permanent tolerance for fenhexamid residues on asparagus.

Recommendations for Tolerances/Registration

ARIA concludes that there is a reasonable certainty that no harm will result to the U.S. Population, including infants and children, from chronic aggregate exposure to fenhexamid residues.

ARIA recommends for a 0.02 ppm tolerance for the residues of fenhexamid in/on asparagus.

Table 1.0. Tolerance Summary for Fenhexamid.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Asparagus	0.02	0.02	Adequate field trial data are available on asparagus.

2.0 INGREDIENT PROFILE

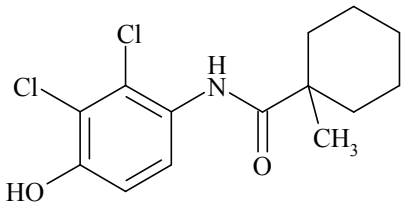
Fenhexamid is a reduced risk, hydroxyanilide fungicide registered in the U.S. for use on a variety of fruit, nut and vegetable crops for controlling *Botrytis cinerea* and *Monolinia spp.* (brown rot / blossom blight / twig blight) and suppressing *Uncinula necator* (powdery mildew). Fenhexamid is a locally systemic, protectant fungicide that is absorbed into the waxy layer of the cuticle. It prevents fungal infections by inhibiting germ tube elongation, mycelial growth and spore germination. Fenhexamid is currently registered in the U.S. to Bayer and Arysta and is formulated as 50% WDGs for uses on food/feed crops.

2.1 Proposed Use

Table 2.1. Summary of Directions for Use of Fenhexamid.						
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations [1]
Asparagus						
Broadcast foliar applications to asparagus in fern stage only. Ground equipment only	50% WDG [66330-35]	0.75	4	3.0	180 (except CA) 90 (CA)	Apply only at the fern stage. Treated ferns must be mowed down or allowed to senesce prior to harvest of asparagus spears. Apply in a minimum of 40 gal/A. The minimum RTI is 7 days.

[1] Do not apply through any type of irrigation system. Do not replant treated fields with food crops other than those with labeled uses within 30 days of the last application.

2.2 Identification of Active Ingredient

Table 2.2. Fenhexamid Nomenclature.	
Compound	
Common name	Fenhexamid
Company experimental name	KBR 2738
IUPAC name	2,3-dichloro-4-(1-methylcyclohexyl-carbonylamine)-phenol
CAS name	N-(2,3-dichloro-4-hydroxyphenyl)-1-methylcyclohexanecarboxamide
CAS #	126833-17-8
End-use product/EP	50% WDG (ELEVATE® 50 WDG Fungicide, EPA Reg. No. 66330-35)

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of the Technical Grade Fenhexamid.

Parameter	Value	Reference
Melting point/range	153°C	Fenhexamid: Pesticide Fact Sheet (May 20, 1999)
pH	8.3 in 1% solution of water	
Density (20ºC)	1.34 g/ml	
Water solubility (mg/L at 20°C)	20	Fenhexamid (KBR 2738)- a Botryticide from a New Chemical Class, Pflanzenschutz-Nachrichten Bayer 52/1999, 2
Solvent solubility (g/L at 20°C)	dichloromethane – 31 2-propanol - 91 n-hexane - <0.1 Toluene – 5.7	
Vapor pressure at 25°C	$7x10^{-9}$ Torr	
Dissociation constant (pK_a)	7.3	
Octanol/water partition coefficient $Log(K_{OW})$	3.51 (pH 7, 20°C)	
UV/visible absorption spectrum	245 and 290 nm	

3.0 HAZARD CHARACTERIZATION

3.1 Hazard and Dose-Response Characterization

Hazard Assessment

In general, the toxicology studies conducted on fenhexamid demonstrated that it has few or no biologically significant toxic effects at relatively low dose levels in many animal studies and only mild or no toxic effects at high dose levels which often approach or exceed the limit dose. It was classified as Toxicity Category IV in all acute studies and was not a dermal sensitizer. In subchronic and chronic oral studies, the most toxicologically significant effects were anemia in dogs, and decreased body weights, increased food consumption and mild liver and/or kidney effects in rats and mice. Fenhexamid is not acutely toxic, neurotoxic, carcinogenic or mutagenic and is not a developmental or reproductive toxicant. Although no increased susceptibility of fetuses was demonstrated in developmental toxicity studies in rats and rabbits, equivocal results, with respect to evaluating potentially increased sensitivity of pups, were observed in the reproduction study in rats.

Minimal or no toxic effects were observed in studies in which fenhexamid was administered by the dermal or inhalation routes of exposure. In an acute neurotoxicity study in rats, the only possibly treatment-related effect was a marginally decreased mean body temperature in male rats following a single high dose of 2000 mg/kg. This effect is not considered to be biologically significant.

In 13-week and 1-year feeding studies in dogs, the most significant treatment-related effects were decreased erythrocyte counts, hemoglobin and hematocrit (i.e. anemia) and increased Heinz bodies in erythrocytes. In the 13-week study, increased Heinz bodies were first observed at 13 weeks in both males and females at the LOAEL of 239/261 mg/kg/day in males and females (M/F), respectively. At the next higher dose of 1748/1866 mg/kg/day (M/F), the highest dose tested (HDT), increased Heinz bodies were first observed at 6 weeks and marginal signs of anemia at 2 weeks in males and at 13 weeks in females. In the 1-year study in dogs, increased Heinz bodies and signs of anemia were first observed at 13 weeks in both males and females at the LOAEL of 124/133 mg/kg/day (M/F). At the same dose level, in females only, minimal effects were also observed in the adrenal gland (increased adrenal weights and increased incidence and severity of intracytoplasmic vacuoles in the adrenal cortex). At the next higher dose of 918/947 mg/kg/day (M/F)(HDT), in addition to increased severity of the effects observed at the LOAEL, decreased body weight gain and decreased food consumption were also observed. The NOAEL of 17/19 mg/kg/day (M/F) in this 1-year dog study was used to establish the RfD for fenhexamid since it was the lowest NOAEL observed in any of the subchronic or chronic feeding studies on fenhexamid. The particular effects on which the RfD is based (increased Heinz bodies and anemia in males and females and mild effects in the adrenal gland of females) are toxicologically significant and were clearly observed in dogs, but were not observed to any appreciable extent in any other studies in any other species. There was, however, a suggestion of possible anemia in the 2-year chronic feeding study in rats in which enlarged spleens, splenic extramedullary hematopoiesis, bone marrow hyperplasia and increased reticulocytes were observed in males and/or females. Although decreased erythrocytes, hemoglobin, or hematocrit were not observed in this study, it is possible that these signs of anemia may have occurred early in the study , been transient, and fully compensated for later in the study when blood samples were first taken (at 6 months). It is most likely that treatment-related anemia occurs in both dogs and rats, but that dogs are more sensitive than rats. The LOAEL for anemia in dogs was 124/133 mg/kg/day (M/F) and for a suggestion of anemia in rats (splenic extramedullary hematopoiesis and bone marrow hyperplasia) was 292/415 mg/kg/day (M/F).

In a 28-day oral (gavage) range-finding study in rats, no treatment-related effects were observed at 1000 mg/kg/day, the highest dose level tested. In a 13-week feeding study in rats, the predominant treatment-related effects in males were decreased body weights and body weight gains, increased food consumption, decreased food efficiency and increased serum levels of alanine amino-transferase enzyme (suggestive of slight liver toxicity). The LOAEL for these effects in males was 904 mg/kg/day and the NOAEL was 415 mg/kg/day. In females, the predominant treatment-related effects were increased food consumption, decreased food efficiency, decreased liver weights and mild histopathological effects in the liver. The LOAEL for these effects in females was 2824 mg/kg/day and the NOAEL was 1132 mg/kg/day. In this study, males appeared to be somewhat more sensitive than females to fenhexamid since the LOAEL/NOAELs for males was lower than for females. Since a biologically meaningful sex difference in sensitivity to fenhexamid was not observed in any other studies on fenhexamid, however,

the differences in LOAEL/NOAELs in this study were also considered to be not biologically meaningful.

In the 2-year chronic feeding/carcinogenicity study in rats, in males at the LOAEL of 292 mg/kg/day, only mild treatment-related effects were observed (increased splenic extramedullary hematopoiesis and increased cecal mucosal hyperplasia). At the next higher dose level of 1280 mg/kg/day (HDT), additional treatment-related effects included increased food consumption, decreased food efficiency, enlarged spleens, increased reticulocytes and mild histopathological changes in the thyroid gland (decreased follicular volume and blue-gray clumps of colloid). In females at the LOAEL of 415 mg/kg/day, treatment-related effects were also mild and included decreased body weight (only after 60 weeks), decreased body weight gain (only after 39 weeks), decreased food efficiency, and bone marrow hyperplasia. At the next higher dose level of 2067 mg/kg/day (HDT), additional treatment-related effects included increased food consumption, enlarged spleens, increased reticulocytes and mild histopathological changes in the thyroid gland (decreased follicle volume and blue-gray clumps of colloid). As previously noted, the enlarged spleens, splenic extramedullary hematopoiesis, bone marrow hyperplasia and increased reticulocytes observed in the animals in this study may be indicative of an earlier occurring transient anemia that was subsequently fully compensated for. In this study, there was no treatment-related increase in tumor incidence, tumor spectrum or latency when compared to controls. The test material was tested at adequate dose levels for carcinogenicity testing since it was tested at the limit dose of 20000 ppm (1280 mg/kg/day in males and 2067 mg/kg/day in females) for rats.

Of particular interest in the 2-year and 13-week feeding studies in rats is the regular and consistent observation of decreased body weights, decreased body weight gains, increased food consumption and decreased food efficiency at relatively high dose levels ($\geq$415 mg/kg/day) in both male and female rats. At this time, there is no available biological explanation for this finding.

In a 14-week feeding (range-finding) study in mice and a 2-year carcinogenicity study in mice, the predominant toxic effects were indicative of kidney damage. In the 14-week study at the LOAEL of 3284/5151 mg/kg/day (M/F) (HDT), the following treatment-related effects were observed in both males and females and suggested kidney damage: increased water consumption, increased serum creatinine levels, decreased kidney weights and histopathological changes in the kidneys (increased basophilic cortical tubules and/or increased protein casts and cellular detritus). Additional effects at the LOAEL included increased serum cholesterol and bilirubin levels in males and females; and increased food consumption, decreased food efficiency and decreased glycogen in hepatocytes in males only. The NOAEL in this study was 267/454 mg/kg/day (M/F). In the 2-year study in mice, in males at the LOAEL of 807 mg/kg/day, decreased kidney weights and histopathological changes in the kidney (decreased sex specific vacuolation of the proximal tubules) was observed. Additional effects observed at the next higher dose level of 2355 mg/kg/day (HDT) in males included increased water consumption, increased serum creatinine level and increased chronic renal disease (all indicative of kidney damage), increased serum bilirubin level, decreased body weight, decreased body

weight gain, and increased serum albumin levels. In females at the LOAEL of 3178 mg/kg/day (HDT), increased water consumption, decreased kidney weights and increased basophilic cortical tubules in the kidney also suggested kidney damage. In this study, there was no treatment-related increase in tumor incidence, tumor spectrum or latency when compared to controls. The test material was tested at adequate dose levels for carcinogenicity testing since it was tested at the limit dose of 7000 ppm (2355 mg/kg/day in males and 3178 mg/kg/day in females) for mice.

In a battery of five mutagenicity studies (with and without metabolic activation, as appropriate for the specific study), technical grade fenhexamid was negative for genotoxicity in all five studies.

In a developmental toxicity study in rats, maternal toxicity (marginally decreased body weight gain and decreased food consumption during the treatment period only) was observed at the LOAEL of 1044 mg/kg/day (only dose level tested). The NOAEL for maternal toxicity was <1044 mg/kg/day. At the same dose level of 1044 mg/kg/day, no treatment-related signs of developmental toxicity were observed in the fetuses. The NOAEL for developmental toxicity was 1044 mg/kg/day and the LOAEL was not established (>1044 mg/kg/day). Although a NOAEL was not determined for maternal toxicity in this study, the study need not be repeated because the effects at the LOAEL were only marginal and of minimal toxicological concern.

In a developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 100 mg/kg/day and the LOAEL was 300 mg/kg/day, based on alterations of excretory products (discolored urine, scant feces, small scybala), decreased body weight gain and decreased food consumption (especially during the first week of dosing) and decreased placental weight. At the next higher dose level of 1000 mg/kg/day, the maternal effects were increased in severity. A decreased gestation index, based on a slightly increased incidence of abortions and total litter resorptions, was not considered to be treatment-related because the incidences of abortions and resorptions fell within the historical control range submitted with the study. The NOAEL for developmental toxicity was 300 mg/kg/day and the LOAEL was 1000 mg/kg/day, based on slightly decreased fetal body weights (<5%) in males only and increased delayed ossification in several bones (especially the 5th sternal segments and the 15th caudal vertebrae).

In a 2-generation (1 litter/generation) reproduction study in rats, there were no treatment-related effects on mortality, clinical signs, behavior or reproductive parameters for adult (parent) animals. The NOAEL for reproductive toxicity was 1814/2043 (M/F) (HDT). The NOAEL for parental toxicity was 38/45 mg/kg/day (M/F) and the LOAEL was 406/477 mg/kg/day (M/F). In males at the LOAEL of 406 mg/kg/day, increased serum creatinine levels and decreased kidney weights indicated mild kidney damage and increased serum alkaline phosphatase levels and decreased liver weights indicated mild liver damage. In females at the LOAEL of 477 mg/kg/day, increased serum alkaline phosphatase levels and very slightly increased serum GGT levels suggested mild liver damage. At the next higher dose level of 1814/2043 mg/kg/day (M/F)(HDT), the effects observed at the LOAEL in both males and females were slightly increased in severity. In

addition, decreased body weight, increased food consumption, and increased serum GGT levels were observed in males and decreased body weights, increased food consumption, increased serum urea nitrogen levels, increased serum creatinine levels and decreased kidney weights were observed in females. The NOAEL for neonatal toxicity was 38/45 mg/kg/day (M/F) and the LOAEL was 406/477 mg/kg/day (M/F). At the LOAEL of 406/477 mg/kg/day, treatment-related decreased pup body weights were observed in F_1 pups on postnatal days 14 and 21 and in F_2 pups on postnatal days 7, 14 and 21. At the next higher dose level of 1814/2043 mg/kg/day (M/F) (HDT), the decreased pup body weights were increased in severity. In addition, an increased mortality was observed among the post weaning F_1 pups selected to be F_1 parents (possibly due to the small size of the pups at weaning, which was 30% less than controls).

The results in this reproduction study are equivocal with respect to evaluating the possibility of increased susceptibility of pups, as compared to adults, to fenhexamid. On the basis of NOAELs/LOAELs, no increased susceptibility of pups to fenhexamid was demonstrated in this study. However, the severity of the effects observed in the pups may have been greater than that observed in the adults at the same dose levels. In addition, several other toxicological considerations, including possibly increased intake of test material in pups resulting from intake in both milk and diet during the lactation period and possibly decreased levels of UDP-glucuronyltransferase enzyme in pups (a normally occurring phenomenon in rat pups) resulting in decreased metabolism or "detoxification" of test material, contributed to the uncertainty of the determination.

In a dermal absorption study in rats using a 50% wettable powder formulation as the test material, the potential cumulative dermal absorption of test material after a 10 hour dermal exposure was determined to be 20%.

In a 21-day dermal toxicity study in rabbits, no treatment-related systemic or skin effects were observed at the limit dose of 1000 mg/kg/day. In a 5-day range-finding inhalation study in rats using technical grade fenhexamid dust as the test material, marginally increased lung weights and gray discoloration of the lungs were observed at the LOAEL of 1.093 mg/L. The NOAEL was 0.098 mg/L. The effects observed in this study were not considered to be systemic, but rather the result of the physical deposition of fenhexamid dust in the lungs.

Dose Response

No acute RfD was selected by HED. No appropriate toxicological endpoint attributable to a single exposure was identified in the available toxicology studies, including the developmental toxicity studies in rats and rabbits and the acute neurotoxicity study in rats. In the developmental toxicity study in rabbits, treatment-related decreased mean fetal body weight in male fetuses (less than 5%) and increased incidence of delayed ossification in several bones (particularly fifth sternal segments and fifteenth caudal vertebrae) were observed at the high dose of 1000 mg/kg/day. Although possibly occurring after a single dose, the magnitudes of both of these effects were so small that HED considered neither of them to be an appropriate toxicological endpoint for acute

dietary risk assessments. In the acute neurotoxicity study in rats, a marginally decreased mean body temperature in males was observed on the first day of treatment at the high dose of 2000 mg/kg. Since this equivocal effect occurred only in one sex, only one time, only at the high dose and no other signs of toxicity were observed in the rats in this study, HED did not consider this possible effect to be an appropriate toxicological endpoint for acute dietary risk assessments.

HED selected a chronic RfD of 0.17 mg/kg/day (NOAEL = 17 mg/kg/day; Uncertainty Factor = 100). This RfD is based on the 1-year chronic oral toxicity study in dogs, in which decreased RBC counts, hemoglobin and hematocrit and increased Heinz bodies in RBC were seen at the LOAEL of 124/133 mg/kg/day in males/females. Also, in females, increased absolute and relative adrenal weights correlated with histopathological observations of increases in incidence and severity of intracytoplasmic vacuoles in the adrenal cortex. The Uncertainty Factor (UF) accounts for both interspecies extrapolation (10X) and intraspecies variability (10X).

Short- and intermediate-term dermal risk assessments are required. HED concluded it would be appropriate to use the dermal dose level of 1000 mg/kg/day (NOAEL), the HDT, from the 21-day dermal toxicity study in rabbits for short- and intermediate-term dermal risk assessments. HED required these dermal risk assessments to be performed because in the oral developmental toxicity study in rabbits, maternal effects (decreased body weight gain and decreased feed consumption, particularly during the first week of dosing) were observed at an oral dose of 300 mg/kg/day (LOAEL). Using a 20% dermal absorption factor, this oral dose is equivalent to a dermal dose of 1500 mg/kg/day. Since treatment-related effects were observed at a dermal equivalent dose of 1500 mg/kg/day in the developmental toxicity study in rabbits, HED required that short- and intermediate-term dermal risk assessments be performed using the NOAEL of 1000 mg/kg/day from the 21-day dermal study in rabbits as the toxicological endpoint. No long-term dermal exposure is expected to occur with the proposed use on asparagus.

Based on the low acute inhalation toxicity (Toxicity Category IV), the low 5-day subchronic toxicity (no systemic toxicity at 1.092 mg/L), the composition of the formulated product (water-dispersible granules), the application rate, and the application method (ground spray, groundboom and airblast), there is minimal concern for potential inhalation exposure/risk. HED determined that a separate inhalation risk assessment is not required for short- and intermediate-term inhalation risk assessments. Based on the use pattern, no long-term inhalation exposure is expected to occur with the proposed use on asparagus.

No cancer risk assessment is required. HED classified fenhexamid as a “not likely” human carcinogen. This classification is based on the lack of evidence of carcinogenicity in male and female rats as well as in male and female mice and on the lack of genotoxicity in an acceptable battery of mutagenicity studies.

3.1.1 Database Summary

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

Acute, sub-chronic, chronic, reproductive and developmental studies were available and considered when preparing this risk assessment.

3.1.1.2 Mode of action, metabolism, toxicokinetic data

Fenhexamid prevents penetration of fungi into plants by inhibiting germ tube and mycelial growth. Fenhexamid appears to be unique in that it apparently does not belong to any previously registered class of compounds. Its toxicological properties, then, are also unique and not directly comparable to those of any other registered chemical at this time.

3.1.1.3 Sufficiency of studies/data

The scientific and regulatory quality of the toxicology data base for fenhexamid is high and is considered sufficient to clearly define the toxicity of this chemical.

3.1.2 Toxicological Effects

In general, the toxicology studies conducted on fenhexamid demonstrate that it has few or no biologically significant toxic effects at relatively low dose levels in many animal studies and only mild or no toxic effects at high dose levels which often approach or exceed the limit dose. In subchronic and chronic oral studies, the most toxicologically significant effects were anemia in dogs, and decreased body weights, increased food consumption and mild liver and/or kidney effects in rats and mice. Fenhexamid is not acutely toxic, neurotoxic, carcinogenic or mutagenic and is not a developmental or reproductive toxicant. Although no increased susceptibility of fetuses was demonstrated in developmental toxicity studies in rats and rabbits, equivocal results, with respect to evaluating potentially increased sensitivity of pups, were observed in the reproduction study in rats. Since there is qualitative evidence of increased susceptibility of the young following exposure to fenhexamid in the rat reproduction study, HED performed a Degree of Concern Analysis. For information regarding the results of this analysis see section 3.3.6.2, below. Minimal or no toxic effects were observed in studies in which fenhexamid was administered by the dermal or inhalation routes of exposure.

3.1.3 Dose-response

No acute dietary endpoint was selected since no appropriate toxicological endpoint attributable to a single exposure was identified in the available toxicology studies. The short- and intermediate-term dermal endpoints are based on decreased body weight gain and food consumption. No other short- and intermediate-term endpoints were selected. Chronic dietary and long-term endpoints are based on decreased RBC count, hemoglobin

and hematocrit and increased Heinz bodies in males and females; increased adrenal weights and intracytoplasmic vacuoles in adrenal cortex in females.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

In a metabolism study in rats, fenhexamid was rapidly and completely absorbed, distributed, metabolized and almost completely excreted within 48 hours. The major route of excretion was feces (62-81%) with lesser amounts in the urine (15-36%). A pronounced first pass effect and enterohepatic circulation was observed. Bile contained mostly the glucuronide conjugate of fenhexamid, which was subsequently hydrolyzed in the intestine back to the parent compound and reabsorbed. The feces contained almost exclusively unchanged parent compound. The urine contained mostly parent compound and the glucuronide conjugate of parent compound. In addition, considerably lesser amounts of additional metabolites (formed by hydroxylation on the cyclohexyl ring) and glucuronide and sulfate conjugates of these same metabolites were also identified in the urine. All the glucuronide and sulfate conjugates of the parent compound and of the hydroxylated metabolites of the cyclohexyl ring are considered to be considerably less toxic than the parent compound because glucuronide and sulfate conjugation is well known to be a commonly occurring "detoxification" mechanism in mammalian species as it results in the formation of more polar, more water-soluble metabolites which are readily and easily excreted from the body (in this case, in the bile and urine).

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

HED concluded that the toxicology database for fenhexamid is complete for FQPA assessment.

3.3.2 Evidence of Neurotoxicity

HED concluded that there is not a concern for neurotoxicity resulting from exposure to fenhexamid.

3.3.3 Developmental Toxicity Studies

In the developmental toxicity studies in rats and, there was no evidence of increased susceptibility to fetuses from *in utero* exposure to fenhexamid.

3.3.4 Reproductive Toxicity Study

The results in the reproduction study are equivocal with respect to evaluating the possibility of increased susceptibility of pups, as compared to adults, to fenhexamid. At 5000 ppm (neonatal LOAEL), statistically significant, treatment-related and dose-related decreased pup body weights were observed. At the same dose level of 5000 ppm (parental LOAEL), treatment-related and dose-related effects were also observed in the

adult (parent) animals. In adult males, increased creatinine levels and decreased absolute and relative kidney weights suggested an effect on the kidney and increased alkaline phosphatase levels and decreased absolute and relative liver weights suggested an effect on the liver. In adult females, increased alkaline phosphatase levels and slightly increased GGT levels (not considered to be biologically relevant) suggested a possible effect on the liver; however, histopathological examination of kidney and liver did not reveal any treatment-related morphological changes in these organs at this dose level (or at the highest dose level of 20000 ppm). Since treatment-related effects were observed in both pups and adults at 5000 ppm, but not at 500 ppm, on the basis of NOAELs and LOAELs, no increased susceptibility of pups to fenhexamid was demonstrated in this study. However, the severity of effects in the pups at 5000 ppm (decreased body weights) may have been greater than that observed in the adults at the same dose level (suggestion of mild effects in the kidney and liver without supporting histopathological changes). In addition, at the highest dose level of 20000 ppm, the severity of effects in the pups (decreased body weights and increased mortality in F_1 pups selected to be F_1 parents) was considered to be greater than that observed at the same dose level in adults (mild effects in the kidney and liver not supported by histopathological changes; decreased body weights and increased food consumption). Interpretation of relative severities of effects in pups and adults at 5000 and 20000 ppm also consider, however, that the pups may be consuming significantly greater amounts of test material than adults (on a mg/kg/day basis) since pups consume considerably more food per unit body weight than do adults, and pups receive test material from not one, but two sources viz. mother's milk and treated diet (particularly during the late lactation period). The body weight decrements in late lactation are supportive of this argument.

Regarding the decreased pup body weights observed at 5000 and 20000 ppm, investigators offered some possible explanations. However, HED did not concur with the investigators conclusion that the decreased pup body weights in the 5000 and 20000 ppm dose groups does not represent a neonatal toxicity concern. To the contrary, this explanation supports a possibly increased sensitivity of the neonates (as compared to adults) to the test material. The demonstrated poor glucuronidation capacity of rat pups, in fact, provides a reasonable and likely pharmacological explanation for a possibly increased sensitivity of pups and serves to support a concern for neonatal toxicity, rather than a reason to dismiss it. Supporting this explanation are the results in the metabolism study on fenhexamid in which glucuronidation of fenhexamid was clearly demonstrated to be the single major route of metabolism, detoxification and excretion of fenhexamid in adult male and female Wistar rats. Further support for a neonatal toxicity concern is also provided by the observation that for the F_1 pups selected post-weaning to be F_1 parents in this study, a treatment-related increased mortality was observed in the 20000 ppm dose group compared to the control group. This increase in the death of pups in the 20000 ppm dose group was attributed by the investigators "to the small size of pups at weaning". Hence the decreased pup body weights observed on lactation days 7 through 21 (neonatal toxicity) actually resulted in increased mortality at a later time in the study.

With respect to determining the possible increased susceptibility of pups to fenhexamid, HED considered the results to be equivocal (i.e. subject to two interpretations). On the

one hand, on the basis of NOAELs and LOAELs, no increased susceptibility was observed. On the other hand, the greater severity of effects in pups and a likely pharmacological explanation for this finding suggested an increased sensitivity of pups, as compared to adults, to fenhexamid.

3.3.5 Additional Information from Literature Sources

None.

3.3.6 Pre-and/or Postnatal Toxicity

HED concluded that there is low concern for pre- and/or postnatal toxicity resulting from exposure to fenhexamid.

3.3.6.1 Determination of Susceptibility

In the developmental toxicity studies in rats and rabbits, HED determined that neither quantitative nor qualitative evidence of increased susceptibility of fetuses to *in utero* exposure to fenhexamid was observed in this study.

In the multigeneration reproduction study, qualitative evidence of increased susceptibility of rat pups is observed. Although the parental and offspring NOAELs and LOAELs are at the same doses (38.2 and 406 mg/kg/day), the offspring effects are considered to be more severe than the parental effects. Quantitative evidence of increased susceptibility of rat pups to fenhexamid, however, was not observed in this study.

3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

Since there is qualitative evidence of increased susceptibility of the young following exposure to fenhexamid in the rat reproduction study, HED performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual uncertainties are identified, HED examines whether these residual uncertainties can be addressed by a FQPA safety factor and, if so, the size of the factor needed. The results of the HED Degree of Concern analysis for fenhexamid follow.

In the rat reproduction study, qualitative susceptibility was evidenced as significantly decreased pup body weights in both generations during the lactation period (on lactation days 7, 14, and 21 in the F_2 generation and lactation days 14 and 21 in the F_1 generation offspring) in the presence of lesser maternal toxicity (alterations in clinical chemistry parameters and decreased organ weights without collaborative histopathology). Considering the overall toxicity profile and the doses and endpoints selected for risk assessment for fenhexamid, HED characterized the degree of concern for the effects

observed in the rat reproduction study as low, noting that there is a clear NOAEL and well-characterized dose response for the offspring effects observed and that these effects occurred in the presence of parental toxicity. No residual uncertainties were identified.

The does selected for risk assessment purposes are protective of the susceptibility of the young.

3.3.7 Recommendation for a Developmental Neurotoxicity (DNT) Study

HED concluded that there is not a concern for developmental neurotoxicity resulting from exposure to fenhexamid; therefore, a DNT study conducted with fenhexamid is not required. This decision was based on the following weight-of-the-evidence considerations:

· lack of evidence of abnormalities in the development of the fetal nervous system in the pre/post-natal studies;
· neither brain weight nor histopathological examination of the nervous system was affected in the subchronic and chronic studies; and
· decreased body temperatures observed in male rats in the acute neurotoxicity study were not considered to be toxicologically significant.

Based on the weight of evidence presented, HED has reaffirmed (2/13/2003) the previous conclusion that a DNT study conducted with fenhexamid is not required.

3.4 FQPA Safety Factor for Infants and Children

Based upon the above-described data, it was concluded that there is low concern for pre- and/or postnatal toxicity resulting from exposure to fenhexamid; therefore HED recommended the FQPA Safety Factor (SF) be reduced to 1X.

3.5 Hazard Identification and Toxicity Endpoint Selection

For more detailed information regarding toxicity endpoint selections, please refer to the HED memo (B. Tarplee, TXR NO. 0051704, 3/26/2003).

3.5.1 Acute Reference Dose (aRfD) - General Population

Study Selected: None
MRID No.: None
Dose and Endpoint for Establishing RfD: Not applicable
Uncertainty Factor(s) (UFs): Not applicable
Comments about Study/Endpoint/Uncertainty Factor: No appropriate toxicological endpoint attributable to a single exposure was identified in the available toxicology studies including the developmental toxicity studies in rats and rabbits and the acute neurotoxicity study in rats.

3.5.2 Chronic Reference Dose (cRfD)

Study Selected: 1-Year Chronic Toxicity Study, Dogs
MRID No.: 44346804
Dose and Endpoint for establishing the RfD: NOAEL = 17 mg/kg/day. Based on decreased RBC counts, hemoglobin and hematocrit, and increased Heinz bodies in RBC at the LOAEL of 124/133 mg/kg/day in males/females. Also, in females, increased absolute and relative adrenal weights correlated with histopathological observations of increases in incidence and severity of intracytoplasmic vacuoles in the adrenal cortex.
Uncertainty Factor: An uncertainty factor of 100 was applied to account for both interspecies extrapolation (10X) and intraspecies variability (10X).
Comments about Study/Endpoint/Uncertainty Factor(s): The RfD derived from the use of the NOAEL and endpoint from the 1-year chronic toxicity study in dogs and an uncertainty factor of 100 is supported by a similar RfD that could have been derived from the use of the NOAEL from the combined chronic/carcinogenicity feeding study in rats (MRID 44346806) and an uncertainty factor of 100. In the rat study, the NOAEL = 28 mg/kg/day and the LOAEL = 292/415 mg/kg/day in males/females, based in males on increased cecal mucosal hyperplasia and increased splenic extramedullary hematopoiesis, and in females on decreased body weight, decreased body weight gain, decreased food efficiency and increased hyperplasia in the bone marrow of the femur and sternum. Had the RfD been derived from this rat study, the RfD would have been 28 mg/kg/day/100 = 0.28 mg/kg/day. The NOAEL from the chronic study in dogs, rather than the NOAEL from the combined chronic/ carcinogenicity study in rats, was used to calculate the chronic RfD because it is the lowest NOAEL for this time period.

3.5.4 Incidental Oral Exposure (Short- and Intermediate-Term)

There are no residential exposure scenarios; therefore, endpoints were not selected.

3.5.5 Dermal Absorption

Dermal Absorption Factor: 20% (rounded from 21, highest mean dermal absorption at 120 hours). This value is considered to represent the potential cumulative dermal absorption of test material that might occur after a 10 hour dermal exposure.
Study Selected: Dermal Absorption Study, Rats
MRID No.: 44346815
Comments about Dermal Absorption: At 10 hours post-dose in the low dose level group, radioactivity (as test material) in the skin test site was 10.1% and in the urine, feces, blood and carcass was 9.75%, whereas by 120 hours, radioactivity in the skin test site decreased to 6.05% and in the urine, feces, blood and carcass increased to 14.94%. These data indicate that radioactivity in the skin test site continued to be absorbed after 10 hours (at which time the skin was washed) up to 120 hours (at which time the study was terminated). Since radioactivity in the skin test site at 10 hours continued to be absorbed in significant amounts for up to 120 hours, HED concluded that all the radioactivity in the test skin site might eventually have been absorbed if the study were continued beyond 120 hours. Therefore, 21%, the mean total amount of radioactivity in test skin site, urine,

feces, blood and carcass at 120 hours was considered to represent the potential cumulative dermal absorption of test material that might occur after a 10 hour exposure.

3.5.6 Dermal Exposure (Short-, Intermediate- and Long-Term)

Short- and Intermediate-Term

Study Selected: 21-Day Dermal Toxicity Study, Rabbits
MRID No.: 44346780
Dose and Endpoint for Risk Assessment: NOAEL = 1000 mg/kg/day (HDT).
Comments about Study/Endpoint: This study is selected because its duration and route of exposure are appropriate for short- and intermediate-term dermal exposure. Results in this study are consistent with those in the oral developmental toxicity study in rabbits (MRID 44346801) in which maternal effects (decreased body weight gain and decreased feed consumption) were observed, particularly during the first week of dosing, at the LOAEL of 300 mg/kg/day. The NOAEL for maternal toxicity in this study was 100 mg/kg/day. Using a 20% dermal absorption factor, the oral NOAEL in this study (100 mg/kg/day) is equivalent to a dermal NOAEL of 500 mg//kg/day and the oral LOAEL (300 mg/kg/day) is equivalent to a dermal LOAEL of 1500 mg/kg/day. Since treatment-related effects were observed at an equivalent dermal dose level of 1500 mg/kg/day, HED concluded it would be appropriate to use the dermal dose level of 1000 mg/kg/day (NOAEL) from the 21-day dermal study for short- and intermediate-term dermal risk assessments.

Long-Term

Long-term exposure is not expected from the proposed use on asparagus.

3.5.7 Inhalation Exposure (Short-, Intermediate- and Long-Term)

Short- and Intermediate-Term

Study Selected: None
MRID No.: None
Dose and Endpoint for Risk Assessment: Not applicable
Comments about Study and Endpoint: The acute inhalation LC50 for technical grade fenhexamid dust (95.5% purity) is >5.057 mg/L (Toxicity Category IV) for both male and female rats and for technical grade fenhexamid aerosolized in PEG 400/ethanol mixture at 0.322 mg/L (the maximum technically possible concentration) is > 0.322 mg/L for both male and female rats. In both of these acute inhalation toxicity studies (MRID 44366513), there were no mortalities, treatment-related clinical signs, changes in body weights or necropsy findings. Further, in a 5-day range-finding inhalation toxicity study in rats using technical grade fenhexamid dust as the test material (MRID 44366514), macroscopic gray colouration of the lungs and marginally increased lung weights were observed at a concentration of 1.092 mg/L, but not at 0.098 mg/L. It is

likely that the effects observed in this study are due to the physical deposition of fenhexamid dust in the lungs and not to any systemic effect of the test material.

Based on the low acute inhalation toxicity (Toxicity Category IV), the low 5-day subchronic toxicity (no systemic toxicity at 1.092 mg/L), the composition of the formulated product (water dispersible granules containing 50% ai) and the application method (ground spray, groundboom and airblast), there is minimal concern for potential inhalation exposure/risk. HED determined that a separate inhalation risk assessment is not required for short- and intermediate-term inhalation risk assessments.

Long-Term

Long-term exposure is not expected from the proposed use on asparagus.

3.5.8 Level of Concern for Margin of Exposure

For occupational exposure: short- and intermediate-term dermal, a MOE of 100 is required. This is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation).

For occupational exposure: long-term dermal and all inhalation durations, MOEs are not applicable (NA) since the use pattern does not indicate a potential for these exposure scenarios.

For residential exposure: No residential use. MOEs are not applicable.

Table 3.5.8. Summary of Levels of Concern for Risk Assessment.

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

3.5.9 Recommendation for Aggregate Exposure Risk Assessments

There are no residential uses for fenhexamid; therefore, aggregate exposure includes only food and water.

3.5.10 Classification of Carcinogenic Potential

Based on the lack of evidence of carcinogenicity in male and female rats as well as in male and female mice and on the lack of genotoxicity in an acceptable battery of mutagenicity studies, fenhexamid is classified as a "not likely" human carcinogen.

3.5.11 Summary of Toxicological Doses and Endpoints for Fenhexamid for Use in Human Risk Assessments

Table 3.5.11 Summary of Toxicological Doses and Endpoints for Fenhexamid for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population including infants and children)	None UF = **NA** **Acute RfD** = **None**	FQPA SF = **1X** **aPAD** = acute RfD / FQPA SF = **None**	Not selected. No appropriate toxicological endpoint attributable to a single exposure was identified in the available toxicology studies.
Chronic Dietary (All populations)	NOAEL = 17 mg ai/kg/day UF = **100** **Chronic RfD** = **0.17** mg/kg/day	1X **cPAD** = chronic RfD / FQPA SF =**0.17** mg/kg/day	1-Year Feeding-Dog. Decreased RBC count, hemoglobin and hematocrit and increased Heinz bodies in males and females; increased adrenal weights and intracytoplasmic vacuoles in adrenal cortex in females. at the LOAEL of 124 mg/kg/day.
Short-Term (1 - 30 days) and **Intermediate-Term** (1 - 6 months) **Dermal**	NOAEL = **1000 mg ai/kg/day**	**Residential** MOE = **NA** **Occupational** MOE = **100**	21-Day **Dermal**-Rabbit. In the developmental toxicity study in rabbits, decreased body weight gain and food consumption at LOAEL of 1500 mg/kg/day (dermal equivalent dose using 20% dermal absorption factor); NOAEL was 500 mg/kg/day (dermal equivalent dose)
Long-Term Dermal (>6 months)	None	**Residential** MOE = **NA** **Occupational** MOE = **NA**	Not selected. It was determined that no long term exposure would occur (see TXR NO. 013258).
Short-Term (1 - 30 days) and	None	**Residential** MOE = **NA**	Not selected. It was determined that a separate

Table 3.5.11 Summary of Toxicological Doses and Endpoints for Fenhexamid for Use in Dietary and Non-Occupational Human Health Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Intermediate-Term (1 - 6 months) **Inhalation**		**Occupational** MOE = **NA**	inhalation risk assessment is not required for short- and intermediate-term inhalation risk assessments (see TXR NO. 013258).
Long-Term Inhalation (>6 months)	None	**Residential** MOE = **NA** **Occupational** MOE = **NA**	Not selected. It was determined that no long term exposure would occur (see TXR NO. 013258).
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.		

Dermal absorption factor: 20%
UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

3.6 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was 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 has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, fenhexamid may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 PUBLIC HEALTH AND PESTICIDE EPIDEMIOLOGY DATA

4.1 Incident Reports

There are no known incidents reported for fenhexamid.

5.0 DIETARY EXPOSURE/RISK CHARACTERIZATION

Residue chemistry data were submitted for this petition and reviewed by ARIA (DP#: 346385, D. Rate, 11/30/2007).

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

Acceptable fenhexamid metabolism studies on grapes, tomatoes, and apples have previously been submitted and reviewed by HED. The results from these studies indicate that most of the terminal residue is unmetabolized parent. Fenhexamid residues are non-systemic and primarily surface residues. Only residues of parent fenhexamid need to be included in the tolerance expression (DP#: 253792, G. Herndon, 3/11/1999). However, additional ^{14}C-fenhexamid metabolism studies (on dissimilar crops) may be required to support future requests for tolerances and registrations. For the purposes of this action, the nature of fenhexamid residues in plants is adequately understood.

5.1.2 Metabolism in Rotational Crops

An acceptable confined accumulation in rotational crop study has previously been submitted and reviewed by HED. HED concluded that a 30-day plant back interval should appear on the label and apply to all crops without a registered use.

Because asparagus is not rotated, no data pertaining to rotational crops are required to support the proposed use.

5.1.3 Metabolism in Livestock

Since there are no asparagus feed items of regulatory interest, a discussion of the metabolism of fenhexamid in livestock commodities is not germane to this action.

5.1.4 Analytical Methodology

An adequate HPLC method using ELCD is available for enforcing tolerances for fenhexamid in/on plant commodities. For this method, residues are extracted with acetone, filtered and concentrated to an aqueous remainder. The aqueous fraction is then loaded onto a Chem Elute column, and residues are eluted with cyclohexane:ethyl acetate (85:15). Residues are concentrated to dryness, redissolved in methanol and analyzed, using external standards. The method LOQ is 0.02-0.05 ppm depending on the matrix.

Samples from the current asparagus field trails were analyzed for residues of fenhexamid using a LC/MS method (Cornel Analytical Laboratory Method, "Residue Analysis of Fenhexamid on Asparagus Using LC with MS detection, Version #8"). This method is similar to the enforcement method, except that MS detection was used instead of ELCD. For the LC/MS method, residues are extracted with acetone, concentrated and purified using a Chem Elute column. Residues are then analyzed by LC/MS using external standards. The m/z 302 and 304 ions are used for quantitation and confirmation of residues. The statistically calculated LOQ is 0.008 ppm and the LOD is 0.003 ppm. The method LOQ is 0.02 ppm. The LC/MS method was adequately validated prior to and in conjunction with the analysis of field trial samples.

5.1.5 Environmental Degradation

Fenhexamid is non-persistent in aerobic environments and only slightly persistent in anaerobic environments. Although the compound is hydrolytically stable and has low to moderate mobility in most soils its transport in the environment will be mitigated by its rapid rate of degradation in aerobic surface soils. The potential for surface water or groundwater contamination associated with fenhexamid use is, therefore, considered to be low. In the event that the compound does reach surface water bodies, the tendency for fenhexamid to bind to aquatic sediments would reduce the potential for exposure to many aquatic organisms. The exception would be benthic organisms that may ingest sediment (e.g., *Hexagenia* sp.). Aqueous photolysis may also contribute to degradation in the environment in clear, shallow water.

5.1.6 Comparative Metabolic Profile

In a metabolism study in rats, fenhexamid was rapidly and completely absorbed, distributed, metabolized and almost completely excreted within 48 hours. The major route of excretion was feces (62-81%) with lesser amounts in the urine (15-36%). A pronounced first pass effect and enterohepatic circulation was observed. Bile contained mostly the glucuronide conjugate of fenhexamid, which was subsequently hydrolyzed in the intestine back to the parent compound and reabsorbed. The feces contained almost exclusively unchanged parent compound. The urine contained mostly parent compound and the glucuronide conjugate of parent compound. In addition, considerably lesser amounts of additional metabolites (formed by hydroxylation on the cyclohexyl ring) and glucuronide and sulfate conjugates of these same metabolites were also identified in the urine. All the glucuronide and sulfate conjugates of the parent compound and of the hydroxylated metabolites of the cyclohexyl ring are considered to be considerably less toxic than the parent compound because glucuronide and sulfate conjugation is well known to be a commonly occurring "detoxification" mechanism in mammalian species as it results in the formation of more polar, more water-soluble metabolites which are readily and easily excreted from the body (in this case, in the bile and urine). Further, based on similarities of chemical structure, the non-conjugated hydroxylated metabolites of the cyclohexyl ring would be expected to be no more toxic than the parent compound.

None of the metabolites of fenhexamid identified in rats, then, are likely candidates for regulatory or risk assessment purposes.

HED has concluded that only the parent compound needs to be included in the tolerance expression and used for dietary risk assessment purposed for both crops and water. In 3 plant metabolism studies submitted, the parent compound accounted for greater than an 87% of the TRR from approximately 1X rates. The studies also showed very low levels of dichlorohydroxyaniline (estimated maxima of 2-6 ppb in grapes and apples). All identified plant metabolites were found in the rat (with exception of glucuronide conjugate in rat versus glucosides in plants). Rotational crop data suggest that fenhexamid is metabolized in the soil to a series of intermediates before entering the general carbon pool and becoming incorporated into lignin and cellulose. There are no obvious concerns with residues of the methyl cyclohexane carboxylic acid that could potentially be in rotational crops as a result of soil metabolism. (The use of just phenyl ring radiolabel precluded a determination of residues of this acid.) Data provided to EFED show very little hydrolysis at environmental pH's. The pesticide binds quickly and irreversibly to soil. Although photolysis occurs in water, the degradate is dechlorinated and has a very short half-life (not detected after 10 hours).

5.1.7 Toxicity Profile of Major Metabolites and Degradates

All the glucuronide and sulfate conjugates of the parent compound and of the hydroxylated metabolites of the cyclohexyl ring are considered to be considerably less toxic than the parent compound because glucuronide and sulfate conjugation is well known to be a commonly occurring "detoxification" mechanism in mammalian species as it results in the formation of more polar, more water-soluble metabolites which are readily and easily excreted from the body. Further, based on similarities of chemical structure, the non-conjugated hydroxylated metabolites of the cyclohexyl ring would be expected to be no more toxic than the parent compound.

5.1.8 Pesticide Metabolites and Degradates of Concern

There are no pesticide metabolites or degradates of concern for fenhexamid.

5.1.9 Drinking Water Residue Profile

The drinking water residues used in the dietary risk assessment were provided by EFED and summarized in the following memoranda: "Drinking Water Assessment for the IR-4 Petition for the Use of Fenhexamid on Asparagus" (DP#: 338651,C. Sutton, 7/26/2007) and 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."

EDWCs for fenhexamid in surface water and groundwater were calculated using the screening model FQPA Index Reservoir Screening Tool (FIRST; v.1.1.0; dated 12/12/2005) and the regression model Screening Concentration in Ground Water (SCI-

GROW; v.2.3; dated 7/29/2003), respectively. The maximum application rate for the proposed use on asparagus does not exceed the previous maximum application rate for any crop. Thus, the values reported in the previous drinking water assessment (DP#: D285210, 5/13/2003), are still current and are recommended for use in HED's risk assessment for fenhexamid.

Table 5.1.9. Maximum EDWCs of Fenhexamid in Groundwater and Surface Water Based on Fenhexamid Use at the Maximum Total Application Rate.

Drinking Water Source (Model Used)	Use/Rate Modeled (lb ai/A)	Maximum EDWC (ppb)	
Groundwater (SCI-GROW2)	Ground spray/0.75 x 2 applications; total of 3.0	Acute and Chronic	0.0007
Surface Water (FIRST)	Ground spray/0.75 x 2 applications; total of 3.0	Acute	29
	Ground spray/0.75 x 2 applications; total of 3.0	Chronic	1.1

5.1.10 Food Residue Profile

The submitted asparagus field trial data (MRID 47056401) are adequate and support the proposed use pattern. Although only two field trials were conducted, HED approved conducting a reduced set of field trials using an exaggerated 5x application rate. As residues of fenhexamid were <LOQ in/on all four samples harvested at 92-100 days after treatment (DAT) following the 5x applications, residues are unlikely to be detectable in asparagus spears harvested at 90 DAT following applications to mature ferns at the proposed 1X rate. The data support setting the tolerance for residues of fenhexamid in/on asparagus at the method LOQ (0.02 ppm).

Based on adequate metabolism studies, results indicate that most of the terminal residue is unmetabolized parent. Fenhexamid residues are non-systemic and primarily surface residues. The MARC concluded that only residues of parent fenhexamid need to be included in the tolerance expression.

There are no asparagus feed items of regulatory interest. HED does not require residue data for any processed commodities associated with asparagus. Therefore, data requirements for processed food and feed are not relevant to this tolerance petition.

5.1.11 International Residue Limits

Canadian, Mexican and Codex MRLs are established for fenhexamid on various fruit and vegetable crops. As with the U.S., the regulated residues for fenhexamid under each organization include only parent compound. As there are no established or proposed Canadian, Mexican or Codex MRLs for fenhexamid on asparagus, there are no issues for international harmonization for the current petition.

5.2 Dietary Exposure and Risk

A fenhexamid chronic dietary-exposure assessment (food and drinking water) was conducted using DEEM-FCID™ Version 2.03, which incorporates consumption data from USDA's CSFII, 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

The dietary exposure analysis was performed by ARIA (DP #: 347171, B. Hanson, 12/5/2007).

5.2.1 Acute Dietary Exposure/Risk

No toxic effects attributable to a single (i.e., acute) exposure to fenhexamid have been identified; therefore, an acute reference dose (RfD) has not been established for fenhexamid and an acute dietary exposure assessment was not conducted.

5.2.2 Chronic Dietary Exposure/Risk

The chronic dietary risk assessment was conducted for fenhexamid assuming tolerance-level residues for all commodities with existing and proposed tolerances, 100%CT information and default DEEM processing factors. The only exceptions to these assumptions were a 0.5X EPA processing adjustment factor for grapes destined for wine and sherry production and a 4.3X factor for currants, dried (grape, raisin PF), previously established for use in dietary assessments by HED. The highest drinking water estimate for chronic exposure, 1.1 ppb, was used in the analysis. The results of the analysis indicate that chronic risk from the dietary (food + drinking water) exposure to fenhexamid will not exceed HED's level of concern (i.e. <100% cPAD) for the general U.S. population, and all population subgroups. The chronic dietary risk estimate for the highest reported exposed population subgroup, all infants (<1 year old), was 27% of the cPAD. The general US population utilizes 10% of the cPAD.

Table 5.2.2 Summary of Chronic Dietary (Food and Drinking Water) Exposure Risk for Fenhexamid		
Population Subgroup	Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.017657	10
All Infants (< 1 year old)	0.030064	18
Children 1-2 years old	**0.045219**	**27**
Children 3-5 years old	0.034218	20
Children 6-12 years old	0.021757	13
Youth 13-19 years old	0.014096	8.3
Adults 20-49 years old	0.014908	8.8
Adults 50+ years old	0.015058	8.9
Females 13-49 years old	0.015358	9.0

5.2.3 Cancer Dietary Risk

Fenhexamid has been classified as a "not likely" human carcinogen; therefore, a cancer dietary risk assessment was not performed.

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

No anticipated residues or %CT information was used in these dietary analyses

6.0 RESIDENTIAL (NON-OCCUPATIONAL EXPOSURE/RISK CHARACTERIZATION

There are no residential (non-occupational) uses of fenhexamid. Therefore, potential risk from such uses is not addressed in this risk assessment.

6.1 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for dimethenamid-P. 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 labeling. The Agency has completed its evaluation of the new data base 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

In accordance with the FQPA, ARIA must consider and aggregate pesticide exposures and risks from non-occupational sources, including; food, drinking water, and residential pathways. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, ARIA considers both the route and duration of exposure.

No acute or short/long-term or cancer aggregate exposure is expected. Acute exposure is not expected because no hazard has been identified for this endpoint. Short/long-term exposures are not expected since there are no residential/non-occupational uses of fenhexamid. Cancer exposure is not expected because fenhexamid has been classified as a "not likely" human carcinogen.

Since the chronic aggregate risk exposure includes only food and water and the chronic dietary analysis already includes both, no further calculations are necessary. Since the chronic dietary risk estimates do not exceed ARIA's level of concern, the chronic aggregate risk estimates do not exceed ARIA's level of concern.

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 fenhexamid and any other substances and fenhexamid does not appear to produce a toxic metabolite produce by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that fenhexamid 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

An occupational risk assessment was completed for this IR-4 registration request of fenhexamid for its use on asparagus (M. Dow, DP#: 340326, 6/15/2007). For more detailed information on the occupational risks associated with this proposed use, please see aforementioned assessment.

Proposed Uses

The use pattern summary is taken from the IR4 submission, Section B and from draft labeling from Arysta. The product proposed for use is Elevate® 50 WDG Fungicide (Reg. No. 66330 - 35). Elevate® is formulated as a water dispersible granule which contains 50 % by weight, fenhexamid active ingredient. The target pest is *Botrytis cinerea*, the plant disease organism that causes gray mold. The rate of application is 0.75 lb ai/A applied in a minimum of 40 gallons of water/A. There is a maximum of 4 applications/A/season. Applications should be separated by 7 - 14 days. There is a maximum permitted of 3.0 lb ai/A/year. All applications must be made to asparagus during the fern stage only. The ferns must be mowed down or allowed to senesce between the last application and harvest of the spears. The preharvest interval (PHI) is 180 days in all states except California. The PHI in California is 90 days.

See Table 9.0 for a summary of the proposed use pattern.

Table 9.0 Summary of Proposed Use Pattern for Fenhexamid on Asparagus

Formulation	Elevate® 50 WDG Fungicide; Reg. No. 66330 - 35 water dispersible granule; 50 % by weight ai
Pest	*Botrytis cinerea* (gray mold)
Method of Applic.	ground boom
Max. Applic. Rate	0.75 lb ai/A
Max. No. Applications	4/season
Applic. Interval	7 - 14 days
Preharvest Interval	180 days except California; 90 days in California
Restricted Entry Interval	12 hours
Manufacturer	Arysta LifeScience

9.1 Occupational Pesticide Handler Exposure and Risk

Based upon the proposed use pattern, ARIA/RD expects the most highly exposed occupational pesticide handlers to be 1) mixer/loaders using open pour loading of granules and 2) applicators using open-cab, ground-boom spray equipment. Due to the volume of spray recommended per acre, ARIA believes aerial application is not a practical option.

ARIA believes that in these cases, most occupational pesticide handlers are likely to be private, grower handlers. The number of acres treated per day is expected to be rather small as compared to most field crops. ARIA herein uses a default assumption of 200 acres treated per day. On average this is likely to be an overestimate and therefore is a conservative assumption. However, 2002 Census of Agriculture data indicate average asparagus farms in California often exceed 200 acres in size.

Short-term duration (1–30 days) exposures are expected. There might be occasions where some handlers might experience 2 or more short-term exposures. Due to the timing and proposed use, it is unlikely that intermediate-term duration (1 – 6 months) exposures will occur.

It is not uncommon for grower (private), pesticide handlers to perform all three handling activities that is, to mix, load and apply the material. However, the available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the Pesticide Handler's Exposure Database (PHED) Surrogate Exposure Guide (August 1998).

No chemical specific data are available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998). The Elevate® label directs applicators and other handlers to wear long-sleeved shirt, long pants, socks, shoes and waterproof gloves.

The toxicological endpoints used herein for purposes of risk assessment are taken from HED. Pertinent to this assessment, a dermal toxicological endpoint was identified from a 21 day dermal developmental toxicity study in the rabbit at a NOAEL of 1,000 mg ai/kg bw/day. A LOAEL was not observed in this study. However, results in this study were consistent with those in the oral developmental toxicity study in rabbits in which maternal effects were observed, particularly during the first week of dosing, at a LOAEL of 300 mg/kg/day. A NOAEL for maternal toxicity in oral study was 100 mg/kg/day. Using a 20% dermal absorption factor, the oral NOAEL (100 mg/kg/day) is equivalent to a dermal NOAEL of 500 mg//kg/day and the oral LOAEL (300 mg/kg/day) is equivalent to a dermal LOAEL of 1,500 mg/kg/day. The dermal NOAEL was for short-term (1-30 days) and intermediate-term (1-6 months) exposure durations. Although a dermal absorption factor has been identified, it is not used for purposes of assessing dermal exposure and risk since the NOAEL was identified from a 21-day dermal developmental study and dermal absorption is already accounted for in the study.

HED did not identify inhalation toxicological endpoints for either short- or intermediate-term exposures. It was determined that a separate inhalation risk assessment is not required for short- and intermediate-term inhalation risk assessment (TXR NO. 013258).

Table 9.1 Summary of Exposure & Risk for Occupational Handlers Applying Fenhexamid to Asparagus				
Unit Exposure[1] mg ai/lb handled	**Applic. Rate[2]** lb ai/unit	**Units Treated[3]**	**Avg. Daily Exposure[4]** mg ai/kg bw/day	**MOE[5]**
Mixer Loader Open Pour Loading Dry Flowable				
Dermal: SLNoGlove 0.066 LC SLWithGlove 0.066 HC	0.75 lb ai/A	200 A/day	Dermal: SLNoGlove 0.14 SLWithGlove 0.14	7,143
Applicator Using Open-cab Ground-boom Sprayer				
Dermal: SLNoGlove 0.014 HC SLWithGlove 0.014 MC	0.75 lb ai/A	200 A/day	Dermal: SLNoGlove 0.03 SLWithGlove 0.03	33,333

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. SL No Gloves = Dermal Single Layer Work Clothing No Gloves; SL W Gloves = Dermal Single Layer Work Clothing With Gloves; Units = mg ai/pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Applic. Rate. = Taken from IR 4 submissions
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; SOP No. 9.1. Science Advisory Council for Exposure; Revised 5 July 2000
4. Average Daily Dose = Unit Exposure * Applic. Rate * Units Treated ÷ Body Weight (70 kg). A 70 kg bw is used in calculations.
5. MOE = Margin of Exposure = No Observeable Adverse Effect Level (NOAEL) (1000 mg ai/kg bw/day) ÷ ADD. (ADD = dermal). The HED did not identify an inhalation exposure NOAEL.
6. HED does not have unit exposure data for water dispersible granules therefore, as a surrogate, unit exposures for a dry flowable formulation are used.

A Margin of Exposure of 100 is adequate to protect occupational pesticide handlers. Since all estimated MOEs are > 100, the proposed use does not exceed ARIA/RD's level of concern.

9.2 Occupational Post-Application Worker Exposure and Risk

There typically is the possibility for agricultural workers to experience post-application exposure to dislodgeable foliar pesticide residues (DFR). The Science Advisory Council for Exposure (ExpoSAC) and the Agricultural Reentry Task Force (ARTF) have identified numerous post-application, agricultural activities which can result in worker exposure to dislodgeable foliar pesticide residues.

In addition to identifying the post-application agricultural activities, the ExpoSAC also identified Transfer Coefficients (TC) expressed as cm^2/hr for each of the post-application, agricultural activities. The TCs are derived from data in surrogate exposure studies conducted during the various activities listed.

The TCs used in this assessment are taken from an interim TC SOP developed by HED's ExpoSAC using proprietary data from the ARTF database (SOP No. 3.1). It is the intention of the ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

There are no compound-specific foliar dislodgeable residue data available for use in estimating post-application exposure to fenhexamid. The highest TC identified for any agricultural activity in asparagus is 500 cm^2/hr and that is for irrigation activities conducted during full foliage development. To be conservative, ARIA/RD uses the 500 cm^2/hr value. Also lacking compound specific data, HED assumes 20% of the application rate is available as dislodgeable foliar residue (DFR) on day zero after application.

The estimated post-application exposure to fenhexamid; MOE = 10,400.

A MOE of 100 is adequate to protect agricultural workers from post-application exposures to fenhexamid. The estimated MOE is based upon conservative assumptions and is >100, therefore estimated risks from estimated post-application exposures do not exceed ARIA/RD's level of concern.

Restricted Entry Interval

The interim Worker Protection Standard (WPS) restricted entry interval (REI) of 12 hours is adequate to protect agricultural workers from post-application exposures (i.e., field treatment) to fenhexamid under these circumstances.

10.0 DATA NEEDS AND LABEL RECOMMENDATIONS

None.

REFERENCES

Dietary Exposure Memorandum

Fenhexamid. Chronic Dietary Exposure Assessment for the Interregional Research Project No. 4 (IR-4) Petition Proposing Tolerances for Residues of Fenhexamid on Asparagus (PP# 7E7187). B. Hanson, DP#: 347171, 12/5/2007.

Drinking Water Memorandum

Drinking Water Assessment for the IR-4 Petition for the Use of Fenhexamid on Asparagus. C. Sutton, DP#: 338651, 7/26/2007.

Residue Chemistry Data Review Memorandum

Fenhexamid. Petition for Registration for Use on Asparagus. Summary of Analytical Chemistry and Residue Data. Petition Number 7E7187. D. Rate; DP #: 346385; 11/30/2007.

Occupational and Residential Exposure Memorandum

Human, Non-Dietary Exposure/Risk Assessment for the Proposed Use of Fenhexamid on Asparagus. M. Dow, DP#: 340326; 6/15/2007.

Risk Assessment Document

Human Health Risk Assessment for Fenhexamid – IR-4 Tolerance Request on Cilantro (Transplant/Greenhouse), Non-Bell Pepper (Transplant) and Pomegranate (Post-Harvest). J. Redden, DP#:: 329137, 6/14/2006.

HED Memorandum

FENHEXAMID - 2nd Report of the Hazard Identification Assessment Review Committee. B. Tarplee, TXR NO. 0051704, 3/26/2003.

Appendix A: INTERNATIONAL RESIDUE LIMIT STATUS

INTERNATIONAL RESIDUE LIMIT STATUS			
Chemical Name: N-(2,3-dichloro-4-hydroxyphenyl)-1-methylcyclohexanecarboxamide	Common Name: Fenhexamid	X Proposed tolerance Reevaluated tolerance Other	Date: 11/07/2007
Codex Status (Maximum Residue Limits)		**U. S. Tolerances**	
No Codex proposal step 6 or above X No Codex proposal step 6 or above for the crops requested		**Petition Numbers**: 7E7187 **DP Number:** 346385 **Other Identifier:**	
Residue definition (step 8/CXL): Fenhexamid		**Reviewer/Branch:** Debra Rate/RIMUERB	
		Residue definition: Fenhexamid	
Crop (s)	**MRL (mg/kg)**	**Crop(s)**	**Tolerance (ppm)**
Almond hulls	2	Asparagus	0.02
Almonds	0.02 (*)		
Apricot	10		
Blackberries	15		
Blueberries	5		
Cherries	7		
Cucumber	1		
Currants, Black, Red, White	5		
Dewberries (including boysenberry and loganberries)	15		
Dried grapes (currants, raisins, and sultanas)	25		
Edible offal (mammalian)	0.05 (*)		
Egg plant	2		
Gherkin	1		
Gooseberry	5		
Grapes	15		
Kiwifruit	15		
Lettuce, Head	30		
Lettuce, Leaf	30		
Meat (from mammals other than marine mammals)	0.05 (*)		
Milks	0.01 (*)		
Nectarine	10		
Peach	10		
Peppers	2		
Plums, including prunes	1		
Raspberries, Red, Black	15		
Squash, Summer	1		
Strawberry	10		

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name: N-(2,3-dichloro-4-hydroxyphenyl)-1-methylcyclohexanecarboxamide	Common Name: Fenhexamid	X Proposed tolerance Reevaluated tolerance Other	Date: 11/07/2007
Tomato	2		
Bilberry	5		
Elderberries	5		
Juneberries	5		

Limits for Canada		**Limits for Mexico**	
□ No Limits X No Limits for the crops requested		□ No Limits X No Limits for the crops requested	
Residue definition: N-(2,3-dichloro-4-hydroxyphenyl)-1-methylcyclohexane carboxamide		Residue definition: Fenhexamid	
Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
Lettuce	23	Durazno (peach)	6
Blackberries, loganberries, raspberries	20	Fresa (strawberry)	3
Apricots, cherries, peaches, nectarines	6	Vid (grapes)	4
Grapes	4		
Raisins	6		
Blueberries, currants, elderberries, gooseberries, huckleberries	4		
Strawberries	3		
Plums	0.5		
Almonds	0.02		
Tomato	1		
Notes/Special Instructions: S.Funk, 11/07/2007			

Appendix B: TOXICOLOGY ASSESSMENT

B.1 Toxicology Data Requirements

The requirements for Fenhexamid are in Table B.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table B.1 Toxicology Data Requirements for Fenhexamid

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)	no	-
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	no
870.3465 90-Day Inhalation	no	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)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90-Day Neuro. Screening Battery (rat)	no	-
870.6300 Develop. Neuro	no	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

B.2 Toxicity Profiles

Table A.1.a Acute Toxicity Profile of Fenhexamid				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute Oral Rats	44346769	M: LD_{50} >5000 mg/kg F: LD_{50} >5000 mg/kg	IV
870.1200	Acute Dermal Rats	44346770	M: LD_{50} >5000 mg/kg F: LD_{50} >5000 mg/kg	IV
870.1300	Acute Inhalation Rats	44366513	DUST M: LC_{50} >5.057 mg/L F: LC_{50} >5.057 mg/L	DUST IV
870.2400	Primary Eye Irritation Rabbits	44346771	Not an eye irritant	IV
870.2500	Primary Skin Irritation Rabbits	44346771	Not a dermal irritant	IV
870.2600	Dermal Sensitization Guinea Pigs	44346772	Not a dermal sensitizer	N/A

B.3 Executive Summaries

B.3.1 Subchronic Toxicity

870.3200 21/28-Day Dermal Toxicity – Rat

Study Selected: 21-Day Dermal Toxicity Study, Rabbits

MRID No.: 44346780

Executive Summary: In a 21-day repeated dose dermal toxicity study in NZW rabbits (MRID 44346780), KBR 2738 (95.4% purity) was applied to the shaved skin of 5 rabbits/sex/dose at a dose level of 1000 mg/kg/day (limit dose), 6 hours/day, for a total of 17 days over a 3-week period.

No rabbits died during this study. No skin irritation was observed in any treated animals. There were no compound related effects on clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, or gross and histologic pathology. Dermal administration of KBR 2738 was well tolerated by both sexes for 21-days at the limit dose of 1000 mg/kg/day. The NOAEL is 1000 mg/kg/day (limit dose) and the LOAEL is greater than 1000 mg/kg/day for both systemic and local effects on the skin.

Dose and Endpoint for Risk Assessment: NOAEL = 1000 mg/kg/day (HDT).

Comments about Study/Endpoint: This study is selected because its duration and route of exposure are appropriate for short- and intermediate-term dermal exposure. Results in this study are consistent with those in the oral developmental toxicity study in rabbits (MRID 44346801) in which maternal effects (decreased body weight gain and decreased feed consumption) were observed, particularly during the first week of dosing, at the LOAEL of 300 mg/kg/day. The NOAEL for maternal toxicity in this study was 100 mg/kg/day. Using a 20% dermal absorption factor, the oral NOAEL in this study (100 mg/kg/day) is equivalent to a dermal NOAEL of 500 mg//kg/day and the oral LOAEL (300 mg/kg/day) is equivalent to a dermal LOAEL of 1500 mg/kg/day. Since treatment-related effects were observed at an equivalent dermal dose level of 1500 mg/kg/day, HED concluded it would be appropriate to use the dermal dose level of 1000 mg/kg/day (NOAEL) from the 21-day dermal study for short- and intermediate-term dermal risk assessments.

870.3465 90-Day Inhalation – Rat

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not applicable

Comments about Study and Endpoint: The acute inhalation LC50 for technical grade fenhexamid dust (95.5% purity) is >5.057 mg/L (Toxicity Category IV) for both male and female rats and for technical grade fenhexamid aerosolized in PEG 400/ethanol mixture at 0.322 mg/L (the maximum technically possible concentration) is > 0.322 mg/L for both male and female rats. In both of these acute inhalation toxicity studies (MRID 44366513), there were no mortalities, treatment-related clinical signs, changes in body weights or necropsy findings. Further, in a 5-day range-finding inhalation toxicity study in rats using technical grade fenhexamid dust as the test material (MRID 44366514), macroscopic gray colouration of the lungs and marginally increased lung weights were observed at a concentration of 1.092 mg/L, but not at 0.098 mg/L. It is likely that the effects observed in this study are due to the physical deposition of fenhexamid dust in the lungs and not to any systemic effect of the test material.

Based on the low acute inhalation toxicity (Toxicity Category IV), the low 5-day subchronic toxicity (no systemic toxicity at 1.092 mg/L), the composition of the formulated product (water dispersible granules containing 50% ai), the application rate (maximum of 3.0 lb/acre), and the application method (ground spray, groundboom and airblast), there is minimal concern for potential inhalation exposure/risk. HED determined that a separate inhalation risk assessment is not required for short- and intermediate-term inhalation risk assessments.

B.3.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

Study Selected: Developmental Toxicity Study, rat

MRID No. 44346781

Executive Summary: In a developmental toxicity study (MRID 44346781), KBR 2738 (95.4% purity) was administered to 30 Sprague-Dawley rats/dose by gavage at dose levels of 0 and 1000 (1044 determined analytically) mg/kg/day from days 6 through 15 of gestation.

When tested at the limit dose of 1000 (1044) mg/kg/day, there were no treatment-related effects on maternal mortality, clinical signs, Cesarean parameters or gross pathology. The LOAEL for maternal toxicity is set at 1044 mg/kg/day based on the observed decrease in body weight gain(-12% of controls)during gestation days 6-16 and a decrease in food consumption (10% of controls) during gestation days 6-11. The NOAEL for maternal toxicity is < 1044 mg/kg/day. The NOAEL for developmental toxicity is set at 1044 mg/kg/day (limit dose). No treatment-related effects were noted in any embryo/fetal parameters. Where noted, statistically significant differences from concurrent control values fell within the range of values of the historical control data supplied by the laboratory for those parameters. Under the conditions of this study, therefore, KBR 2738 was not embryotoxic, fetotoxic or teratogenic at a dose of 1044 mg/kg/day (the highest dose tested).

870.3700b Prenatal Developmental Toxicity Study – Rabbit

Study Selected: Developmental Toxicity Study, rabbit

MRID No. 44346801

Executive Summary: In a developmental toxicity study (MRID 44346801), KBR 2738 (95.4% purity) was administered to 16 female Russian rabbits (CHBB:HM)/dose by gavage at dose levels of 0, 100, 300 or 1000 mg/kg/day from days 6 through 18 of gestation. Does were naturally inseminated and were sacrificed on gestation day 29.

No treatment-related effects were seen on mortality, clinical signs or behavior. The LOAEL for maternal toxicity is set at 300 mg/kg/day based on observations at this dose and above of alterations of excretory products (discolored urine, small scybala), decreased body weight gain and feed consumption (mainly during the first week of the treatment period) and decreased placental weights. One abortion at 300 mg/kg/day and one abortion and two total litter resorptions at 1000 mg/kg/day were not considered to be treatment-related because the incidences fell within the ranges of historical control data submitted with the study. Reduced and/or light feces were also noted at 1000 mg/kg/day. Pale livers were noted in the 2 dams that aborted. The NOAEL for maternal toxicity is set at 100 mg/kg/day. The LOAEL for developmental toxicity is 1000 mg/kg/day based on marginally decreased male fetal body weights and evidence of delayed ossification. Administration of the test compound did not induce any treatment-related fetal malformations or deviations at any of the doses tested under the conditions of this study. All effects on intrauterine development were correlated with maternal toxicity and, therefore, no primary developmental effect was evident. The NOAEL for developmental toxicity is 300 mg/kg/day. KBR 2738 was not teratogenic up to and including 1000 mg/kg/day, the limit dose.

Comments: In neither the developmental toxicity study in rats (MRID 44346781) nor in the developmental toxicity study in rabbits (MRID 44346801) was there any evidence for increased susceptibility of fetuses to *in utero* exposure to fenhexamid. In the rat study, the LOAEL for maternal toxicity was 1044 mg/kg/day (HDT), but no developmental toxicity (including any effect on the fetuses) was observed at that dose level. In the rabbit study, the NOAEL for maternal toxicity was 100 mg/kg/day and the LOAEL was 300 mg/kg/day. In the same study, the NOAEL for developmental toxicity was 300 mg/kg/day and the LOAEL was 1000 mg/kg/day, based on marginally decreased fetal body weights in male fetuses and delayed ossification in several bones (especially the 5th sternal segments and the 15th caudal vertebrae).

B.3.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

Study Selected: 2-generation reproduction study, rats

MRID No. 44346803

Executive Summary: In a 2-generation reproduction study (1 litter/generation)(MRID 44346803), KBR 2738 (93.8-95.2% purity) was administered to 30 Sprague-Dawley rats/sex/dose in the diet at dose levels of 0, 100, 500, 5000 or 20000 ppm (0, 7.6, 38.2, 406 or 1814 mg/kg/day for males and 0, 9.0, 44.8, 477 or 2043 mg/kg/day for females determined for the 10-week premating period).

There were no compound-related effects on mortality, clinical signs, behavior or reproductive parameters for adult animals. The NOAEL for reproductive toxicity was 20000 ppm (1814/2043 mg/kg/day), the highest dose tested.

The neonatal NOAEL was 500 ppm (38.2/44.8 mg/kg/day); the neonatal LOAEL was 5000 ppm (406/477 mg/kg/day) based on significantly decreased pup body weights on lactation days 14 and 21 for F_1 pups (6-11% less than controls) and on lactation days 7, 14 and 21 for F_2 pups (9-11% less than controls). At 20000 ppm (1814/2043 mg/kg/day), significantly decreased pup body weights were observed on lactation days 7, 14 and 21 for F_1 pups (15-30% less than controls) and for F_2 pups (11- 19% less than controls). Treatment-related decreased pup body weights were not observed at birth or on lactation day 4. An additional effect observed at 20000 ppm was an increase in the number of pups among the post-weaning F_1 pups selected to be F_1 parents which died viz. 0/66, 2/68, 0/68, 0/68 and 10/78 for the control, 100, 500, 5000 and 20000 ppm dose groups respectively. This effect was attributed by the testing laboratory to the small size of the pups at weaning (30% less than controls).

The parental NOAEL was 500 ppm (38.2/44.8 mg/kg/day); the parental LOAEL was 5000 ppm (406/477 mg/kg/day) based, in males, on increased creatinine levels in P-generation (but not F1-generation) males at premating (20%, $p<0.05$) and at termination (20%, not significant); slightly increased alkaline phosphatase levels in P-generation and F1-generation males at premating and at termination (20-34%, not significant); decreased absolute liver weight in P-generation and F1-generation males (11-12%, $p<0.05$) and decreased liver/body weight ratios in P-generation and F1-generation males (8-9%, $p<0.05$ for P-generation and not significant for F1-generation); decreased absolute kidney weights in F1-generation (but not P-generation) males (12%, $p<0.05$); and decreased kidney/body weight ratios in F1-generation (but not P-generation) males (8%, $p<0.05$). The parental LOAEL was based, in females, on increased alkaline phosphatase levels in F1-generation (but not P-generation) females at premating (43%, $p<0.05$) and at termination (63%, $p<0.05$); and on very small increases in GGT (not considered to be biologically relevant). In males at 5000 ppm, the increased creatinine levels and decreased absolute and relative kidney weights suggested a possible treatment-related effect on the kidney and the increased alkaline phosphatase levels and decreased absolute and relative liver weights suggested a possible treatment-related effect on the liver. Histopathological examination of kidney and liver in males, however, did not indicate any treatment-related morphological changes in these organs (i.e. was negative). In females at 5000 ppm, the increased alkaline phosphatase levels and GGT levels suggested a possible treatment-related effect on the liver. Histopathological examination of liver in females, however, was negative.

At 20000 ppm (1814/2043 mg/kg/day), in males, treatment-related effects on parental parameters were the following: increased creatinine levels in P-generation males (20%, $p<0.05$); increased alkaline phosphatase levels in P-generation and F1-generation males (16-44%, not significant); slightly increased GGT levels in P-generation males ($p<0.05$, but not considered to be biologically relevant); decreased absolute liver weights in P-generation and F1-generation males (9-19%, $p<0.05$ for P-generation, not significant for F1-generation); decreased liver/body weight ratios in P-generation and F1-generation males (3-11%, $p<0.05$ for P-generation, not significant for F1-generation); decreased absolute kidney weights in F1-generation males (13%, $p<0.05$); decreased kidney/body

weight ratios in F1-generation males (8%, $p<0.05$); decreased body weights (6-16%, $p<0.01$); and increased food consumption (12-26%, $p<0.01$). Histopathological examination of kidney and liver was negative. At 20000 ppm, in females, treatment-related effects on parental parameters were the following: increased urea nitrogen levels in P-generation females (43%, not significant) and F1-generation females (55%, $p<0.05$); increased creatinine levels in F1-generation females (17%, $p<0.05$); increased alkaline phosphatase levels in P-generation females (23-25%, not significant) and F1-generation females (56-87%, $p<0.05$); slightly increased GGT in P-generation females ($p<0.05$, but not considered to be biologically relevant); decreased absolute kidney weights in P-generation and F1-generation females (15-19%, $p<0.05$); decreased kidney/body weight ratios in P-generation and F1-generation females (5-6%, $p<0.05$); decreased premating body weights (6-16%, $p<0.01$); decreased gestation body weights (7-9%. $p<0.01$); decreased lactation body weights (7-12%, $p<0.01$); and increased food consumption (4-11%, $p<0.05$). Histopathological examination of kidney and liver was negative. Overall, treatment-related effects observed at 5000 ppm in males and females were also observed at 20000 ppm, but were slightly increased in severity. Toxicologically relevant additional toxicological effects observed at 20000 ppm were decreased body weights and increased food consumption in males and increased urea nitrogen and creatinine levels, decreased kidney weights, decreased body weights and increased food consumption in females.

Comments: The results in this reproduction study are equivocal with respect to evaluating the possibility of increased susceptibility of pups, as compared to adults, to fenhexamid. At 5000 ppm (neonatal LOAEL), statistically significant, treatment-related and dose-related decreased pup body weights were observed on lactation days 14 and 21 for F_1 pups (6-11% less than controls) and on lactation days 7, 14 and 21 for F_2 pups (9-11% less than controls). At the same dose level of 5000 ppm (parental LOAEL), treatment-related and dose-related effects were also observed in the adult (parent) animals. In adult males, increased creatinine levels (20%) and decreased absolute (12%) and relative (8%) kidney weights suggested an effect on the kidney and increased alkaline phosphatase levels (20-34%) and decreased absolute (11-12%) and relative (8-9%) liver weights suggested an effect on the liver. In adult females, increased alkaline phosphatase levels (43-63%) and slightly increased GGT levels (not considered to be biologically relevant) suggested a possible effect on the liver. Histopathological examination of kidney and liver from these same adult animals, however, did not reveal any treatment-related morphological changes in these organs at this dose level (or at the highest dose level of 20000 ppm). Since treatment-related effects were observed in both pups and adults at 5000 ppm, but not at 500 ppm, on the basis of NOAELs and LOAELs, no increased susceptibility of pups to fenhexamid was demonstrated in this study. However, the severity of effects in the pups at 5000 ppm (decreased body weights of up to 11% on lactation days 7 to 21, but not at birth or lactation day 4) may have been greater than that observed in the adults at the same dose level (suggestion of mild effects in the kidney and liver without supporting histopathological changes). In addition, at the highest dose level of 20000 ppm, the severity of effects in the pups (decreased body weights of up to 30% on lactation days 7 to 21 and increased mortality in F_1 pups selected to be F_1 parents) was considered to be greater than that observed at the same

dose level in adults (mild effects in the kidney and liver not supported by histopathological changes; decreased body weights of up to 16%; and increased food consumption of up to 26%). Interpretation of relative severities of effects in pups and adults at 5000 and 20000 ppm should also consider, however, that the pups may be consuming significantly greater amounts of test material than adults (on a mg/kg/day basis) since pups consume considerably more food per unit body weight than do adults, and pups receive test material from not one, but two sources viz. mother's milk and treated diet (particularly during the late lactation period). The body weight decrements in late lactation (but not through post natal day 4) are supportive of this argument.

With respect to determining the possible increased susceptibility of pups to fenhexamid in this reproduction study, HED considered the results to be equivocal (i.e. subject to two interpretations). On the one hand, on the basis of NOAELs and LOAELs, no increased susceptibility was observed. On the other hand, the greater severity of effects in pups and a likely pharmacological explanation for this finding suggested an increased sensitivity of pups, as compared to adults, to fenhexamid.

B.3.4 Chronic Toxicity

870.4100b Chronic Toxicity – Dog

Study Selected: 1-Year Chronic Toxicity Study, Dogs

MRID No. 44346804

Executive Summary: In a 1-year chronic oral toxicity study (MRID 44346804), KBR 2738 (94.6-95.8% purity) was administered to 4/sex/dose beagle dogs in the diet at dose levels of 0, 500, 3500 or 25000 ppm (0, 17.4, 124.3 or 917.8 mg/kg/day for males and 0, 19.2, 132.7 or 947.1 mg/kg/day for females) for 52 weeks.

There were no compound related effects on mortality, clinical signs, clinical tests (ECG, heart rate, blood pressure, pulse, reflexes, body temperature), ophthalmoscopic examinations, clinical chemistry, urinalysis, or gross pathology. Decreases in RBC, Hb and Hct and increases in Heinz bodies in both sexes were noted in mid and high dose dogs. Decreased body weight gain was observed in both sexes of the 25000 ppm treatment group. The decreased body weight gain by high dose females may be attributed, in part, to the decreases in food consumption observed sporadically during the latter half of the study period. Treatment-related increases in absolute and relative adrenal weights in mid and high dose females were corroborated by the histopathological observations of increases in incidence and severity of intracytoplasmic vacuoles in the adrenal cortex of these animals. No neoplastic changes were observed in any animals of any dose group.

The LOAEL is 3500 ppm (124.3/132.7 mg/kg/day in males and females, respectively) based on decreases in RBC, Hb and Hct and on significant increases in Heinz bodies in both sexes; increased adrenal weight parameters in females and the presence of

intracytoplasmic vacuoles in the adrenal cortex of 3/4 female dogs. As well as decreased body weight gains (both sexes) and decreased food consumption (females) at the highest dose of 25000 ppm, more pronounced treatment-related effects were seen in hematology parameters in both sexes (decreased RBC, Hb, Hct, increased Heinz bodies) and may indicate the potential of KBR 2738 to induce Heinz body anemia in Beagle dogs. The hematotoxic effect of KBR 2738 was also noted in the 90-day dog study. The NOAEL is 500 ppm (17.4/ 19.2 mg/kg/day for males and females, respectively). Dosing was considered adequate based on the observation at the high dose of 25000 ppm of decreased body weight gains, food consumption and hematotoxic effects.

Dose and Endpoint for establishing the RfD: NOAEL = 17 mg/kg/day. Based on decreased RBC counts, hemoglobin and hematocrit, and increased Heinz bodies in RBC at the LOAEL of 124/133 mg/kg/day in males/females. Also, in females, increased absolute and relative adrenal weights correlated with histopathological observations of increases in incidence and severity of intracytoplasmic vacuoles in the adrenal cortex.

Uncertainty Factor: An uncertainty factor of 100 was applied to account for both interspecies extrapolation (10X) and intraspecies variability (10X).

Comments about Study/Endpoint/Uncertainty Factor(s): The RfD derived from the use of the NOAEL and endpoint from the 1-year chronic toxicity study in dogs and an uncertainty factor of 100 is supported by a similar RfD that could have been derived from the use of the NOAEL from the combined chronic/carcinogenicity feeding study in rats (MRID 44346806) and an uncertainty factor of 100. In the rat study, the NOAEL = 28 mg/kg/day and the LOAEL = 292/415 mg/kg/day in males/females, based in males on increased cecal mucosal hyperplasia and increased splenic extramedullary hematopoiesis, and in females on decreased body weight, decreased body weight gain, decreased food efficiency and increased hyperplasia in the bone marrow of the femur and sternum. Had the RfD been derived from this rat study, the RfD would have been 28 mg/kg/day/100 = 0.28 mg/kg/day. The NOAEL from the chronic study in dogs, rather than the NOAEL from the combined chronic/carcinogenicity study in rats, was used to calculate the chronic RfD because it is the lowest NOAEL for this time period.

B.3.5 Carcinogenicity

870.4200b Carcinogenicity (feeding) - Mouse

MRID No.: 44346805

Executive Summary: In a carcinogenicity study, KBR 2738 (95.4% purity) was administered to 50 B6C3F1 mice/sex/dose in the diet at dose levels of 0, 800, 2400 or 7000 ppm (0, 247.4, 807.4 or 2354.8 mg/kg/day for males, and 0, 364.8, 1054.5 or 3178.2 mg/kg/day for females) for two years. An additional 10 mice/sex/dose were assigned for the interim sacrifice at 52 weeks.

Survival was not affected by treatment with KBR 2738. There were no compound-related effects on clinical signs, food consumption, hematology or gross pathology. A marginal decrease in body weights (up to 8%) and body weight gain (17%) was observed in males at 7000 ppm. The LOAEL for males is 2400 ppm (807.4 mg/kg/day) based on the observation of decreased kidney weights and decreases in sex-specific vacuolation of the proximal tubules in the kidneys in males. Additional toxicologically significant effects at the highest dose of 7000 ppm (LOAEL for females)included decreased body weights and weight gain in males, significantly increased water consumption (both sexes), increased levels of serum creatinine, bilirubin and albumin(males), decreased kidney weights (females), renal histopathology (increased incidence of basophilic cortical tubules in females; chronic renal disease in males).The LOAEL for females is 7000 ppm (3178.2 mg/kg/day) based on the observations noted above. The NOAEL for males/females is 800/2400 ppm (247.4/1054.5 mg/kg/day, respectively). KBR 2738 is non-oncogenic in mice at doses up to and including 7000 ppm (2354.8 mg/kg/day in males and 3178.2 mg/kg/day in females). There was no treatment related increase in tumor incidence, tumor spectrum or latency when compared to controls. In this study, KBR 2738 was tested at adequate dose levels for carcinogenicity testing since it was tested at the limit dose of 7000 ppm (2354.8 mg/kg/day in males and 3178.2 mg/kg/day in females) for mice.

Discussion of Tumor Data: There was no evidence of carcinogenicity**.**

Adequacy of the Dose Levels Tested: In this study, KBR 2738 was tested at adequate dose levels for carcinogenicity testing since it was tested at the limit dose of 7000 ppm (2354.8 mg/kg/day in males and 3178.2 mg/kg/day in females) for mice.

Classification of Carcinogenic Potential: HED classified Fenhexamid as a "not likely" human carcinogen according to the EPA *Proposed Guidelines for Carcinogen Risk Assessment* (April 10, 1996). This classification is based on the lack of evidence of carcinogenicity in male and female rats as well as in male and female mice and on the lack of genotoxicity in an acceptable battery of mutagenicity studies.

B.3.6 Mutagenicity

Five acceptable mutagenicity studies on technical grade Fenhexamid are available:

1) Reverse gene mutation, S. typhimurium (MRID 44346807)
2) Forward gene mutation, Chinese hamster lung cells in culture/HGPRT locus (MRID 44346810)
3) Chromosome aberration, Chinese hamster ovary cells in culture (MRID 44346809)
4) Unscheduled DNA synthesis, rat hepatocytes in culture (MRID 44346812)
5) In vivo cytogenetics, micronucleus assay in mice (MRID 44346811)

Results in all five studies were negative for genotoxicity. These five studies satisfy the new revised mutagenicity guideline requirements for a new chemical (published in 1991).

B.3.7 Neurotoxicity

870.6100 Delayed Neurotoxicity Study – Hen

Study Selected: None required

870.6200 Acute/Subchronic Neurotoxicity Screening Battery

Study Selected: Acute Neurotoxicity Study, Rats

MRID No.: 44346813

Executive Summary: In an acute neurotoxicity study, a single oral dose of KBR 2738 (95.4% purity) was administered to 12 Wistar rats/sex/dose by gavage at dose levels of 0, 200, 630 or 2000 mg/kg in 2% aqueous Cremophor EL (10 ml/kg). The rats were observed for 14 days. Functional Observational Battery (FOB) and motor activity testing were performed 7 days prior to dosing, approximately 20 minutes to 3 hours post-dosing, and on days 7 and 14.

There were no compound related effects on mortality, clinical signs, body weights, brain weights, or gross and histologic pathology or neuropathology. FOB testing revealed no treatment-related effects in any females. High dose males had a marginally lower ($p<0.05$) mean body temperature (colonic) on the day of treatment (day 0), but which reverted to normal by day 7. No treatment-related effects on measures of motor/locomotor activity or habituation were evident in either sex at doses up to and including 2000 mg/kg. **The LOAEL in males is 2000 mg/kg based on marginal acute toxicity as evidenced by the lower body temperatures. The NOAEL in males is 630 mg/kg. The NOAEL in females is 2000 mg/kg, the highest dose tested.**

Comments: Decreased body temperature may be a sign of acute general systemic toxicity or may possibly be due to a CNS mediated (neurotoxic) effect of the test material on the brain since the brain controls temperature regulation in the body. There is insufficient data in this study to distinguish between these two possibilities. Therefore, this observation should be considered to be a possible neurotoxic effect of the test material. Since it is only a marginal effect and occurs only at a very high dose level (2000 mg/kg), however, this possible effect should not be considered to be a toxicologically significant neurotoxic effect and in the absence of additional signs of neurotoxicity in this or in other studies on fenhexamid is considered to be insufficient evidence to support requirement of a developmental neurotoxicity study.

B.3.8 Metabolism

870.7600 Dermal Absorption – Rat

Dermal Absorption Factor: 20% (rounded off from 21.0%, highest mean dermal absorption at 120 hours). This value is considered to represent the potential cumulative

dermal absorption of test material that might occur after a 10 hour dermal exposure. See Comments below.

Study Selected: Dermal Absorption Study, Rats

MRID No.: 44346815

Executive Summary: In a dermal absorption study, [Phenyl-UL-^{14}C]-TM-402 50 WP formulation (50% active ingredient) was applied to the shaved skin of Crl:CD BR male rats weighing 182-219 g at dose levels of 0.00138, 0.0147 or 0.148 mg/cm^2. A volume of 100 *u*L was applied to a skin area of approximately 12.5 cm^2 on each rat. Four rats/dose level were sacrificed at 0.5, 1, 2, 4, 10, 24 and 120 hours postdose. An additional 2 rats served as a vehicle (water) control group. Skin at the application site was washed just before sacrifice (0.5, 1, 2, 4 and 10 hour postdose groups) or at 10 hours (24 and 120 hour postdose groups). Urine and feces were collected at the time of sacrifice or at 24 hour intervals for the 120 hour postdose group. Mean radioactivity for each group was determined for skin test site cover, skin test site, skin wash, urine, feces, blood and carcass. Corresponding mean percentages of the applied dose were calculated.

Mean total recovery of radioactivity ranged from 90.3% to 97.6% of the applied dose. The majority of radioactivity was recovered from the skin wash (69.9% to 96.1%). Radioactivity in the skin test site ranged from 0.44% to 10.2%; in the urine from "not detectable" to 3.34%; and in the feces from "not detectable" to 11.6% of the applied dose. Radioactivity in blood did not exceed 0.03% and in the carcass did not exceed 9.37%. Estimates of dermal absorption were based on the sum of radioactivity (as test material) in the skin test site, urine, feces, blood and carcass. The percentage dermal absorption decreased with increasing dose level. The percentage dermal absorption at 10 hours postdose was 19.85%, 7.62% and 2.63% and at 120 hours postdose was 21.0%, 6.91% and 2.13% for the low, mid and high dose levels respectively.

Comments about Dermal Absorption: At 10 hours postdose in the low dose level group, radioactivity (as test material) in the skin test site was 10.1% and in the urine, feces, blood and carcass was 9.75%, whereas by 120 hours, radioactivity in the skin test site decreased to 6.05% and in the urine, feces, blood and carcass increased to 14.94%. These data indicate that radioactivity in the skin test site continued to be absorbed after 10 hours (at which time the skin was washed) up to 120 hours (at which time the study was terminated). Since radioactivity in the skin test site at 10 hours continued to be absorbed in significant amounts for up to 120 hours, HED concluded that all the radioactivity in the test skin site might eventually have been absorbed if the study were continued beyond 120 hours. Therefore, 21.0%, the mean total amount of radioactivity in test skin site, urine, feces, blood and carcass at 120 hours was considered to represent the potential cumulative dermal absorption of test material that might occur after a 10 hour exposure.

Appendix C: REFERENCES (in MRID order)

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Appendix D: REVIEW OF HUMAN RESEARCH

No MRID - PHED Surrogate Exposure Guide