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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

November 2, 2007

MEMORANDUM

SUBJECT: Ethalfluralin: Human Health Risk Assessment for (IR-4) Proposed Uses on Dill and Potato.

PC Code: 113101
Petitions: 1E6326 and 2E6360
DP Barcodes: D323068 and D323069

Regulatory Action: *Section 3 Registration*
Risk Assessment Type: *Single Chemical Aggregate*

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1.0 Executive Summary

Ethalfluralin [*N*-ethyl-*N*-(2-methyl-2-propenyl)-2,6-dinitro-4-(trifluoromethyl)-benzenamine] is a selective preemergence herbicide registered for use on a variety of food and feed crops. Registered products containing ethalfluralin include granular (G), dry flowable (DF), and emulsifiable concentrate (EC) formulations. These formulations may be applied preplant, postplant prior to emergence, postemergence, or post-transplant as a soil incorporated, band, or broadcast application using ground equipment. Tolerances are currently established for ethalfluralin residues in bean, dry seed; canola, seed; peanut; pea, dry, seed; safflower, seed; soybean; sunflower, seed; and vegetable, cucurbit, crop group 9, all at 0.05 ppm.

The Interregional Research Project No. 4 (IR-4) submitted petitions for the establishment of permanent tolerances for residues of the herbicide ethalfluralin in dill at 0.05 ppm and in potato at 0.05 ppm. In dill, the proposed use pattern is for a single broadcast soil-incorporated application after seeding but before emergence of the dill. The proposed application rate is a maximum of 4 pints/A (1.5 lbs ai/A; pounds active ingredient/acre). In potato, the proposed use pattern is for a single broadcast soil-incorporated application after seeding but before emergence of potatoes; the proposed application rate in potato is a maximum of 2 2/3 pints/A (1.0 lb ai/A). No preharvest interval (PHI) is proposed for either formulation because the proposed use patterns involve preemergence applications.

The toxicity database for ethalfluralin is complete, and indicates it has low acute toxicity by oral, dermal, and inhalation routes of exposure. It is moderately irritating to the eye and produces moderate to severe skin irritation. In one study ethalfluralin was negative for dermal sensitization, but in another, it was considered positive.

In general, subchronic and chronic feeding studies in rats, mice, and dogs indicate the liver as the target organ, with consistent effects of enzymatic changes, liver weight increases, and histopathology (chronic mouse). A combined chronic/carcinogenicity study in rats showed no non-neoplastic effects at the highest dose tested (32 mg/kg/day). However, mammary gland fibroadenomas were increased in a dose-related manner, and therefore ethalfluralin was classified as a possible human carcinogen in 1994. The Cancer Peer Review Committee (CPRC) recommended a quantitative approach for cancer risk assessment using a cancer potency factor, or Q_1^* of 8.9×10^{-2} $(mg/kg/day)^{-1}$. The mouse carcinogenicity study showed no increase in tumor incidence. Consistent with other studies, liver effects were found in the highest dose group (163 mg/kg/day).

Ethalfluralin does not produce developmental toxicity in rats at doses up to1000 mg/kg/day. There are several rabbit developmental toxicity studies available; together, these studies indicate the potential for ethalfluralin to induce skeletal malformations at doses of $\geq$150 mg/kg/day. Maternal toxicity was observed at similar doses. Ethalfluralin did not produce reproductive or offspring effects in the 3-generation reproduction studies; the parental effects consisted of decreased body weight gains.

In a rat metabolism study with oral dosing, ethalfluralin was well absorbed and rapidly and extensively metabolized, and 95% of the chemical was excreted in urine and feces within seven

days. The major route of elimination was via the feces, and the levels remaining in the tissues were negligible.

HED has fully evaluated the toxicity database of ethalfluralin with respect to the potential for special sensitivity of infants and children, and concludes that there is low concern for pre- and postnatal susceptibility for infants and children. The FQPA safety factor has been reduced to 1X because (1) the toxicity database is complete and adequate to characterize potential pre- and postnatal risk for infants and children; (2) no reproductive or developmental effects were observed in rats; (3) there was no evidence of neurotoxicity in the submitted studies; and (4) although there were slight developmental effects observed (skeletal malformations) in rabbits (fetuses), they were seen in the presence of maternal toxicity. Additionally, the dose chosen for acute dietary risk assessment is protective of the slight developmental effects observed in the rabbit developmental toxicity studies. A developmental neurotoxicity study, or any other study to further elucidate potential pre- and/or postnatal effects, is not required at this time.

A single dose effect applicable to the general population was not observed in the toxicity database for ethalfluralin, and therefore, an acute dietary endpoint for the general population including infants and children was not identified. The dose for acute dietary risk assessment for females 13-49 years old is the No Observed Adverse Effect Level (NOAEL) of 75 mg/kg/day, based on skeletal malformations observed at the Lowest Observed Adverse Effect Level (LOAEL) of 150 mg/kg/day. The dose selected for chronic dietary risk assessment for all populations is the NOAEL of 4 mg/kg/day from a 1-year oral toxicity study in dogs, based on altered red cell morphology and urinary bilirubin observed at the LOAEL of 20 mg/kg/day. The uncertainty factor (UF) for acute and chronic dietary assessments consists of the combined intra- and interspecies factors of 10X, for a total UF of 100.

Occupational exposures for non-cancer risk are expected to be short-term in duration. An endpoint for dermal risk assessment was not identified in the toxicity database, and therefore dermal risks are not of concern for non-cancer effects. A dermal absorption factor of 2.8% was used in conducting cancer risk assessments for occupational workers. For inhalation exposures, an oral study was selected for risk assessment in order to determine screening-level risks from the inhalation route. Inhalation toxicity of ethalfluralin is expected to be low, but in the absence of an inhalation study, the NOAEL from a 3-generation reproduction study (12.5 mg/kg/day), based on decreased body weight gains (males) at the LOAEL of 37.5 mg/kg/day was selected for short-term inhalation risk assessment. A default assumption of 100% inhalation absorption was used to extrapolate from the oral study to the inhalation route.

Adequate residue chemistry data, including an acceptable analytical enforcement method, have been submitted to support the proposed tolerances and the risk assessment. When ethalfluralin is used in accordance with the proposed labels, residues in or on dill (fresh and dry) are less than the limit of quantitation (LOQ) of 0.05 ppm. Likewise, the results from potato field trials show that ethalfluralin residues are below the lowest limit of method validation (LLMV) of 0.05 ppm in potato tubers. In the environment, ethalfluralin is expected to dissipate by binding to soil particles and then degrading both aerobically and anaerobically. It also photodegrades rapidly in water, with a half life of 6 hours. Modeled estimated drinking water concentrations (EDWCs) were higher for surface water sources of drinking water obtained from the PRZM-EXAMs model

than ground water concentrations generated using the SciGrow model. For both surface and ground water, the scenario chosen to represent maximum potential drinking water residues was the existing use on canola, at a maximum application rate of 1.5 lbs ai/A. The surface water EDWCs included directly in the dietary model were 11 ppb for acute dietary exposure, and 0.4 ppb for chronic exposure; the cancer assessment was further refined with the use of drinking water monitoring data from the USDA Pesticide Data Program (PDP).

With the proposed uses, dietary exposure from food and drinking water is not of concern. For acute dietary (food + water) exposure for females 13-49, the estimated dietary risk is <1 % aPAD at the 95th percentile of exposure. For chronic dietary (food + water) exposure, children 1-2 was the most highly exposed subpopulation, with an estimated risk of <1% cPAD. Finally, cancer dietary (food + water) risk for the general US population is 2 x 10^{-6}. Additional refinement with %CT estimates would lead to a lower estimate of dietary cancer risk. EPA generally considers cancer risks of 10^{-6} or less to be below the level of concern. The precision which can be assumed for cancer risk estimates is best described by rounding to the nearest integral order of magnitude on the log scale; for example, risks falling between 3.16 x 10^{-7} and 3.16 x 10^{-6} are expressed as 10^{-6}. Considering the precision with which cancer hazard can be estimated and the rounding procedure described above, cancer risk should generally not be assumed to exceed the benchmark level of concern of 10^{-6} until the calculated risk exceeds approximately 3 x 10^{-6}. Since the calculated cancer risk for ethalfluralin falls below this level, estimated cancer risk is considered to be below the level of concern. Dietary exposure to ethalfluralin results in acute, chronic and cancer risks below HED's level of concern. Additional refinements are possible, since 100 % crop treated was used. At this time, there are no current or proposed residential uses for ethalfluralin. Therefore, aggregate exposure and risk consist of only the dietary (food + water) pathway of exposure. Aggregate acute, chronic and cancer risks are not of concern for the proposed and existing uses.

Short-term inhalation exposure and risk to occupational handlers mixing, loading, and applying ethalfluralin are not of concern, with margins of exposure (MOEs) considerably higher than 100. Estimates of occupational handler cancer risks (from combined inhalation and dermal exposure) range from 5.9 x 10^{-6} to 4.4 x 10^{-5}, which are below HED's level of concern (LOC) for handler cancer risk. Estimated cancer risk from post-application exposures to workers is 1.4 x 10^{-5}, which does not exceed HED's LOC for occupational cancer risk.

Given these considerations, HED recommends for the establishment of ethalfluralin ((*N*-ethyl-*N*-(2-methyl-2-propenyl)-2,6-dinitro-4-(trifluoromethyl)benzenamine) herbicide tolerances of 0.05 ppm in dill and potato:

Tolerance Summary for Ethalfluralin.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Commodity definition
Dill, fresh leaves	0.05	0.05	Dill, fresh and dried
Dill, dried leaves	0.05	0.05	Dill, fresh and dried
Potato	0.05	0.05	Potato

Furthermore, HED recommends for the proposed uses of CURBIT® EC on dill and Sonalan® HFP on potato.

Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with US 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. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

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

2.0 Ingredient Profile

Ethalfluralin (*N*-ethyl-*N*-(2-methyl-2-propenyl)-2,6-dinitro-4-(trifluoromethyl)benzenamine is a dinitroaniline herbicide with established tolerances on bean, dry, seed; canola, seed; peanut; safflower, seed; soybean; sunflower, seed; and vegetable, cucurbit, group 9. The tolerances are published under 40 CFR 180.416. Ethalfluralin is a preemergence herbicide used to control a variety of annual grasses and broadleaf weeds on agricultural sites.

Under petition PP# 1E6326; the CURBIT® EC formulation (31.5% ai) was proposed for use on dill. The Sonalan® HFP (31.5% ai) was proposed for use on potato under petition PP# 2E6360.

2.1 Summary of Proposed Uses

Table 2.1. Summary of Proposed Directions for Ethalfluralin.						
Applic. Timing, Type, and Equip.	Formulation	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Dill						
Soil surface broadcast	CURBIT® EC	1.5	1	1.5	91 – 100	Sprinkler irrigation may be used to incorporate compound into soil
Potato						
Soil surface broadcast	Sonalan® HFP	1.0	1	1	65 - 143	Sprinkler irrigation may be used to incorporate compound into soil

2.2 Structure and Nomenclature

The structure and nomenclature of ethalfluralin is presented in Table 2.2.

2.3 Physical and Chemical Properties

The physical and chemical properties of ethalfluralin are summarized in Table 2.3.

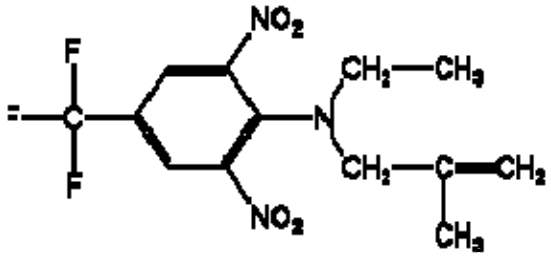
Table 2.2. Test Compound Nomenclature	
Chemical Structure	
Empirical Formula	$C_{13}H_{14}F_3N_3O_4$
Common name	Ethalfluralin
Company experimental name	N/A
IUPAC name	N-ethyl-α,α,α-trifluoro-N-(2-methylallyl)-2,6-dinitro-p-toluidine
CAS name	N-ethyl-N-(2-methyl-2-propenyl)-2,6-dinitro-4-(trifluoromethyl)benzenamine
CAS Registry Number	5523-68-6
End-use product/EP	CURBIT® EC Herbicide (Reg. No. 34704-610) and Sonalan® HFP Herbicide (Reg. No. 62719-188)
Chemical Class	Dinitroaniline herbicide
Known Impurities of Concern	N/A

TABLE 2.3. Physicochemical Properties

Parameter	Value	Reference
Molecular Weight	333.27	Ethalfluralin Registration Eligibility Decision (RED), EPA 738-R-95-001, March 1995
Melting point/range	57ºC	Ethalfluralin RED, EPA 738-R-95-001, March 1995
pH	7.68	DP Num: 276090, MRID#'s 45406501 and 45406502
Density	4.783	Texas Risk Reduction Program
Water solubility (20°C)	4.783 mg/L	Texas Risk Reduction Program
Solvent solubility (temperature not specified), mg/L	> 0.50 in acetone > 0.50 in acetonitrile > 0.50 in chloroform > 0.50 in cyclohexanone > 0.165 in ethyl cellosolve > 0.250 in heavy aromatic naphtha > 0.082 in hexane > 0.082 in methanol > 0.50 in xylene > 0.50 in methylene chloride	DP Num: 199662, MRID# 00135194
Vapor pressure (25°C)	8.538 x 10-6	Texas Risk Reduction Program
Octanol/water partition coefficient, log P_{OW} (25°C)	4.783	Texas Risk Reduction Program

3.0 Hazard Characterization/Assessment

Based on the proposed use pattern, the ethalfluralin toxicity database is complete for the purpose of selecting doses and endpoints for risk assessment, and for characterization of potential pre- and/or post-natal risk for infants and children. (See detailed Hazard Profile in Appendix A.3)

3.1 Hazard and Dose-Response Characterization

The data base of ethalfluralin indicates it has low acute toxicity by oral, dermal, and inhalation routes of exposure (for details, see Appendix A.2). It is moderately irritating to the eye and produces moderate to severe skin irritation. A guinea pig dermal sensitization study conducted by the modified Buehler method found no sensitization, whereas a study conducted by the Magnusson and Kligman maximization method was positive.

The data from the subchronic feeding studies in mice show liver to be consistently affected as indicated by increases in alanine aminotransferase (SGPT), alkaline phosphatase (ALP), and increased liver weights. A 3-month feeding study in dogs showed liver effects as characterized by increases in ALP and slight fatty changes of the liver. A one year feeding study in rats also showed increases in liver weights, and decreases in RBC, hematocrit, and hemoglobin. A 21-day dermal toxicity study in rabbits indicated no systemic toxicity at the limit dose (1000 mg/kg/day). In general, based on subchronic and chronic feeding studies in rats, mice, and dogs, liver appeared to be the target organ with consistent effects of enzymatic changes and liver weight increases.

A chronic feeding/carcinogenicity study in rats showed no non-neoplastic effects at the highest dose tested (32 mg/kg/day). However, mammary gland fibroadenomas increased in a dose-related manner, and ethalfluralin was classified as a possible human carcinogen in 1994. The mouse carcinogenicity study showed no increase in tumor incidence. Liver effects, characterized by increase in ALP and focal hepatocellular hyperplasia, were found in the highest dose group (163 mg/kg/day). The chronic dog feeding study indicated hematological changes, elevated ALP, and siderosis of the liver in the high dose animals (80 mg/kg/day).

Ethalfluralin does not produce developmental effects in rats at doses up to ≥ 1000 mg/kg/day, but systemic effects observed were decreases in maternal body weight gains and dark urine at ≥ 250 mg/kg/day. There are several rabbit developmental toxicity studies available. In the first pilot study no maternal or fetoxicity was seen at doses from 10 to 150 mg/kg/day, but skeletal and visceral examinations were not conducted. In the second pilot study, abortion was seen in 1/3 dams at 500 mg/kg/day. Like the first pilot study, no skeletal and visceral examinations were conducted. Subsequently, three full developmental toxicity studies were conducted using lower and lower dose levels because of increased incidence of abortion found in dams at all doses in the first study. In one study, at 500 mg/kg/day, increased incidences of dwarf-like appearance, open eyelids, and cleft palate were seen. A second study was conducted with dose levels of 75 and 250 mg/kg/day. At 250 mg/kg/day, a cluster of the external findings was reported. No external findings were seen in the 75 mg/kg/day group. A third study was conducted using doses ranging from 25 to 300 mg/kg/day. A slight increase in the incidence of sternal variations and incomplete cranial development was seen in 150 mg/kg/day groups. Although the increased

incidence in sternal variation, incomplete cranial development, and resorption at 150 mg/kg/day appears to be slight, this suggests the potential for ethalfluralin to induce malformation at doses of 150 mg/kg/day and above. Clear maternal effects were seen in 300 mg/kg group characterized by increased incidence of abortion (5/20); decreased body weight gain; enlarged, fatty liver; decreased food consumption, increased resorptions, and increased liver weights. A decrease in food consumption, slight increase in abortion (1/20), and a slight increased in resorption were seen in 150 mg/kg/day dams. Therefore the dose level of 150 mg/kg/day was established as the maternal LOAEL; the maternal NOAEL was 75 mg/kg/day. Evaluating all the results of these studies together, the developmental toxicity LOAEL was established as 150 mg/kg/day based on slight increase in the incidence of sternal variations, cranial variations, incomplete cranial development, and of resorption; the NOAEL was 75 mg/kg/day.

Ethalfluralin did not produce reproductive or offspring effects in the 3-generation reproduction studies; the parental effects consisted of decreased body weight gains.

In metabolism studies, Fischer 344 rats were treated orally with a single low dose, a single high dose, or repeated low doses of radiolabeled ethalfluralin. Absorption of ethalfluralin was estimated at 79-87% of the dose for all dose levels. Ethalfluralin was rapidly and extensively metabolized, and 95% of the chemical was excreted in urine and feces by seven days. The major route of elimination for the radiolabel was in the feces, 50.9-63.2%, and the levels remaining in the tissues after 72 hours were negligible.

3.2 FQPA Considerations

In 1999, an *ad hoc* FQPA Safety Factor Committee evaluated the toxicity data relevant to the determination of the FQPA Safety Factor (SF). Based on the oral developmental toxicity study in rabbits (MRID 00250596), the *ad hoc* committee determined the appropriate SF for assessing acute dietary risk to be 3X and for assessing chronic dietary risk to be 1X. In a subsequent assessment conducted in 2002, the Agency retained the 10X factor for both acute and chronic dietary exposure assessment, pending a complete evaluation of the toxicity database with respect to the special sensitivity of infants and children. With the current proposed uses on dill and potato, HED has fully evaluated the toxicity database for ethalfluralin with respect to the FQPA SF.

In considering the FQPA SF, the hazard is evaluated in conjunction with the toxicity endpoints selected for risk assessment. The toxicity endpoint selected for the acute dietary exposure assessment was based on slightly increased number of resorptions and increased sternal and cranial variations at the 150 mg/kg/day LOAEL of the developmental toxicity study in rabbits. After evaluating all the information, HED concludes the 10X FQPA SF can be removed (reduced to 1X) for the following reasons:

- The developmental effects seen at the LOAEL of 150 mg/kg/day are slight and are mainly sternal variations in one or two fetuses, incomplete cranial development in 2 fetuses, and a slight increase in resorptions.

- The dose used for risk assessment is the NOAEL of 75 mg/kg/day, a clear NOAEL from the two developmental toxicity studies in rabbits. The use of this NOAEL for risk assessment is protective of the effects of concern seen in the developmental toxicity studies.

- There are no pre- or post-natal toxicity concerns for infants and children, based on the results of the rat and rabbit developmental toxicity studies or the 3-generation reproductive toxicity study in rats.

- There is no evidence of neurotoxicity in the submitted toxicity studies, there are no data gaps, and no additional special studies have been required.

3.3 Developmental Toxicity Studies

Ethalfluralin does not produce developmental effects in rats at doses up to 1000 mg/kg/day, but systemic effects observed were decreases in maternal body weight gains and dark urine at doses ≥ 250 mg/kg/day. In a pilot study no maternal or fetoxicity was seen at doses from 10 to 150 mg/kg/day. Abortion was observed in another pilot study in 1/3 dams at 500 mg/kg/day. Subsequently, three full developmental toxicity studies were conducted using successively lower dose levels because of increased incidence of abortion found in all dose dams in the first study. In the one study, dams dosed at 500 mg/kg/day exhibited increased incidence of dwarf-like appearance, open eyelids, and cleft palate. In a second study conducted with dose levels of 75 and 250 mg/kg/day, a cluster of external findings was reported at 250 mg/kg/day. No external findings were seen in the 75 mg/kg/day group. A third study (MRID 00250596) was conducted using doses ranging from 25 to 300 mg/kg/day. A slight increase in the incidence of sternal variations and incomplete cranial development was seen in the 150 mg/kg/day groups. Although the increased incidence in sternal variation, incomplete cranial development, and resorption at 150 mg/kg/day appears to be slight, the presences of these suggest that ethalfluralin has the potential to induce malformation at doses of ≥ 150 mg/kg/day. Clear maternal effects were seen in the 300 mg/kg group characterized by increased incidence of abortion (5/20); decreased body weight gain; enlarged and fatty liver; decreased food consumption, increased resorptions, and increased liver weights. A decrease in food consumption, slight increase in abortion (1/20), and a slight increase in resorptions were seen in 150 mg/kg/day dams. Therefore, the maternal LOAEL and NOAEL were established at 150 mg/kg/day and 75 mg/kg/day, respectively. Evaluating all the results of these studies together, the developmental toxicity LOAEL was established as 150 mg/kg/day based on a slight increase in the incidence of sternal variations, cranial variations, incomplete cranial development, and of resorption; the developmental NOAEL was 75 mg/kg/day.

3.4 Reproductive Toxicity Study

In a three-generation reproduction study in Fischer 344 rats, the parental NOAEL was 12.5 mg/kg/day. The parental LOAEL of 37.5 mg/kg/day was based on depressed mean body weight gains in males in all generations. No treatment-related effects were noted on reproductive parameters and the NOAEL was 37.5 mg/kg/day or greater. In a seven-month multigeneration bridging study in Fischer 344 rats, the parental NOAEL was 20 mg/kg/day. The parental

LOAEL was 61 mg/kg/day, based on increased liver weights. No treatment-related effects were noted on reproductive parameters and the reproductive NOAEL was equal to or greater than 61 mg/kg/day.

Ethalfluralin did not produce reproductive effects in the 3-generation reproduction studies; the parental effects consisted of decreased body weight gains.

3.5 Additional Information from Literature Sources

Additional literature sources were not consulted for information related to ethalfluralin toxicity.

3.6 Hazard Identification and Toxicity Endpoint Selection

Based on the currently available toxicity data, use patterns and exposure data, the relevant toxicity endpoints and doses for risk assessment shown in Table 3.6 were selected. These endpoints were considered the most appropriate, sensitive, and health protective.

3.6.1 Acute Population Adjusted Dose (aPAD) - Females age 13-49

The dose for risk assessment is the NOAEL of 75 mg/kg/day, a clear NOAEL from two developmental toxicity studies conducted in rabbits. The use of this NOAEL for risk assessment is protective of the slight developmental effects seen in the rabbit developmental toxicity studies.

Study Selected: Oral developmental toxicity study in rabbits
MRID No.: 00250596
Dose and Endpoint for Risk Assessment: NOAEL = 75 mg/kg/day based on increased number of resorptions and increased sternal and cranial variations seen at LOAEL = 150 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: A developmental toxicity study in rabbits was used to select the dose and endpoint for establishing the acute reference (aRfD) dose of 0.75 mg/kg/day. The effects seen in the rabbit developmental study could be the result of a single dose, and therefore serve as appropriate endpoints for the subpopulation consisting of females 13-49. Standard uncertainty factors applied are the 10X intra-species and 10X interspecies factors. The acute population adjusted dose is the same as the acute reference dose.

3.6.2 Acute Population Adjusted Dose (aPAD) - General Population

No toxicological endpoint attributable to a single dose of ethalfluralin was identified as appropriate for any population subgroup except for females 13 to 49 years; therefore, there are no concerns for acute toxicity for the general US population, including infants and children.

3.6.3 Chronic Population Adjusted Dose (cPAD)

Study Selected: One-year oral toxicity study in dogs
MRID No.: 00260434 and 00262711
Dose and Endpoint for Risk Assessment: NOAEL = 4.0 mg/kg/day based on altered red cell morphology and urinary bilirubin seen at LOAEL = 20 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: The combined chronic/carcinogenicity study in rats was used to select the dose and endpoint for establishing the chronic reference dose (cRfD) of 0.04 mg/kg/day. The duration and route of exposure in the study are considered appropriate for assessing chronic dietary exposure and risk for ethalfluralin. The NOAEL selected from the dog study is protective of liver effects seen at higher doses in both the dog study and studies in rats and mice. The standard 100X uncertainty factor has been retained for chronic dietary exposure assessment. The chronic reference dose is 0.004 mg/kg/day, and the cPAD is the same since the FQPA SF was reduced to 1X.

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

Not applicable, since there are not residential uses for ethalfluralin.

3.6.5 Dermal Absorption

A study (MRID Nos. 00132820 and 00072180) with Rhesus monkeys indicated that 2.8% of a dermal dose was absorbed through the skin. This factor was used for estimated dermal exposure in the cancer risk assessment for occupational workers.

3.6.6 Dermal Exposure (Short-Term)

A 21-day dermal toxicity study in rabbits indicates no systemic toxicity at the limit dose of 1000 mg/kg/day. No toxicity endpoints for short-term dermal exposure were selected, and there is no short-term dermal risk associated with the proposed or existing uses. Since exposures associated with existing and proposed use patterns are short term in duration, no endpoints were selected for longer durations.

3.6.7 Inhalation Exposure (Short-Term)

Ethalfluralin has a low inhalation toxicity category (III). The maximum attainable concentration (gravimetric) was tested in an acute inhalation toxicity study, and no deaths occurred to exposed rats. Clinical signs included hypoactivity, dyspnea, ataxia, chromodacryorrhea, poor grooming, and yellow urine; these were reversible after 4 days (LC_{50} >0.94 mg/L; Toxicity Category III). This maximum attainable concentration is considered to be non-lethal. HED had previously concluded that a separate risk assessment was not required for inhalation exposure (*ad hoc* Hazard Identification Assessment Review Committee [HIARC], 3/4/99, W. Burnam).
HED continues to conclude that toxicity via the inhalation route of exposure is likely to be low; however, a screening level assessment was conducted for short-term inhalation exposure to occupational handlers.

Study Selected: 3-generation rat reproduction study

MRID No.: 00094784
Dose and Endpoint for Risk Assessment: NOAEL = 12.5 mg/kg/day based on decreased body weight gains in males of all generations seen at the LOAEL = 37.5 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: A 3-generation rat reproduction study was used to select the dose and endpoint for short-term inhalation exposure. The dose and endpoint selected are considered to provide a conservative screening-level assessment, since effects on body weight gains are protective for the liver effects seen at higher doses, and because ethalfluralin is known to have low toxicity via the inhalation route of exposure. An assumption of 100% inhalation absorption is used for route-to-route extrapolation.

3.6.8 Level of Concern for Margin of Exposure

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	Not Applicable	Not Applicable	Not Applicable
Inhalation	100	Not Applicable	Not Applicable

3.6.9 Recommendation for Aggregate Exposure Risk Assessments

At this time, there are no current or proposed residential uses for ethalfluralin. Therefore, aggregate risks consist of the dietary (food + water) pathway of exposure.

3.6.10 Classification of Carcinogenic Potential

The mouse carcinogenicity study showed no increase in tumor incidence. Liver effects, characterized by increase in ALP and focal hepatocellular hyperplasia, were found in the highest dose group. The chronic dog feeding study indicated hematological changes, elevated ALP, and siderosis of the liver in the high dose animals.

Ethalfluralin has been classified as a possible human carcinogen (Group C) by the CPRC (6/29/94 and 11/16/94). The decision was based on findings from a 2-year chronic carcinogenicity study in rats, showing an increased incidence of mammary gland fibroadenomas and combined adenomas/fibroadenomas in female rats. The CPRC recommended using the Q_1^* approach for risk assessment. The Q_1^* is 8.9×10^{-2} $(mg/kg/day)^{-1}$.

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

Table 3.6.11a. Ethalfluralin - Summary of Toxicological Doses and Endpoints for Use in Dietary Human Health Risk Assessments.

Exposure Scenario	Point of Departure	Uncertainty/ FQPA SFs	Population Adjusted Dose for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	A single dose effect relevant to the general US population including infants and children was not identified in the toxicity studies conducted with ethalfluralin.			
Acute Dietary (Females 13-49 years of age)	NOAEL = 75 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF= 1x	aPAD = 0.75 mg/kg/day	Rabbit Dev. Toxicity Study LOAEL = 150 mg/kg/day based on increased number of resorptions and increased sternal and cranial variations
Chronic Dietary (All Populations)	NOAEL = 4 mg/kg/day	UF_A = 10x UF_H =10x FQPA SF= 1x	cPAD = 0.04 mg/kg/day	Dog, Chronic Oral Toxicity Study LOAEL = 20 mg/kg/day based on altered red blood cell morphology and urinary bilirubin
Cancer (oral, dermal, inhalation)	$Q^* = 8.9 \times 10^{-2}$ $(mg/kg/day)^{-1}$ based on increased mammary gland fibro-adenomas & combined adenomas/fiboadenomas in female rats			Rat 2-year chronic/carcinogenicity study

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic).

Table 3.6.11b Summary of Toxicological Doses and Endpoints for Ethalfluralin for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal, Short-term durations (1 to 30 days)	Dermal risks are not of concern because no systemic effects were observed up to the limit dose (1000 mg/kg) in a dermal study.			
Inhalation, Short-term durations (1 to 30 days)	12.5 mg/kg/day	UF_H=10X UF_A=10X IA = 100%	LOC occupational = 100	3-Generation Reproduction study in Rats The LOAEL = 37.5 based on decreased body weight gains in males in all generations.
Cancer (oral, dermal, inhalation)	Q_1* = 8.9 x 10^{-2} $(mg/kg/day)^{-1}$ based on increased mammary gland fibro-adenomas and combined adenomas/fiboadenomas in female rats. [For the dermal route, a dermal absorption factor of 2.8% was used]			Rat, 2-year chronic/carcinogenicity study

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. N/A = not applicable. IA = inhalation absorption factor.

3.7 Endocrine disruption

The Environmental Protection Agency (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 recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use Federal Fungicide Insecticide and Rodenticide Act (FIFRA) and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

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

4.0 Dietary Exposure/Risk Characterization

4.1 Pesticide Metabolism and Environmental Degradation

4.1.1 Metabolism in Primary Crops

The Ethalfluralin RED Document concluded that the qualitative nature of the residue in beans and peanuts is understood. The major portion of the radioactivity was characterized as lignin, cellulose, and protein. The parent, ethalfluralin, was a minor residue. The terminal residue of concern in plants is ethalfluralin *per se*; the current tolerance expression for plants is adequate. Previously, a cucurbit metabolism study was considered outstanding and was required before plant metabolism could be considered fully understood. A cucumber study was subsequently submitted and the metabolism data requirement was determined to be fulfilled.

In 1995, the HED Metabolism Assessment Review Committee (MARC) concluded that the residue of concern for both tolerance and risk assessment purposes is ethalfluralin *per se*.

4.1.2 Metabolism in Rotational Crops

Field rotational crop studies are not required since no residues of concern were found at significant levels in rotational crops. Furthermore, tolerances for rotational crop commodities and plantback restrictions need not be established.

4.1.3 Metabolism in Livestock

The Ethalfluralin RED Document concluded that the qualitative nature of the residue in animals is adequately understood based on acceptable poultry and ruminant metabolism studies. The residue of concern in milk, eggs, and animal tissues is ethalfluralin *per se*. However, as a result of the low levels of radiolabeled residues found with exaggerated (200x) feeding levels, HED has waived requirements for animal feeding studies. It was also concluded that residues of ethalfluralin from up to a 10x dietary burden would not be quantifiable (<0.05 ppm). Therefore, according to 40 CFR §180.6 (a)(3), if there is no reasonable expectation of finite residues in livestock commodities, then no tolerances are needed for eggs, milk, fat, and meat byproducts of cattle, goats, hogs, horses, poultry, and sheep. Previously established ethalfluralin tolerances in edible livestock commodities have been revoked. In addition, the proposed uses do not result in the need for tolerances for ethalfluralin in livestock commodities.

4.1.4 Analytical Methodology

Adequate residue analytical methods are available for the purpose of tolerance enforcement. Two gas chromatograph (GC) methods, Methods I and II, both with electron capture detection (ECD) are listed in the Pesticide Analytical Manual (PAM, Vol. II, Section 180.416). Methods I and II are applicable for the analysis of ethalfluralin residues in/on plant and animal commodities, respectively. The limits of detection (LODs) are 0.01 and <0.01 ppm for methods I and II, respectively.

The methods for enforcement are adequate in light of the tolerance expression and have passed Agency validation. The method used in the dill and potato field trials is suitable for data collection.

4.1.5 Environmental Degradation

Based on laboratory studies, ethalfluralin is expected to dissipate by binding to soil particles and then degrading both aerobically and anaerobically. There are no major degradates detected; in laboratory studies, several minor degradates were identified, all of which retain the trifluromethyl phenolic ring structure. Freundlich Kads values ranged from 12 to 97 ml/g and in the field ethalfluralin did not leach. Laboratory metabolism half-lives in soil were 46 days for aerobic systems and 14 days for anaerobic systems. Ethalfluralin does not hydrolyze, but does photodegrade rapidly in water with a half-life of approximately 6 hours. The laboratory volatility study indicates this is not a major route of dissipation.

4.1.6 Pesticide Metabolites and Degradates of Concern

Ethalfluralin *per se* is the only compound of toxicological significance.

Plant metabolism studies were considered in which ethalfluralin, universally radiolabeled in the benzene ring, was applied to beans, peanuts, and cucumbers. In the beans and peanuts trials, the radiolabeled residue consisted of lignin, complex polar materials, and cellulose. In contrast, the cucumber study yielded 42% total radioactive residue (TRR) as 2,2,2-trifluoroacetamide in vines and 86% TRR (0.014 ppm) as 2,2,2-trifluoroacetamide in cucumbers. Ethalfluralin was 0% - 2% in these studies. The apparent difference in cucumber versus bean and peanut metabolism may be a reflection of different post-treatment intervals. At the time, the HED MARC concluded that the residue of concern for both regulatory (tolerance) and risk evaluation purposes is parent ethalfluralin only.

Table 4.1.6 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Ethalfluralin	Ethalfluralin
	Rotational Crop	Ethalfluralin	Ethalfluralin
Livestock	Ruminant	Not Applicable	Not Applicable
	Poultry	Not Applicable	Not Applicable
Drinking Water		Ethalfluralin	Not Applicable

4.1.7 Drinking Water Residue Profile

Tier II drinking water assessments for surface water for ethalfluralin were performed based on Index Reservoir settings. The maximum simulation, the 1-in-10 year peak value, used for acute dietary exposure, was calculated for the use on canola using a maximum application rate of 1.15 lb ai/A. The estimated drinking water concentration (EDWC) from this simulation was 11 ppb. The maximum simulation for chronic exposures, or the 1-in-10 probability yearly, was calculated for the use on dill, with a maximum application rate of 1.5 lb ai/A. The EDWC from this simulation was 0.4 ppb. For cancer risk assessment, the average of yearly means was estimated to be 0.2 ppb.

For ground water sources, the Tier I drinking water assessment predicted maximum EDWCs of 0.02 ppb for both acute and chronic exposure for the use on dill, with a maximum application rate of 1.5 lb ai/A. Table 4.1.7 summarizes the EDWC values. These values were used directly in the DEEM dietary risk assessments, the 11 ppb value in the acute assessment and the 0.4 ppb value in the chronic assessment.

For the cancer assessment, an anticipated residue value generated from the USDA PDP drinking water monitoring data was used; there were no residues detected in 1,253 samples analyzed from 2003 – 2005. The ½ LOD value of 23 ppt (0.023 ppb) was used directly in the dietary assessment. These data were considered to be appropriate to use for the cancer risk assessment for the following reasons: 1) application rates for both existing and proposed uses are similar; while peak drinking water estimates differ slightly from one crop to another, EFED's modeled drinking water numbers for the average of yearly means did not differ significantly by crop, supporting the notion that the existing monitoring data can support proposed uses; 2) the drinking water monitoring data were collected from a variety of states which include potential ethalfluralin use areas; 3) the lack of findings of detectable residues is supported by the modeled estimates and by the fate properties of ethalfluralin (e.g., 6-hour half-life for aqueous photolysis).

Table 4.1.7. Summary of Modeled Surface Water and Groundwater Concentrations for Ethalfluralin.

	Ethalfluralin	
	Surface Water Conc., ppb [a]	Groundwater Conc., ppb [b]
Acute	11	0.02
Chronic (non-cancer)	0.4	0.02
Chronic (cancer)	0.2	0.02

[a]From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on a 172.8 ha watershed draining into a 5.3 ha reservoir with a depth of 2.74 m.
[b]From the SCI-GROW model assuming K_{oc} values ranging form 32 – 180 mL/g and half lives ranging from 13 – 1000 days.

4.1.8 Food Residue Profile

Residue data submitted in support of the proposed uses have been evaluated in a memorandum dated 9/4/07 (DP Barcode No. D306146, D306147 and D333867; J.R. Tomerlin). The submitted

field trial data are adequate to support the proposed use pattern, and were conducted in accordance to the Agency's guidelines with respect to geographic representation.

Ethalfluralin residues in or on dill (fresh and dry) were less than the limit of quantitation (LOQ) of 0.05 ppm when ethalfluralin was applied according to the proposed use patterns. Likewise, the results from potato field trials show that ethalfluralin residues were below the lowest limit of method validation (LLMV) of 0.05 ppm for all treatments in potato tubers when the test substance was applied according to the proposed potato use pattern; further examination of the raw data (chromatograms) indicated that residues in potato tubers and processed fractions were below the calculated limit of detection (LOD) of 0.016 ppm. Field trials were supported by adequate storage stability data.

Regarding processed potato fractions, there was no evidence of concentration in any processed potato fraction; however, the residue profile for ethalfluralin suggests that concentration of residues is unlikely. Given that residues were not detected (i.e., were below the calculated LOD of 0.016 ppm), no concentration was assumed in the dietary assessment, and no additional potato processing data are required.

4.1.9 International Residue Limits

There are currently no Codex, Canadian, or Mexican Maximum Residue Limits (MRLs) for residues of ethalfluralin on dill or potato, therefore there are no international harmonization issues associated with this action.

4.2 Dietary Exposure and Risk

Acute and chronic dietary exposure and risk assessments were conducted using anticipated residues, proposed tolerances for dill and potato, 100 % crop treated, and included the direct incorporation of estimated drinking water concentrations into the DEEM-FCID™ model. For the cancer dietary (food + water) assessment, monitoring data from the USDA PDP were used for soybean, watermelon, and drinking water, and the LOD value of 0.016 ppm was used for potatoes. Risk estimates are summarized in Table 4.2.3.

4.2.1 Acute Dietary Exposure/Risk

Estimated dietary (food + water) exposure for females 13-49 years was 0.0006 mg/kg/day, equivalent to <1 % of the aPAD, at the 95th percentile of exposure, which is well below HED's level of concern for acute dietary risk (100 % PAD).

4.2.2 Chronic Dietary Exposure/Risk

The chronic non-cancer dietary analysis for ethalfluralin resulted in an exposure estimate of 0.00006 mg/kg/day for the U.S. population, or <1 % of the cPAD, which is below HED's level of concern. Similarly, the exposure estimate of 0.00013 mg/kg/day for the most exposed population subgroup, children 1 to 2 years, is <1 % of the cPAD, and therefore not of concern.

4.2.3 Cancer Dietary Risk

The risk estimate for chronic cancer dietary exposure (0.000022 mg/kg/day) to ethalfluralin for the U.S. population yields a cancer risk of 2×10^{-6}. Additional refinement with %CT estimates would lead to a lower estimate of dietary cancer risk. EPA generally considers cancer risks of 10^{-6} or less to be below the level of concern. The precision which can be assumed for cancer risk estimates is best described by rounding to the nearest integral order of magnitude on the log scale; for example, risks falling between 3.16×10^{-7} and 3.16×10^{-6} are expressed as 10^{-6}. Considering the precision with which cancer hazard can be estimated and the rounding procedure described above, cancer risk should generally not be assumed to exceed the benchmark level of concern of 10^{-6} until the calculated risk exceeds approximately 3×10^{-6}. Since the calculated cancer risk for ethalfluralin falls below this level, estimated cancer risk is considered to be below the level of concern.

Table 4.2.3. Results of Acute and Chronic Dietary (Food + Water) Exposure and Risk Estimates for Ethalfluralin.

Population Subgroup	PAD, mg/kg/day	DEEM-FCID	
		Exposure, mg/kg/day	% PAD
Acute Dietary Estimates 95th Percentile of Exposure			
Females 13 – 49 years old	**0.75**	**0.000604**	**< 1**
Chronic Dietary Estimates			
U.S. Population	0.04	0.000064	< 1
All infants (< 1 yr)	0.04	0.000099	< 1
Children 1-2 yrs	**0.04**	**0.000133**	**< 1**
Children 3-5 yrs	0.04	0.000124	< 1
Children 6-12 yrs	0.04	0.000085	< 1
Youth 13-19 yrs	0.04	0.000063	< 1
Adults 20-49 yrs	0.04	0.000054	< 1
Adults 50+ yrs	0.04	0.000053	< 1
Females 13-49 yrs	0.04	0.000051	< 1
Cancer Dietary Estimate			
U.S. Population	**Q_1* = 0.089**	**0.000022**	**2×10^{-6}**

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

For the acute and chronic non-cancer dietary assessments, anticipated residues from field trials were used; studies evaluated for the RED indicated residues were below the LOD of 0.01 ppm for dry bean, peanuts, dry peas, soy beans, and sunflower seed. Tolerance level residues were assumed for all other existing uses, and the proposed tolerances were used for dill and potato. For the cancer dietary exposure assessment, anticipated residues from the USDA Pesticide Data Program (PDP) were used for soybean, watermelon and drinking water. No residues were detected during monitoring of these commodities, and the ARs were based on nondetect

residues, estimated at ½ LOD. For the cancer assessment, an anticipated residue of the LOD of 0.016 ppm was used for potatoes. For all the dietary assessments, HED used the conservative assumption of 100 % crop treated.

5.0 Residential (Non-Occupational) Exposure/Risk Characterization

An assessment is not required, since there are no existing or proposed uses of ethalfluralin in residential settings.

5.1 Other (Spray Drift, *etc*.)

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

6.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. For ethalfluralin, no residential exposure is expected, and aggregate risk consists of food and drinking water exposure only; these risks are not of concern as indicated in Table 4.2.3.

7.0 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 ethalfluralin and any other substances and ethalfluralin does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that ethalfluralin 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 (OPP) 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/.

8.0 Occupational Exposure/Risk Pathway

Exposure to ethalfluralin is expected to occur for occupational handlers applying products containing the active ingredient in accordance with the proposed use pattern. For handlers, inhalation exposure and risk were estimated for non-cancer effects, and combined dermal and inhalation exposures were assessed for cancer risks. No chemical-specific data were submitted to support the proposed uses, so handler risks were calculated by using the proposed application rates and application parameters to determine unit exposures from the Pesticide Handlers Exposure Database (PHED).

Post-application exposure is also expected, when occupational workers re-enter treated areas to conduct crop maintenance activities. These exposures are considered to be short-term in nature. Since there is no non-cancer risk associated with short-term dermal exposure, only a cancer risk assessment was completed for occupational post-application.

8.1 Short-Term and Cancer Handler Risk

Based upon the proposed use patterns, HED believes the most likely methods of application will be by ground-boom spray and granular broadcast machinery. Regarding the proposed new uses, HED further believes that the most highly exposed occupational pesticide handlers will be mixer/loaders using open-pour loading of liquid formulations, mixer/loaders using open-pour loading of granules, applicators using open-cab, ground-boom sprayers and applicators using open-cab, broadcast granular spreaders.

HED believes pesticide handlers will typically be exposed to short-term duration (1 - 30 days) exposures but not to intermediate-term (1 - 6 months) duration exposures. Although intermediate-term exposures might be possible for commercial applicators, it is considered unlikely that pesticide handlers would be exposed continuously for 30 days or more. Private (i.e., grower) applicators may perform all functions, that is, mix, load and apply the material. Nevertheless, according to guidance from HED's Exposure Science Advisory Committee (ExpoSAC; SOP Number 12, 3/29/00), handler functions were assessed separately.

No chemical specific data were 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). For pesticide handlers, it is HED practice to estimate dermal exposure for workers wearing "baseline" protective clothing, namely, a single layer of work clothing consisting of a long sleeved shirt, long pants, shoes plus socks and no protective gloves. Additionally, estimates are made for "baseline" plus protective gloves or other personal protective equipment (PPE) as might be necessary.

In addition to the PHED surrogate data used in the current assessment, HED used standard assumptions with respect to body weight, acres treated per day, and maximum application rates.

In conducting dermal and inhalation cancer risk assessments, HED typically assumes 10 days per year of exposure over a 35 year "working" lifetime and a 70 year expected lifespan for private growers who might apply/handle a compound or perform agricultural functions. HED assumes 30 days per year of exposures for commercial occupational pesticide handlers and agricultural

workers who might "follow" crops as opposed to occasional exposure from work on one or few farms by "private" individuals. (Pers. Comm. J. Dawson to M. Dow, HED/OPP, 4 April 2005). The Lifetime Average Daily Dose (LADD) is calculated as shown in the following equation:

$$LADD = ADD \times \frac{\text{10 (or 30) working days exposed/year x 35 year working life span}}{\text{365 days/year x 70 year expected life span}}$$

The Average Daily Dose (ADD) is the sum of dermal exposure + inhalation exposure. Post-application inhalation exposure is considered negligible. The label requires the use of protective gloves by occupational pesticide handlers, therefore exposures were estimated only for handlers wearing protective gloves. The cancer risk estimates were below the level of concern for occupational cancer risk (1×10^{-4}).

Table 8.1a. Short-Term Occupational Exposure Estimates for Ethalfluralin.

Exposure Scenario (Scenario #)	Crop	Daily Dermal Dose (mg/kg/day)	Daily Inhalation Dose (mg/kg/day)	Dermal MOE	Inhalation MOE
Mixer/Loader					
Liquid, Open-pour	Canola, Dill and Potato	0.0028	0.0051	N/A	2450
Granular, Open-pour		0.00081	0.0051	N/A	2450
Applicator					
Groundboom, Open cab	Canola, Dill and Potato	0.0017	0.0032	N/A	3900
Granular Broadcast, Open cab		0.00083	0.0051	N/A	2450
All estimates assume baseline PPE plus gloves.					

Table 8.1b Estimates of Occupational Cancer Risk for Ethalfluralin

Crop or Target	Exposure Scenario	Application Rate (lb ai/acre)	Area Treated Daily (acres)	Short-Term Dermal + Inhalation mg/kg/day	Cancer Risk	
					Private Handler	Commercial Handler
Canola, Dill and Potato	Mixer/Loader Liquid, Open pour	1.5	200	0.0079	9.6×10^{-6}	2.9×10^{-5}
	Mixer/Loader Granular, Open pour	1.5	200	0.0059	9.8×10^{-6}	1.8×10^{-5}
	Applicator Groundboom, Open Cab	1.5	200	0.0049	5.9×10^{-6}	2.2×10^{-5}
	Applicator Granular Broadcast, Open Cap	1.5	200	0.0059	7.2×10^{-6}	4.4×10^{-5}

8.2 Cancer Postapplication Risk

It is possible for agricultural workers to have post-application exposures to pesticide residues during the course of typical agricultural activities. HED in conjunction with the Agricultural Re-entry Task Force (ARTF) has identified a number of post-application agricultural activities that may occur and which may result in post-application exposure to pesticide residues. HED has also identified Transfer Coefficients (TC) (cm²/hr) for each activity which express the amount of foliar contact over time, during each of the activities identified**.** For the proposed new crop use sites, the highest TC is 1,500 cm^2/hr for scouting or irrigation activities in canola and potato. Therefore, as a screening level assessment HED has used a TC of 1,500 cm²/hr.

Lacking compound specific dislodgeable foliar residue (DFR) data, HED typically assumes 20% of the application rate is available as DFR on day zero after application. This is adapted from the ExpoSAC SOP No. 003 (5/7/98, Revised 8/7/00).

The following convention may be used to estimate post-application exposure.

ADD mg/kg/day = DFR µg/cm^2 * TC cm^2/hr * hr/day * 0.001 mg/µg * 1/70 kg

and where:

Surrogate DFR = application rate * 20% available as dislodgeable residue * $(1\text{-}D)^t$ * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2 .

1.15 lbs ai/A * 0.20 * $(1\text{-}0)^0$ * 4.54 x 10^8 µg/lb * 2.47 x10^{-8} A/cm² = 2.58 µg/cm^2 , therefore,

2.58 µg/cm^2 * 1,500 cm^2/hr * 8 hr/day * 0.001 mg/µg * 0.028 (% dermal absorption) ÷ 70 kg bw = 0.012 mg/kg bw/day.

Estimated cancer risk from post-application exposures is 1.4 x 10^{-5}, which does not exceed HED's level of concern for occupational cancer risk.

9.0 Data Needs and Label Recommendations

9.1 Toxicology

None.

9.2 Residue Chemistry

None.

9.3 Occupational and Residential Exposure

None.

10.0 References:

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DP Num: 295884, J. Lin, 10/5/05
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DP Num: 333865, M. Dow, 12/7/06
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DP Num: 333868, C. Swartz, 10/19/07

Appendix A – Toxicity Profiles for Ethalfluralin

A.1. Toxicology Data Requirements.

Test		Technical	
		Required	**Satisfied**
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21/28-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	---
870.3465	90-Day Inhalation	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
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	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)	no	---
870.6200b	Chronic Neurotox. Screening Battery (rat)	no	---
870.6300	Develop. Neuro	no	---
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	yes

A2. Ethalfluralin Acute Toxicity Profile.

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity rats	00135189	LD50 >5000 mg/kg/	IV
870.1200 Acute dermal toxicity rabbit	00135189	LD50 >5000 mg/kg/	IV
870.1300 Acute inhalation toxicity rats	00135189	LC50> 0.94 mg/L	III
870.2400 Acute eye irritation rabbits	00135189	Moderate	II
870.2500 Acute dermal irritation rabbits	41613909	Moderate to severe	II
870.2600 Dermal sensitization guinea pigs	00094788	sensitizer	--

A.3. Ethalfluralin Subchronic, Chronic and Other Toxicity Profile.

A.3. Subchronic, Chronic and Other Toxicity Table.		
Guideline No. Study Type	MRID No./(year) Classification/Doses	Results
870.3100 90-Day Oral Toxicity, mice	0094774 (1978) Acceptable 0, 68, 136, 285, 538, 1205 mg/kg/day	NOAEL = 136 mg/kg/day LOAEL = 285 mg/kg/day based on increased absolute and relative liver weights and increased ALP in males.
870.3100 90-Day Oral Toxicity, rats	00135191 (1978) 0, 14, 29, 63, 146, 313 mg/kg/day	NOAEL = 29 mg/kg/day LOAEL = 63 mg/kg/day based on increased liver weights (absolute and relative), decreased RBC, hematocrit and hemoglobin, and increased relative kidney weights
870.3150 90-Day Oral Toxicity, dogs	00135193 (1974) Acceptable 0, 6.3, 27.5, 125 mg/kg/day Note – dose of 125 later adjusted to 80 mg/kg/day	NOAEL = 80 mg/kg/day LOAEL = 125 mg/kg/day based on vomiting and anorexia.
870.3200 21-Day dermal toxicity, rabbits	00145767 (1985) Acceptable/guideline 0, 1000 mg/kg/day (6 hours/day)	NOAEL=1000 mg/kg/day (HDT) LOAEL= >1000 mg/kg/day; no systemic effects were seen at the HDT. Dermal effects included erythema, edema, and epidural fissures at 1000 mg/kg/day.
870.3700 Prenatal developmental toxicity, rats	0015337 (1985) Acceptable 0, 50, 250, 1000 mg/kg/day	Maternal NOAEL=50 mg/kg/day Maternal LOAEL=250 mg/kg/day based on decreased body weight gain and dark urine. Developmental NOAEL=1000 mg/kg/day Developmental LOAEL>1000 mg/kg/day, no effects seen at the HDT.

A.3. Subchronic, Chronic and Other Toxicity Table.		
Guideline No. Study Type	MRID No./(year) Classification/Doses	Results
870.3700 Prenatal developmental toxicity, rabbits	00250596 (1983) [Includes Pilot studies – R-7048, B-7438, B-7079, B-7160] Doses ranged from 0, 10 – 1000 mg/kg/day Taken in total, the studies are acceptable.	Maternal NOAEL=75 mg/kg/day Maternal LOAEL=150 mg/kg/day based on abortions and decreased food consumption. Developmental NOAEL=75 mg/kg/day Developmental LOAEL=150 mg/kg/day based on slightly increased resorptions, and increased sternal and cranial variations.
870.3800 Reproduction and fertility effects, rats	0094784 (1981) 0, 5, 12.5, 37.5 mg/kg/day 42300301 (1992) 0, 8, 20, 61 mg/kg/day The 2 studies together are acceptable.	Parental/Systemic NOAEL=12.5 mg/kg/day Parental/Systemic LOAEL=37.5 mg/kg/day based on decreased body weight gains in males of all generations. Reproductive NOAEL=37.5 mg/kg/day (HDT) Reproductive LOAEL>37.5 mg/kg/day; no systemic effects observed at the highest dose tested.
870.4100a Chronic toxicity, rats	00094775 (1979) Acceptable M: 0, 3.9, 9.7, 28.4 mg/kg/day F: 0, 4.9., 11.9, 34.4 mg/kg/day	NOAEL=9.7/11.9 mg/kg/day LOAEL=28.4/34.4 mg/kg/day based on significant increased blood creatinine and BUN values at termination.
870.4100a Chronic toxicity, mice	0009477 (1981) Acceptable, Nonguideline M: 0, 12, 47, 173 mg/kg/day F: 0, 12, 49, 184 mg/kg/day	NOAEL=12 mg/kg/day LOAEL=47/49 mg/kg/day based on increased ALP and increased relative liver weights.
870.4100b Chronic toxicity, dogs	00153371, 92062014 (1985) Acceptable 0, 4, 20, 80 mg/kg/day	NOAEL=4 mg/kg/day LOAEL= 20 mg/kg/day based on increased urinary bilirubin, variations in erythrocyte morphology, increased thrombocyte count, and increased erythroid series of the bone marrow.
870.4300 Combined chronic toxicity/carcinogenicity, rats	00094776 (1981) 92062013 (1981) Acceptable 0, 4.2, 10.7, 32.2 mg/kg/day	NOAEL=32.2 mg/kg/day(HDT) LOAEL=>32.2 mg/kg/day; no systemic effects were seen at the HDT. Mammary gland fibroadenomas were found in dosed female rats at statistically significant incidences in mid and high doses.
870.4300 Combined chronic toxicity/carcinogenicity in mice	00094777 (1981) 92062016 (1981) Acceptable 0, 10.3, 41.9, 163.3 mg/kg/day	NOAEL=10/3 mg/kg/day LOAEL=41.9 mg/kg/day based on focal hepatocellular hyperplasia in both sexes and

A.3. Subchronic, Chronic and Other Toxicity Table.		
Guideline No. Study Type	MRID No./(year) Classification/Doses	Results
		increased liver, kidney, and heart weights in females. No increase in neoplasms was attributed to the treatment.
870.5100 Bacterial reverse mutation test	00128693 (1983) 00128694 (1983) Acceptable	Ethalfluralin was weakly mutagenic in activated strains TA1535 and TA100 of Salmonella typhimurium, but not in strains TA1537, TA1538 and TA98 in an Ames assay. In a modified Ames assay with Salmonella typhimurium and Escherichia coli, ethalfluralin was weakly mutagenic in strains TA1535 and TA100, with and without activation, and in strain TA98 without activation, at the highest dose.
870.5300 In vitro mammalian cell mutation test	00128696 (1983) Acceptable	No mutagenicity was found in the mouse lymphoma assay for forward mutation.
870.5550 Unscheduled DNA synthesis in mammalian cells in culture	00128695 (1980) Acceptable	Ethalfluralin did not induce unscheduled DNA synthese in rat hepatocytes.
870.5375 In vitro mammalian chromosome aberration test	00152219 (1985) Acceptable	In Chinese hamster ovary cells, ethalfluralin was negative without S9 activation, but it was clastogenic with activation.
870.7485 Metabolism and pharmacokinetics	42822901 (1993) Acceptable	Rats were treated orally with a single low dose, a single high dose, or repeated low doses of radiolabeled ethalfluralin. Absorption of ethalfluralin was estimated at 79-87% of the dose for all dose levels. Ethalfluralin was rapidly and extensively metabolized, and 95% of the chemical was excreted in the urine and feces by seven days. The major route of elimination for the radiolabel was in the feces, 50.9-63.2%, and the levels remaining in the tissues after 72 hours were negligible.
870.7600 Dermal penetration	00132820 (1982) Acceptable	A dermal penetration study with rhesus monkeys indicated that 2.7% of a dermal dose was absorbed through the skin.