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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 6-JUN-2001

SUBJECT: PP#: 8F04954. **MESOTRIONE IN/ON FIELD CORN. Health Effects Division (HED) Risk Assessment.** PC Code: 122990. DP Barcode: D260267. Case #: 289589. Submission #: S569871.

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The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed uses of mesotrione [2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione] (designated by the company code ZA1296) in/on field corn. This is the first food use request for mesotrione.

A summary of the findings and an assessment of human risk resulting from the proposed uses of mesotrione is provided in this document. The risk assessment, the residue chemistry data review, and the dietary risk assessment were provided by Sarah Levy (RAB1), the hazard characterization by David Nixon (RAB1), the occupational/residential exposure assessment by Dana Vogel (RAB1), and the drinking water assessment by Alex Clem of the Environmental

Fate and Effects Division (EFED).

Recommendation for Tolerances and Registration

Provided that the petitioner submits revised Sections B and F and a successful Agency petition method validation (PMV) of the analytical method is reported, the residue chemistry and toxicological databases support a conditional registration and permanent tolerances for residues of mesotrione [2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione] *per se* in/on the following raw agricultural commodities (RACs):

Corn, field, grain	0.01 ppm
Corn, field, forage	0.01 ppm
Corn, field, stover	0.01 ppm

HED recommends that conversion of conditional registration to unconditional registration may be considered upon submission of the following data:

Chemistry

- Adequate storage stability data in the plant and livestock metabolism studies.
- Revised interference study.

Toxicology

- Developmental neurotoxicity (DNT) study in the mouse. (A DNT study is required in the mouse in order to better characterize the effects of tyrosinemia on the developing nervous system and to correlate plasma tyrosine levels to neurotoxic effects.)
- 28-day inhalation study.

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1.0 EXECUTIVE SUMMARY

Mesotrione is a triketone herbicide that inhibits the enzyme p-hydroxyphenylpyruvate dioxygenase (HPPD), disrupting carotenoid biosynthesis. This process leads to the destruction of chlorophyll, resulting in a bleaching effect in susceptible plants. Mesotrione is intended for preemergence and postemergence use for selective control of annual broadleaf weeds. There are no existing tolerances, uses, or exemptions for mesotrione. The field corn petition represents the first proposed use for mesotrione. There are currently no registered or proposed residential uses of mesotrione.

Hazard Assessment

Mesotrione has low acute toxicity via the oral, dermal, and inhalation routes. It is a mild eye irritant, but is not a dermal irritant or a dermal sensitizer. In subchronic and chronic oral studies, ocular lesions, liver and kidney effects, and/or body weight decrements were the major adverse effects seen in the rat, mouse, and dog. Plasma tyrosine levels were increased in the rat, mouse and dog in the chronic and reproduction studies in which levels were measured. The ocular, liver and kidney effects are believed to be mediated by the high tyrosine levels in the blood caused by inhibition of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD). Even though the rat is the most sensitive species to this effect compared to the dog and the mouse, the Mechanism of Toxicity Science Assessment Review Committee (SARC) concluded that the mouse is a more appropriate model for assessing human risk than is the rat. There was no evidence of carcinogenic potential in either the rat chronic toxicity/carcinogenicity or mouse carcinogenicity studies and no concern for mutagenicity. No evidence of neurotoxicity or neuropathology was seen in the acute and subchronic neurotoxicity studies. In the multi-generation mouse reproduction study, one F_1 male and one F_1 female had retinal detachment with marked cataractous changes at the highest dose tested (>1000 mg/kg/day). In the subchronic toxicity dog study, the high-dose females had decreased absolute and relative brain weights; however, no microscopic abnormalities were noted in any brain tissue from the high-dose group and the effect was not observed in the chronic toxicity dog study. Therefore, there is some concern about the effects of elevated plasma tyrosine levels on the developing nervous system in children due to a report by Ruetschi *et al* (2000)[1] that some patients with tyrosinemia III (an autosomal recessive disorder in which HPPD is deficient) were presented with mental retardation or neurological symptoms. There was evidence of increased susceptibility of rats, mice and rabbits to *in utero* and/or post-natal exposure to mesotrione.

[1] Ruetschi, U., et.al., (2000) Mutations in the 4-hydroxyphenylpyruvate dioxygenase gene (HPD) in patients with tyrosinemia type III. Hum. Genet. 106(6): 654-662.

Dose Response Assessment

The HED Hazard Identification Assessment Review Committee (HIARC) met on March 13, 2001 to select endpoints for risk assessment and to evaluate the potential for increased susceptibility of infants and children from exposure to mesotrione. The Food Quality Protection Act (FQPA) Safety Factor Committee (SFC) met on April 16, 2001 to evaluate the hazard and exposure data for mesotrione and recommended that the FQPA safety factor be retained (10x) in assessing the potential risk posed by this chemical.

No appropriate endpoint was available to quantitate risk to the general U.S. population or to females 13-50 years old from a single-dose administration of mesotrione. Therefore, there is no acute reference dose (aRfD) or acute population adjusted dose (aPAD). The short-term incidental oral endpoint is based upon decreases in body weight gain during treatment and decreases in food consumption. The short-term dermal and inhalation endpoints are based upon delays in skeletal ossification and changes in *manus/pes* (forepaws/hindpaws) ossification assessments seen in oral developmental studies. The chronic and intermediate-term endpoints for all routes of exposure are based upon tyrosinemia in adults and pups and ocular discharge in pups observed in a mouse reproduction study. The chronic RfD is 0.007 mg/kg/day and the chronic population adjusted dose (cPAD) is 0.0007 mg/kg/day. Mesotrione is classified as "not likely to be carcinogenic to humans" based upon lack of evidence of carcinogenicity in rats and mice. Therefore, a cancer risk assessment is not required. Since oral studies were selected for all durations of dermal and inhalation exposure, a 25% dermal-absorption factor (based on comparison of rabbit oral developmental study and rabbit dermal study) and a 100% inhalation-absorption factor (relative to oral absorption) were used in the route-to-route extrapolation.

FQPA Decision

The FQPA SFC recommended that the 10x safety factor to account for enhanced sensitivity of infants and children *be retained* for the general U.S. population and all population subgroups and scenarios (HED Document Number 014552, B. Tarplee, 30-APR-2001). Consequently, the cPAD value is 0.0007 mg/kg/day. This decision was based on quantitative evidence of increased susceptibility demonstrated in the oral prenatal developmental toxicity studies in rats, mice, and rabbits and in the multi-generation reproduction study in mice. Quantitative evidence of increased susceptibility was not demonstrated in the multi-generation reproduction study in rats since no no-observed-adverse-effect-level (NOAEL) was established for parental or offspring systemic toxicity. However, there is evidence of a qualitative increase in susceptibility since the tyrosinemia observed in the young was much more severe than that observed in the adults.

Occupational Exposure Estimates

The proposed use of the herbicide Callisto™, a suspension concentrate (SC) formulation containing 40% of the active ingredient (a.i.), mesotrione, is for pre- and postemergence control of broadleaf weeds in field corn. Mesotrione may be applied either by ground sprayers or by aerial application up to corn height of 30 inches tall. A maximum of two applications per season and 0.43 lbs a.i./A/season are proposed. For preemergence application, Callisto™ is proposed for use at 0.188-0.24 lbs ai/A by groundboom. In a single postemergence application, 0.094 lbs a.i./A should not be exceeded.

In the case of mesotrione, the short-term dermal endpoint [rat developmental endpoint (LOAEL = 100 mg/kg/day)] is appropriate for the 0 to 30 day exposure period since it provides protection for developmental effects seen below maternally toxic doses. For the proposed use of mesotrione, no longer than 30 days of exposure is expected for both private and commercial handlers.

Based on the proposed use patterns, short-term dermal and inhalation exposures are expected for private applicators (farmers treating their own crops) and commercial applicators. Since no chemical-specific data are available to assess potential exposure to workers, the exposure and risk assessment presented in this document are based on the Pesticide Handler Exposure Database Version 1.1 (PHED, Surrogate Exposure Guide, August 1998). The maximum application rate listed on the label was used for all calculations. The standard values for acreage were taken from HED Exposure Science Advisory Committee (Expo SAC) Policy #09, effective 5-JUL-2000. Both the low and high number of acres treated per day were used to demonstrate a range of potential exposure. When wearing the label required personal protective equipment (PPE) (single layer of clothing and gloves), all Margins of Exposure (MOEs) are below HED's level of concern.

Workers having potential re-entry exposure to mesotrione from the proposed use include scouts and workers re-entering treated fields to perform irrigation tasks. Since mesotrione will be applied at the early stages of crop growth (pre- or post-emergent), low potential for post-application exposure is expected. In order to demonstrate that minimal exposure and risk are expected, a post-application exposure assessment was done for scouts. The estimated MOE for scouting activities related to the proposed use of mesotrione on field corn do not exceed HED's level of concern.

Dietary Exposure Estimates

A chronic dietary exposure analysis was conducted using the Dietary Exposure Evaluation Model (DEEM™, ver 7.72), which utilizes consumption data from the USDA 1989-92 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). Acute and cancer dietary exposure analyses were not conducted since no acute doses or endpoints were selected for the general U.S. population (including infants and children) or the females 13-50 years old

population subgroup and mesotrione was classified as not a carcinogen, respectively. All mesotrione residues were <LOQ (0.01 ppm) in the crop field trials and there was no concentration of residues in the processing study. There is no reasonable expectation of finding finite mesotrione residues of concern in eggs, milk, or the meat, fat, or meat byproducts of poultry or ruminants as a result of the proposed uses on field corn [Category 180.6(a)(3)]. The following conservative assumptions were made for the chronic dietary analysis: HED-recommended tolerance level residues for field corn RACs, DEEM™ default processing factors for field corn commodities, and assuming all field corn RACs were 100% treated with mesotrione. The chronic dietary food exposure estimates were less than HED's level of concern (<100% cPAD) for the general U.S. population and all population subgroups (D274113, S. Levy, 17-MAY-2001). Specifically, the most highly exposed population subgroup was "all infants (<1 year old)" at 4.3% of the cPAD.

Drinking Water

The registrant has submitted (without request from the Agency) two interim reports on a prospective groundwater monitoring (PGM) study at a site in Michigan. However, until the studies are completed and submitted to the Agency, these data cannot be used. Since HED does not have ground or surface water monitoring data to calculate quantitative aggregate exposure, estimates of mesotrione levels in surface and ground water were made using computer modeling. The estimated environmental concentrations (EECs) for surface water [from GENEEC (Generic Environmental Concentration) modeling] are 20 ppb and 13 ppb for the acute and chronic (56-day) scenarios, respectively. Note that it is HED policy (HED SOP 99.5) to divide the 56-day surface water average by a factor of three. Therefore, the surface water EEC is 4.3 ppb (13 ppb/3 = 4.3 ppb). The EEC for ground water [from SCI-GROW (Screening Concentration in Ground Water) modeling] is 0.15 ppb to be used for both acute and chronic scenarios. All the EEC values are less than the lowest drinking water levels of concern (DWLOC) value of 6.7 ppb (specifically for the "all infants (<1 year old)", and "children 1-6 years old" subpopulations) determined for the chronic scenario, and therefore do not exceed HED's level of concern.

Exposure Scenarios and Risk Conclusions

For the proposed uses on field corn, human health risk assessments have been conducted for the following exposure scenarios: chronic dietary exposure (food only), aggregate chronic exposure (food and water), and short- and intermediate-term occupational exposure. Other scenarios were not evaluated for mesotrione since no acute doses or endpoints were selected for any population, it has not been classified as a carcinogen, no residential uses have been proposed at this time, and long-term occupational exposure is not expected. All exposure estimates are below HED's level of concern.

Recommendation for Tolerances and Registration

Provided that the petitioner submits revised Sections B and F and a successful Agency PMV of the analytical method is reported, the residue chemistry and toxicological databases support a conditional registration and permanent tolerances for residues of mesotrione [2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione] *per se* in/on the following RACs:

Corn, field, grain ..... 0.01 ppm
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HED recommends that conversion of conditional registration to unconditional registration may be considered upon submission of the following data:

Chemistry

- Adequate storage stability data in the plant and livestock metabolism studies.
- Revised interference study.

Toxicology

- DNT study in the mouse. (A DNT study is required in the mouse in order to better characterize the effects of tyrosinemia on the developing nervous system and to correlate plasma tyrosine levels to neurotoxic effects.)
- 28-day inhalation study.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1 Identification of Inert Ingredient

- Chemical Name: [2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione]
- Common Name: Mesotrione (designated by the company code ZA1296)
- Chemical Type: Herbicide
- PC Code Number: 122990
- CAS Registry No.: 104206-82-8
- EPA File Symbol No. 100-RRGR
- Empirical Formula: $C_{14}H_{13}O_7NS$
- Molecular Weight: 339.9 g/mol

2.2 Structural Formula

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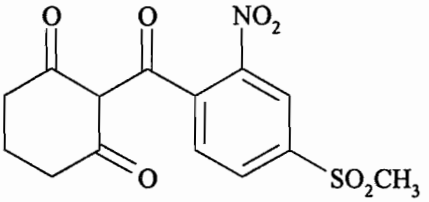
2.3 Physical and Chemical Properties



The following data for mesotrione were taken from the product chemistry review conducted by RD (D263245, H. Podall, 24-FEB-2000) (note that all property values are given at 20°C):

- Vapor Pressure: 4.3×10^{-8} torr
- Water Solubility: 160 ppm in unbuffered water; 0.22 g/100 mL at pH 4.8; 1.5 g/100 mL at pH 6.9; and 2.2 g/100 mL at pH 9
- Partition Coefficient (Octanol/Water): $\log P_{ow} = 0.11$ in unbuffered water; $\log P = 0.90$ in pH 5 buffer; and $\log P < -1$ at pH 7 and 9 buffered water
- Melting Point Range: 148.7-152.5°C
- Relative Density: 1.46 g/ml

Mesotrione is a solid at room temperature with a low vapor pressure; thus, any losses due to volatilization/sublimation are expected to be minimal.

3.0 HAZARD CHARACTERIZATION

The existing toxicological database for mesotrione supports the establishment of permanent tolerances for residues of mesotrione *per se* in/on corn RACs resulting from the proposed use on field corn.

3.1 Hazard Profile

Mesotrione is a triketone herbicide with a primary mode of action that inhibits the enzyme HPPD, an enzyme that is integral in the catabolism of tyrosine in animals, and humans. The toxicology database for mesotrione is *not* complete; however, it is adequate for a conditional registration. The HIARC recommended that a DNT study be required in order to better characterize the effects of tyrosinemia on the developing nervous system and to correlate plasma tyrosine levels to neurotoxic effects. The HIARC also requested a 28-day inhalation study to characterize the direct effects of mesotrione on the pulmonary system and systemic effects via the inhalation route. Mesotrione has low acute toxicity via the oral, dermal, and inhalation routes. It is a mild eye irritant, but is not a dermal irritant or a dermal sensitizer.

The eye, liver, and kidney are the primary target organs of mesotrione. Ocular effects such as corneal opacity, corneal vascularization, and keratitis were observed in the rat in subchronic, chronic, and reproduction studies and in the dog in a chronic study. Lenticular opacity was also noted in the chronic dog study. Ocular effects were observed in mice in the reproduction study.

Liver effects included increased liver weights seen in the rat subchronic, chronic, and reproduction studies and hepatocyte fat vacuolation noted in the rat chronic study. Kidney effects included increased kidney weights observed in the rat subchronic and chronic studies and in the rat and mouse reproduction studies, and hydronephrosis noted in the rat subchronic and reproduction studies. Body weight decrements and/or decreased food efficiency were noted in the mouse chronic and carcinogenicity studies and the rat developmental study.

Plasma tyrosine levels were increased in the rat, mouse and dog in the chronic and reproduction studies in which levels were measured. The ocular, liver and kidney effects are believed to be mediated by the high tyrosine levels in the blood caused by inhibition of the enzyme HPPD. The rat is the most sensitive species to this effect compared to the dog and the mouse. The Mechanism of Toxicity SARC determined that for tyrosine-mediated toxicological effects, the mouse is a more appropriate model for assessing human risk than is the rat. This decision was based on comparative data on the activity of tyrosine aminotransferase (TAT) in the rat, mouse and human, and the similarities of the response to elevated plasma tyrosine levels in humans and the mouse (D272633; 27-MAR-2001).

Long-term dietary administration of mesotrione did not result in an overall treatment-related increase in incidence of tumor formation in rats or mice. The HIARC classified mesotrione as "not likely to be carcinogenic to humans" by all routes of exposure based upon lack of evidence of carcinogenicity in rats and mice.

Mesotrione did not show evidence of mutagenicity in *in vitro* or *in vivo* studies.

Oral rat, mouse, and rabbit developmental studies showed an increased susceptibility of the fetus to mesotrione *in utero*. Delayed ossification was seen in the fetuses at doses below those at which maternal toxic effects were noted. The maternal toxic effects were decreased body weight gain during treatment, decreased food consumption, abortions, and gastrointestinal (GI) effects in both the rat and rabbit. No maternal toxic effects were noted in the mouse. Multi-generation reproduction studies also showed an increased susceptibility of the young to mesotrione. In the mouse, the young exhibited significant tyrosinemia and ocular discharge at doses below those at which parental toxic effects were noted. The parental effects were tyrosinemia and increased kidney weights. In the rat, no NOAEL was determined for parental effects (tyrosinemia, increased liver weights) or offspring systemic effects (tyrosinemia); however, the tyrosinemia was much more severe in the young than in the adults. Decreased litter size was noted at the next highest dose.

No evidence of neurotoxicity or neuropathology was seen in the acute and subchronic neurotoxicity studies. In the multi-generation mouse reproduction study, one F_1 male and one F_1 female had retinal detachment with marked cataractous changes at the highest dose tested (>1000 mg/kg/day). In the subchronic toxicity dog study, the high-dose females had decreased absolute and relative brain weights; however, no microscopic abnormalities were noted in any brain tissue from the high-dose group and the effect was not observed in the chronic toxicity dog

study. Therefore, there is some concern about the effects of elevated plasma tyrosine levels on the developing nervous system in children due to a report by Ruetschi *et al* (2000) that some patients with tyrosinemia III (an autosomal recessive disorder in which HPPD is deficient, resulting in high plasma tyrosine levels) were presented with mental retardation or neurological symptoms and that no correlation of the severity of the mutation and enzyme deficiency and mental function has been found. Also, tyrosine levels did not correlate with the clinical phenotype.

A series of rat metabolism studies with [^{14}C-aromatic]mesotrione indicated that mesotrione was readily absorbed and distributed in the body. Tissue distribution was about the same in both sexes, although one study showed higher residues in the kidneys in females, with the highest residues of the test compound in the liver and kidney. Higher doses resulted in higher residues in the liver and kidney, while repeated doses resulted in reduced accumulation of residues in all tissues. Levels of radioactivity in tissues of iv-dosed animals were essentially the same as in orally-dosed animals. Over 50% of the administered dose was excreted in the urine in both sexes and around 25% was excreted in the feces within 72 hours. Females exhibited slightly higher total urinary excretion than males, but total fecal excretion was about the same in both sexes. Increasing the dose or repeated doses had little effect on the pattern of excretion in both sexes. The overall pattern of excretion was similar between orally-dosed and iv-dosed rats. The metabolite profile was similar between the sexes in each group and between the single-dosed and repeated-dosed animals. The parent compound, mesotrione, was the major component identified in the urine accounting for 47-64% of the dose. In addition, the following minor metabolites were identified: MNBA (4-(methylsulfonyl)-2-nitrobenzoic acid) (1-4% of the dose), AMBA (2-amino-4-(methylsulfonyl)benzoic acid) (3-12%), 5-hydroxymesotrione ($\leq$ 2%), and 4-hydroxymesotrione (3-6%). In bile cannulated rats administered [^{14}C-aromatic]mesotrione or [^{14}C-dione]mesotrione, the major component in fecal excreta and bile was the parent compound. Analysis of the bile identified mesotrione and 4-hydroxymesotrione as two minor components. Another minor component in the feces was 5-hydroxymesotrione. Metabolism in the mouse was very similar to the rat except that males had slightly increased total fecal excretion when compared to females and, females in the low-dose group excreted higher (1.5x) levels of parent compound in the urine than males. Free mesotrione was the major component in the urine and feces ($\geq$ 50% of the dose). Minor components in the fecal extracts included AMBA (1-4%) and MNBA ($\leq$ 2%).

Table 1. Acute Toxicity of MESOTRIONE Technical.

Guideline No./Study Type	MRIDs	Results	Tox Category
870.1100 Acute Oral	44373512	LD_{50} > 5000 mg/kg	IV
870.1200 Acute Dermal	44373514	LD_{50} > 2000 mg/kg	III

870.1300 Acute Inhalation	44373516	LC_{50} > 4.75 mg/L	IV
870.2400 Primary Eye Irritation	44373518	Mild eye irritant	IV
870.2500 Primary Skin Irritation	44373520	Not a dermal irritant	IV
870.2600 Dermal Sensitization	44373522	Not a dermal sensitizer	N/A

Table 2. Toxicity Profile of Mesotrione Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents (rat)	44505020 (1997) Acceptable/guideline 0, 2.5, 5, 7.5, or 150 ppm M: 0, 0.21, 0.41, 0.63, or 12.46 mg/kg/day F: 0, 0.23, 0.47, 0.71, or 12.46 mg/kg/day	NOAEL = 0.41/0.47 mg/kg/day (M/F) LOAEL = 0.63/0.71 mg/kg/day (M/F), based upon corneal lesion in males
870.3100 90-Day oral toxicity rodents (rat)	44505019 (1995) Acceptable/guideline 0, 1, 125, 1250, or 12500 ppm M: 0, 0.09, 11, 112, or 1111 mg/kg/day F: 0, 0.10, 13, 126, or 1213 mg/kg/day	NOAEL = 0.09/0.10 mg/kg/day (M/F) LOAEL = 11/13 mg/kg/day (M/F), based upon corneal abnormalities in both sexes and decreased body weight gain in males
870.3100 90-Day oral toxicity rodents (mouse)	44505022 (1997) Acceptable/guideline 0, 10, 50, 350, or 7000 ppm M: 0, 1.7, 8.4, 61.5, or 1212 mg/kg/day F: 0, 2.4, 12.4, 80.1, or 1537 mg/kg/day	NOAEL = 1212/1537 mg/kg/day (M/F) LOAEL > 1212/1537 mg/kg/day (M/F) No effects noted
870.3150 90-Day oral toxicity nonrodents (dog)	44505023 (1997) Acceptable/guideline M & F: 0, 100, 600, or 1000 mg/kg/day	NOAEL = 1000 mg/kg/day (M/F) LOAEL > 1000 mg/kg/day (M/F) No effects noted

Table 2. Toxicity Profile of Mesotrione Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3200 21/28-Day dermal toxicity (rabbit)	44505024 (1997) Acceptable/guideline M & F: 0, 10, 500 or 1000 mg/kg/day	NOAEL = 1000 mg/kg/day (M/F) LOAEL > 1000 mg/kg/day (M/F) No systemic effects noted
870.3250 90-Day dermal toxicity	NA	NA
870.3465 90-Day inhalation toxicity	NA	NA
870.3700a Prenatal developmental rodents (rat)	44505023 (1997) Acceptable/guideline F: 0, 100, 300, or 1000 mg/kg/day	**Maternal** NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day, based upon decreased maternal body weight gains during treatment and decreased food consumption **Developmental** NOAEL not established LOAEL = 100 mg/kg/day, based upon delays in skeletal ossification and changes in *manus/pes* ossification assessments
870.3700a Prenatal developmental rodents (mouse)	44920802 (1997), 44901708 (1999) Acceptable F: 0, 10, 60, 150, or 600 mg/kg/day	**Maternal** NOAEL = 600 mg/kg/day LOAEL > 600 mg/kg/day; No effects noted **Developmental** NOAEL = 150 mg/kg/day LOAEL = 600 mg/kg/day, based upon decreased ossification of the cervical vertebrae centra

Table 2. Toxicity Profile of Mesotrione Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700b Prenatal developmental nonrodents (rabbit)	44901707 (1999), 44505032 (1999) Unacceptable/not upgradable F: 0, 100, 250, or 500 mg/kg/day	**Maternal** NOAEL = 100 mg/kg/day LOAEL = 250 mg/kg/day based upon abortions and clinical signs of toxicity **Developmental** NOAEL not established LOAEL = 100 mg/kg/day based upon delayed ossification of the 7th cervical transverse process and odontoid and increases in extra full 13th rib and 27 pre-sacral vertebra
870.3800 Reproduction and fertility effects (rat)	44505033 (1997) Acceptable/guideline 0, 2.5, 10, 100 or 2500 ppm M: 0, 0.3, 1.1, 11.7, or 287.7 mg/kg/day F: 0, 0.3, 1.2, 12.4, or 311.4 mg/kg/day	**Parental/Systemic** NOAEL not established LOAEL = 0.3 mg/kg/day (M/F), based upon significantly increased plasma tyrosine levels and increased liver weights in F_2 males **Offspring/Systemic** NOAEL not established LOAEL = 0.3 mg/kg/day (M/F), based upon significantly increased plasma tyrosine levels in F_2 male pups **Reproductive** NOAEL = 0.3 mg/kg/day LOAEL = 1.1/1.2 mg/kg/day (M/F), based upon decreased F_2 mean litter size

Table 2. Toxicity Profile of Mesotrione Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3800 Reproduction and fertility effects (mouse)	44505034 (1997) Acceptable/guideline 0, 10, 50, 350, 1500 or 7000 ppm M: 0, 2.1, 10.1, 71.4, 306.7 or 1455.5 mg/kg/day F: 0, 2.4, 11.7, 82.5, 362.7 or 1652.3 mg/kg/day	**Parental/Systemic** NOAEL = 10.1/11.7 (M/F) LOAEL = 71.4/82.5 mg/kg/day (M/F), based upon increased kidney weights and tyrosinemia in the F_1 males **Offspring/Systemic** NOAEL not established LOAEL = 2.1/2.4 mg/kg/day (M/F), based upon tyrosinemia and ocular discharge in the F_1 and F_2 offspring **Reproductive** NOAEL = 1455.5/1652.3 mg/kg/day (M/F) LOAEL > 1455.5/1652.3
870.4300 Combined chronic toxicity/ carcinogenicity rodents (rat)	44505035 (1997), 44505036 (1998) Acceptable/guideline 0, [1.0, 2.5], 7.5, 100 or 2500 ppm M: 0, [0.06, 0.16], 0.48, 6.48 or 159.9 mg/kg/day F: 0, [0.08, 0.19], 0.57, 7.68, or 189.5 mg/kg/day	NOAEL = 0.16/0.19 mg/kg/day (M/F) [The NOAEL only applies to ocular lesions; a NOAEL was not determined for kidney and liver weights or hepatocyte fat vacuolation in males] LOAEL = 0.48/0.57 mg/kg/day (M/F), based upon ocular lesions, increases in kidney and liver weights, and hepatocyte fat vacuolation in males **No evidence of carcinogenicity**
870.4100a Chronic toxicity rodents (mouse)	44505026 (1997) Acceptable/guideline 0, 10, 50, 350 or 7000 ppm M: 0, 1.5, 7.8, 56.2 or 1114 mg/kg/day F: 0, 2.1, 10.3, 72.4 or 1494.5 mg/kg/day	NOAEL = 56.2/72.4 mg/kg/day (M/F) LOAEL = 1114/1494.5 mg/kg/day (M/F), based upon decreases in body weight gain and food utilization in males

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Table 2. Toxicity Profile of Mesotrione Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4100b Chronic toxicity nonrodents (dog)	44505027 (1997) Acceptable/guideline M & F: 0, 10, 100 or 600 mg/kg/day	NOAEL was not established LOAEL = 10 mg/kg/day, based upon evidence of tyrosinemia in both sexes and increased incidence of erythrophagocytosis in the mesenteric lymph nodes of females
870.4200b Carcinogenicity (mouse)	44505028 (1997) Acceptable 0, 10, 350 or 7000 ppm M: 0, 1.4, 49.7 or 898 mg/kg/day F: 0, 1.8, 63.5 or 1103 mg/kg/day	NOAEL = 49.7/63.5 mg/kg/day (M/F) LOAEL = 898/1103 mg/kg/day (M/F), based upon decreased body weight, body weight gain, and food efficiency in males **no evidence of carcinogenicity**
870.5100 Gene Mutation reverse gene mutation assay in bacteria	44373526 (1993) Acceptable	There was *no evidence* of induced mutant colonies over background
870.5300 Gene Mutation *in vitro* forward gene mutation assay in mouse lymphoma cells	44373525 (1994) Acceptable	There were no treatment-related increases in mutant frequency in the presence or absence of S9 activation
870.5375 Cytogenetics *in vitro* mammalian cytogenetics assay	44373524 (1994) Acceptable	Not clastogenic with S9 activation and equivocal for clastogenic activity without S9 activation
870.5395 bone marrow micronucleus assay	44373527 (1994) Acceptable	There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time.

Table 2. Toxicity Profile of Mesotrione Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.6200a Acute neurotoxicity screening battery	44505017 (1997), 44505018 (1997) Acceptable M & F: 0, 20, 200 or 2000 mg/kg/day	NOAEL = 2000 mg/kg/day (M/F) LOAEL > 2000 mg/kg/day (M/F) No effects noted
870.6200b Subchronic neurotoxicity screening battery	44505025 (1997) Acceptable/guideline M: 0, 0.2, 8.25 or 403 mg/kg/day F: 0, 0.23, 9.29 or 467 mg/kg/day	NOAEL = 0.20/0.23 mg/kg/day (M/F) LOAEL = 8.25/9.29 mg/kg/day (M/F), based upon corneal opacities and/or vascularization of the cornea of the eye in males
870.6300 Developmental neurotoxicity	NA	NA

Table 2. Toxicity Profile of Mesotrione Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism (rat)	44505101 (1995), 44505102 (1996), 44505103 (1996), 44505104 (1996), 44505105 (1996), 44505106 (1996) Acceptable M & F: 1 or 100 mg/kg single oral dose, 1 mg/kg single iv dose, repeated dose at 1 mg/kg; special study - 50 mg/kg single oral dose	Mesotrione was readily absorbed and distributed in the body. Tissue distribution was about the same in both sexes, although one study showed higher residues in the kidneys in females, with the highest residues of the test compound in the liver and kidney. Higher doses resulted in higher residues in the liver and kidney, while repeated doses resulted in reduced accumulation of residues in all tissues. Levels of radioactivity in tissues of iv-dosed animals were essentially the same as in orally-dosed animals. Over 50% of the administered dose was excreted in the urine in both sexes and around 25% was excreted in the feces within 72 hours. Females exhibited slightly higher total urinary excretion than males, but total fecal excretion was about the same in both sexes. Increasing the dose or repeated doses had little effect on the pattern of excretion in both sexes. The overall pattern of excretion was similar between orally-dosed and iv-dosed rats. The metabolite profile was similar between the sexes in each group and between the single-dosed and repeated-dosed animals. The parent compound, mesotrione, was the major component identified in the urine (> 47%) and feces (> 55%). Minor metabolites identified were MNBA, AMBA, 5-hydroxymesotrione, and 4-hydroxymesotrione.

Table 2. Toxicity Profile of Mesotrione Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism (mouse)	44537101 (1997) M & F: 1 or 100 mg/kg single oral dose	Metabolism in the mouse was very similar to the rat (above) except that males had slightly increased total fecal excretion when compared to females and, females in the low-dose group excreted higher (1.5x) levels of parent compound in the urine than males. Free mesotrione was the major component in the urine and feces (≥ 50% of the dose). Minor components in the fecal extracts included AMBA and MNBA.
870.7600 Dermal penetration	NA	NA

3.2 FQPA Considerations

On March 13, 2001, the HIARC reviewed the recommendations of the toxicology reviewer for mesotrione with regard to the proposed toxicological endpoints for the acute and chronic RfDs and the toxicological endpoint selection for occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to mesotrione was also evaluated as required by the FQPA of 1996 (Memo, D. Nixon, 12-APR-2001, HED Doc. No. 014536). The HIARC concluded the following:

- There is quantitative evidence of increased susceptibility demonstrated in the oral prenatal developmental toxicity studies in rats, mice, and rabbits. Delayed ossification was seen in the fetuses at doses below those at which maternal toxic effects were noted. Maternal toxic effects in the rat were decreased body weight gain during treatment and decreased food consumption and in the rabbit, abortions and GI effects. No maternal toxic effects were noted in the mouse.

- There is quantitative evidence of increased susceptibility demonstrated in the multi-generation reproduction study in mice. The young exhibited significant tyrosinemia and ocular discharge at doses below those at which parental toxic effects were noted. The parental effects were tyrosinemia and increased kidney weights.

- Quantitative evidence of increased susceptibility was not demonstrated in the multi-generation reproduction study in rats since no NOAEL was established for parental or offspring systemic toxicity, but there is evidence of a qualitative increase in susceptibility since tyrosinemia observed in the young was much more severe than that observed in the adults.

- A DNT study is required in the mouse in order to better characterize the effects of tyrosinemia on the developing nervous system and to correlate plasma tyrosine levels to neurotoxic effects.

The FQPA SFC met on April 16, 2001 (Memo, B. Tarplee, 30-APR-2001, HED Doc. No. 014552) to evaluate the hazard and exposure data for mesotrione and recommended that the FQPA safety factor (as required by FQPA of August 3, 1996) be retained (10x) in assessing the risk posed by this chemical because:

- There is quantitative evidence of increased susceptibility of the young exposed to mesotrione in the prenatal developmental toxicity studies in mice, rats, and rabbits and in the multigeneration reproduction study in mice;
- There is qualitative evidence of increased susceptibility of the young exposed to mesotrione in the multigeneration reproduction study in rats; and
- A DNT study is required to assess the effects of tyrosinemia on the developing nervous system exposed to mesotrione.

The FQPA SFC recommended that the FQPA safety factor be **retained** and applied to **all population subgroups for all exposure durations** since there is evidence of increased susceptibility following pre- and postnatal exposure in three species and a DNT study is required.

3.3 Dose Response Assessment

As noted previously, the Mechanism of Toxicity SARC determined that the petitioner has adequately demonstrated that for tyrosine-mediated toxicological effects, the mouse is a more appropriate model for assessing human risk than is the rat; therefore the HIARC preferentially selected endpoints based on mouse toxicity data for tyrosine-mediated effects wherever possible.

Acute Dietary Endpoint: No appropriate endpoint was available to quantitate risk to the general U.S. population or to females 13-50 years old from a single-dose administration of mesotrione. The developmental effect, delayed ossification in the rat, was considered by the HIARC as not occurring after a single day of dosing. The developmental effects in the rabbit developmental study were not chosen as an acute endpoint since the study was considered unacceptable due to questions concerning the timing of dosing that may have had an effect on the number of fetuses available for analysis of developmental effects. Increases in an extra full 13th rib and 27 pre-sacral vertebra were only statistically significant in fetuses, not litters. The overall incidence in litters was very high in all groups, including the controls, and the dose-response for these effects was weak.

Chronic Dietary Endpoint: The mouse reproduction study was used to select the endpoint for establishing the chronic RfD of 0.007 mg/kg/day. The standard 100x uncertainty factor (UF) was applied to account for interspecies extrapolation and intraspecies variation, along with a 3x factor for using a lowest-observed-adverse-effect-level (LOAEL) instead of a NOAEL (no NOAEL was established.) The LOAEL of 2.1 mg/kg/day was based upon tyrosinemia in F_1 adults and F_{2a} pups and ocular discharge in F_1 pups. No NOAEL was established. The FQPA SFC determined that the safety factor of 10x is applicable for chronic dietary risk assessment. Thus, the cPAD is 0.0007 mg/kg/day.

Carcinogenicity: In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the HIARC classified mesotrione as "not likely to be carcinogenic to humans" by all routes of exposure based upon lack of evidence of carcinogenicity in rats and mice; therefore, a cancer risk assessment is not required.

Short-Term Incidental Oral Endpoint: A short-term incidental oral endpoint was selected from a rat developmental study. The maternal NOAEL of 100 mg/kg/day was based upon decreased body weight gains during treatment and decreased food consumption at the LOAEL of 300 mg/kg/day. This dose/endpoint is appropriate for the population of concern (infants and children) and the duration of exposure.

Intermediate-Term Incidental Oral Endpoint: An intermediate-term incidental oral endpoint was selected from a mouse reproduction study. The offspring LOAEL of 2.1 mg/kg/day was based upon tyrosinemia in F_1 and F_{2a} offspring and ocular discharge in F_1 pups. No NOAEL was established. This dose/endpoint is appropriate for the population of concern (infants and children) and the duration of exposure.

Dermal Penetration:

Dermal-Absorption Factor: 25% (relative to oral absorption)

There are no dermal-absorption studies available for review. The rabbit dermal (870.3250) NOAEL is 1000 mg/kg/day with no systemic effects noted. The rabbit maternal (870.3700b) NOAEL/LOAEL (based on abortions and clinical signs of toxicity) is 100/250 mg/kg/day. An upper-bound estimate of dermal-absorption was calculated by comparing the maternal LOAEL from the rabbit developmental study with the NOAEL from the rabbit dermal study.

Short-Term Dermal Endpoint: A short-term dermal endpoint was selected from a rat developmental study. A 21-day dermal study was submitted with no systemic effects noted; however, the dermal study did not evaluate developmental toxicity. Since the rat, mouse and rabbit developmental toxicity studies had developmental effects at doses below those at which maternal toxic effects were seen, it is appropriate to choose an oral developmental study for this risk assessment and do route-to-route extrapolation to adequately protect against potential developmental hazards via dermal exposure. A dermal-absorption factor of 25% (relative to oral absorption) should be applied. The developmental LOAEL of 100 mg/kg/day was based upon delays in skeletal ossification and changes in *manus/pes* ossification assessments. No NOAEL was established. This dose/endpoint is appropriate for short-term exposure risk assessment.

Intermediate-Term Dermal Endpoint: An intermediate-term dermal endpoint was selected from a mouse reproduction study. A 21-day dermal study was submitted with no systemic effects noted; however, the dermal study did not evaluate offspring and reproductive effects. Since there are definitive effects in offspring at doses below those where effects are seen in adults, it is appropriate to choose an oral study for this risk assessment and do route-to-route extrapolation to adequately protect against reproductive hazards via dermal exposure. A dermal-absorption factor of 25% (relative to oral absorption) should be applied. The offspring LOAEL of 2.1 mg/kg/day was based upon tyrosinemia in F_1 and F_{2a} offspring and ocular discharge in F_1 pups. No NOAEL was established. This dose/endpoint is appropriate for intermediate-term exposure risk assessment since the treatment period extends into the exposure period of concern (1 week to several months).

Long-Term Dermal Endpoint: A long-term dermal endpoint was selected from a mouse reproduction study. The offspring LOAEL of 2.1 mg/kg/day was based upon tyrosinemia in F_1 and F_{2a} offspring and ocular discharge in F_1 pups. No NOAEL was established. A dermal-absorption factor of 25% (relative to oral absorption) should be applied. This dose/endpoint is

appropriate for long-term exposure risk assessment.

Short-Term Inhalation Endpoint: A short-term inhalation endpoint was chosen from a rat developmental toxicity study, since no inhalation study was available. The developmental LOAEL of 100 mg/kg/day was based upon delays in skeletal ossification and changes in *manus/pes* ossification assessments. No NOAEL was established. An inhalation-absorption factor of 100% (relative to oral absorption) should be applied. This dose/endpoint is appropriate for short-term exposure risk assessment.

Intermediate-Term Inhalation Endpoint: An intermediate-term inhalation endpoint was chosen from a mouse reproduction study. The offspring LOAEL of 2.1 mg/kg/day was based upon tyrosinemia in F_1 and F_{2a} offspring and ocular discharge in F_1 pups. No NOAEL was established. An inhalation-absorption factor of 100% (relative to oral absorption) should be applied. This dose/endpoint is appropriate for intermediate-term exposure risk assessment since the treatment period extends into the exposure period of concern (1 week to several months).

Long-Term Inhalation Endpoint: A long-term dermal endpoint was selected from a mouse reproduction study. The offspring LOAEL of 2.1 mg/kg/day was based upon tyrosinemia in F_1 and F_{2a} offspring and ocular discharge in F_1 pups. No NOAEL was established. An inhalation-absorption factor of 100%(relative to oral absorption) should be applied. This dose/endpoint is appropriate for long-term exposure risk assessment.

MOE for Occupational/Residential Risk Assessments: A MOE of 300 is required for short-, intermediate-, and long-term occupational risk assessments for both dermal and inhalation routes of exposure. This includes the conventional 100 and additional 3x for the use of a LOAEL. For long-term dermal and short-, intermediate-, and long-term inhalation exposures, the following route-to-route extrapolation was followed: the inhalation (using 100% absorption) and dermal (using 25% absorption) exposures were converted to equivalent oral doses, combined, and then compared to their respective oral NOAELs or LOAELs since all of the dermal and inhalation endpoints are based on oral equivalents. Table 3 summarizes the toxicological dose and endpoints for mesotrione for use in human risk assessment.

Table 3. Summary of Toxicological Dose and Endpoints for Mesotrione for Use in Human Risk Assessment[1].

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary all populations	Not Applicable	Not Applicable	No appropriate study available.
Chronic Dietary all populations	LOAEL= 2.1 mg/kg/day UF =3 **Chronic RfD** = 0.007 mg/kg/day	FQPA SF = 10X **cPAD** = chronic RfD / FQPA SF = 0.0007 mg/kg/day	Reproduction Study - mouse Offspring LOAEL = 2.1 mg/kg/day based upon tyrosinemia in F_1 and F_{2a} offspring and ocular discharge in F_1 pups.
Short-Term Incidental Oral (1-7 days) (Residential)	NOAEL = 100 mg/kg/day	**LOC for MOE** = 1000 (Residential)	Developmental Toxicity Study - rat Maternal NOAEL = 100 mg/kg/day based upon decreased body weight gains during treatment and decreased food consumption.
Intermediate-Term Incidental Oral (7 days - several months) (Residential)	LOAEL = 2.1 mg/kg/day	**LOC for MOE** = 3000 (Residential)	Reproduction Study - mouse Offspring LOAEL = 2.1 mg/kg/day based upon tyrosinemia in F_1 and F_{2a} offspring and ocular discharge in F_1 pups.
Short-Term Dermal (1-7 days) (Occupational/ Residential)	Oral study LOAEL = 100 mg/kg/day (dermal-absorption rate = 25%)	**LOC for MOE** = 300 (Occupational) **LOC for MOE** = 3000 (Residential)	Developmental Toxicity Study - rat Developmental LOAEL = 100 mg/kg/day based upon delays in skeletal ossification and changes in *manus/pes* ossification assessments.

Table 3. Summary of Toxicological Dose and Endpoints for Mesotrione for Use in Human Risk Assessment[1].

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and LOC for Risk Assessment	Study and Toxicological Effects
Intermediate-Term Dermal (1 week - several months) (Occupational/ Residential)	Oral study LOAEL = 2.1 mg/kg/day (dermal-absorption rate = 25%)	**LOC for MOE** = 300 (Occupational) **LOC for MOE** = 3000 (Residential)	Reproduction Study - mouse Offspring LOAEL = 2.1 mg/kg/day based upon tyrosinemia in F_1 and F_{2a} offspring and ocular discharge in F_1 pups.
Long-Term Dermal (several months - lifetime) (Occupational/ Residential)	Oral study LOAEL = 2.1 mg/kg/day (dermal-absorption rate = 25%)	**LOC for MOE** = 300 (Occupational) **LOC for MOE** = 3000 (Residential)	Reproduction Study - mouse Offspring LOAEL = 2.1 mg/kg/day based upon tyrosinemia in F_1 and F_{2a} offspring and ocular discharge in F_1 pups.
Short-Term Inhalation (1-7 days) (Occupational/ Residential)	Oral study LOAEL = 100 mg/kg/day (inhalation-absorption rate = 100%)	**LOC for MOE** = 300 (Occupational) **LOC for MOE** = 3000 (Residential)	Developmental Toxicity Study - rat Developmental LOAEL = 100 mg/kg/day based upon delays in skeletal ossification and changes in *manus/pes* ossification assessments.
Intermediate-Term Inhalation (1 week - several months) (Occupational/ Residential)	Oral study LOAEL = 2.1 mg/kg/day (inhalation-absorption rate = 100%)	**LOC for MOE** = 300 (Occupational) **LOC for MOE** = 3000 (Residential)	Reproduction Study - mouse Offspring LOAEL = 2.1 mg/kg/day based upon tyrosinemia in F_1 and F_{2a} offspring and ocular discharge in F_1 pups.

Table 3. Summary of Toxicological Dose and Endpoints for Mesotrione for Use in Human Risk Assessment[1].

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and LOC for Risk Assessment	Study and Toxicological Effects
Long-Term Inhalation (several months - lifetime) (Occupational/ Residential)	Oral study LOAEL = 2.1 mg/kg/day (inhalation-absorption rate = 100%)	**LOC for MOE** = 300 (Occupational) **LOC for MOE** = 3000 (Residential)	Reproduction Study - mouse Offspring LOAEL = 2.1 mg/kg/day based upon tyrosinemia in F_1 and F_{2a} offspring and ocular discharge in F_1 pups.
Cancer (oral, dermal, inhalation)	"not likely"	Not Applicable	Acceptable oral rat and mouse carcinogenicity studies; no evidence of carcinogenic or mutagenic potential.

[1] 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.

3.4 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 bases 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, mesotrione may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

4.1 Summary of Proposed Uses

The petitioner provided a proposed label for the 4 lbs. a.i./gal SC formulation (EPA File Symbol No. 100-RRGR; Product Name = Callisto™ Herbicide) proposed for use on all varieties of field corn (including production seed corn, and silage corn), excluding sweet corn and popcorn. Corn up to 30 inches tall may be treated. A maximum of two applications per season and a maximum seasonal application rate of 0.43 lbs a.i./A/season are proposed. Mesotrione may be applied by either ground sprayers or by aerial application. Applications may be made in a spray volume of 10-30 gal/A using broadcast ground equipment or a minimum of 5 gal/A using aerial equipment. (The label does not specify in the general "Application Procedures" section of the label what substance the 10-30 gal/A or 5 gal/A should be; therefore, the petitioner should specify 10-30 gal water/A and 5 gal water/A. The label specifies the substance as water later in the individual procedure sections). Application using irrigation equipment is prohibited. Callisto™ is not effective for the control of most grass weeds. Tank mixing of Callisto™ with other preemergent or postemergence grass herbicides is recommended (all recommended herbicides have established tolerances for field corn commodities) to provide broad spectrum weed control in field corn.

For preemergence application, Callisto™ is proposed for use at 0.188-0.24 lbs a.i./A by ground sprayers in a spray volume of 10-30 gal water/A. For postemergence application (used alone), mesotrione is proposed for a maximum seasonal rate of 0.188 lbs a.i./A by ground sprayers in a spray volume of 10-30 gal water/A. In a single postemergence application, 0.094 lbs a.i./A should not be exceeded. For postemergence aerial application, a minimum of 5 gal/A (the label does not specify what substance the 5 gal/A should be; therefore, the petitioner should specify 5 gal *water*/A) should be used.

The proposed label specifies that corn may be replanted immediately, following any crop failure. Soybeans, small grains, alfalfa, and clover may be planted 120 days after application. All other rotational crops may be planted the spring following application of mesotrione. Planting at shorter than recommended intervals may result in injury to the rotational crop. A 12-hour restricted entry interval (REI) is proposed.

HED concludes that the submitted Section B is *not* adequate. A pre-harvest interval (PHI) for field corn forage must be proposed. **The available field trial data support a PHI of 45 days.** Furthermore, HED recommends that the petitioner add a statement to the label specifying that postermergence applications must be made at the V3 to V8 leaf corn growth stage for field corn. In addition, HED notes that, if it is the petitioner's intention not to exceed a maximum seasonal rate of 0.43 lb a.i./A, the following combinations of two applications may be applied: two postemergence applications [maximum total = 0.188 lbs a.i./A (0.094 lbs a.i./A + 0.094 lbs a.i./A)]; two preemergence applications [maximum total = 0.43 lbs a.i./A (0.24 lbs a.i./A + 0.188 lbs a.i./A)]; and one preemergence and one postemergence applications [maximum total = 0.33

lbs a.i./A (0.24 lbs a.i./A + 0.094 lbs a.i./A)]. The petitioner should amend the label to specify a minimum spray volume of 10-30 gal *water*/A and 3 gal *water*/A when applying Callisto™ by ground or aerial application, respectively. (The label does not specify in the general "Application Procedures" section of the label what substance the 10-30 gal/A or 5 gal/A should be. The label specifies the substance as water later in the individual procedure sections). **A revised Section B is required.**

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Background

No tolerances have been established for residues of mesotrione. The field corn petition represents the first proposed use for this herbicide. Field corn residue chemistry data were reviewed in the HED memorandum dated 6-JUN-2001 (S. Levy, D245477). The mesotrione residue chemistry database was reviewed by the Chemistry Science Advisory Council (ChemSAC) in a meeting held on 4-APR-2001.

Syngenta Crop Protection Inc. (formerly Zeneca Ag. Products) submitted a petition for a Section 3 registration of a 4 lb/gal SC flowable formulation (Product name = Callisto™ Herbicide) and establishment of permanent tolerances for residues of the herbicide mesotrione [2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione] (designated by the company code ZA1296) *per se* in/on the commodities listed below:

Field corn	0.01 ppm
Field corn, fodder	0.01 ppm
Field corn, forage	0.01 ppm

Nature of the Residue

Plants: Metabolism data were submitted for field corn RACs. The HED Metabolism Assessment Review Committee (MARC) concluded that for the tolerance expression and risk assessment purposes, the residue of concern in/on field corn is mesotrione *per se* (D274111, S. Levy and D. Nixon, 26-APR-2001). The selection of the residue of concern was based on levels of the metabolites found in the metabolism and magnitude of the residue studies.

Livestock: Metabolism data were submitted for livestock commodities derived from hens and dairy cows. The MARC concluded that for the tolerance expression and risk assessment purposes, the residue of concern in/on livestock commodities is mesotrione *per se* (D274111, S. Levy and D. Nixon, 26-APR-2001). This decision was based on the fact that the ruminant and poultry metabolism studies were conducted at 540x-700x and 1100x, respectively, the maximum theoretical dietary burden (MTDB). Based on the residue identification/characterization

performed in the metabolism study and the MTDB, it was concluded that there was no reasonable expectation of finite residues in livestock commodities (Category 180.6(a)(3)). If in the future, the registrant proposes a use which increases the MTDB, then this conclusion will be re-evaluated.

Residue Analytical Methods

The petitioner proposed HPLC method TMR0643B with fluorescence detection for the enforcement of tolerances for field corn forage, stover, and grain. Method validation recoveries indicate that this method adequately recovers residues of mesotrione and its metabolite MNBA from field corn forage, stover, and grain. Adequate radiovalidation and independent laboratory validation (ILV) data have been submitted for this method. HED notes that the radiovalidation study did not include the oxidation step of the enforcement method. It is thus possible that there could be other compounds which co-elute with mesotrione and/or MNBA and can be oxidized to AMBA. As all residues in the field trials were <LOQ, this concern is not an issue for this petition. However, if the petitioner should seek registration on additional crops, the radiovalidation study should be performed with all steps of the enforcement method. This method was forwarded to the Agency's Analytical Chemistry Laboratory (ACL) for a PMV (Memo, S. Levy, 9-NOV-1999, D260569). The method was also subjected to an interference study to investigate whether other pesticides registered for use on corn would interfere during the analysis of mesotrione. However, this study has deficiencies; **a new interference study is recommended by HED.**

The petitioner also included a description and adequate ILV for a modified version of method TMR0643B, Method TMR0882B. This method was also forwarded to ACL for a PMV (personal communication with D. Griffith, ACL/Biological and Economic Analysis Division (BEAD), 8-MAR-2001). **Until a successful PMV of the analytical method is reported by ACL, the data requirement for analytical methods has not been satisfied.** Method validation recoveries indicate that this modified method adequately recovers residues of mesotrione and its metabolite MNBA from field corn forage, stover, and grain and sugarcane. Since this method does not differ significantly from Method TMR0643B, radiovalidation data are not required.

Method TMR0643B was used for the determination of residues of mesotrione and its metabolite MNBA in/on plant commodity samples collected from the crop field, processing, and field rotational crop studies. The concurrent method recovery data indicate that this method is adequate for data collection.

The petitioner proposed a confirmatory method as part of their enforcement method. The petitioner states that unexpected positive results can be confirmed through the use of an alternate HPLC column. Due to the ionic nature of analytes, their retention characteristics can be further modified by alternating the HPLC mobile phase. Additionally, the multiresidue method (MRM) is available as a confirmatory method.

The petitioner did not propose a livestock enforcement method. Because the residues observed from the ruminant and poultry metabolism studies are negligible, no data are required pertaining to this requirement. HED concluded that there is no reasonable expectation of finding quantifiable mesotrione residues of concern in eggs, milk, and the meat, fat, or meat byproducts of poultry or ruminants as a result of the proposed uses on field corn [Category 180.6(a)(3)].

Multiresidue Method (MRM)

A report on MRM testing of mesotrione has been received and was forwarded to FDA (Memo, S. Levy, 16-NOV-1999, D260571) for updating PAM-I, Appendix I. Acceptable recoveries of mesotrione were obtained in corn forage using Protocol C and D.

Crop Field Trials

An adequate number of geographically-representative corn field trials were provided to indicate that the proposed tolerances of 0.01 ppm in/on corn grain, forage, and stover are appropriate. The results indicate that residues of mesotrione *per se* will not exceed the LOQ of 0.01 ppm in/on field corn forage harvested 46-92 days and field corn stover and grain harvested 68-114 days following two applications as follows: first application at 0.30 lb a.i./A/application (preplant, at planting, preemergence, or preplant incorporated) and second application at 0.20 lb a.i./A/application (postemergence) for a total application rate of 0.50 lb a.i./A (~1.2x maximum proposed seasonal application rate).

The petitioner must, however, submit a **revised Section F** to correct the commodity definitions as follows: "field corn" should be revised to "corn, field, grain;" "field corn fodder" should be revised to "corn, field, stover;" and "field corn forage" should be revised to "corn, field, forage."

Processed Food/Feed

The submitted field corn processing data are adequate. The data indicate that residues of mesotrione were below the analytical method's LOQ (<0.01 ppm) in/on samples of the RAC, field corn grain, following two broadcast applications (one application at planting followed by a second postemergence application) for a total of ~5.8x the maximum proposed total seasonal rate. Mesotrione residues were below the LOQ in the dry milled fractions (corn grits, meal, flour, and crude and refined oil) and the wet milled fractions (corn starch and crude and refined oil) processed from field corn grain bearing non-quantifiable residues. Based on the results of the current processing study, tolerances for mesotrione residues in the processed commodities of field corn are not required.

Meat, Milk, Poultry, Eggs (MMPE)

Because the residues observed from the ruminant and poultry metabolism studies are negligible, after taking into account the exaggerated doses, magnitude of the residue data for MMPE are not required at this time. HED concludes that there is no reasonable expectation of finding finite mesotrione residues of concern in eggs, milk, or the meat, fat, or meat byproducts of poultry or ruminants as a result of the proposed uses on field corn [Category 180.6(a)(3)]. If in the future, the registrant proposes a use which increases the MTDB, then this conclusion will be re-evaluated.

Confined Accumulation in Rotational Crops

The submitted confined rotational crop study is adequate. TRRs accumulated at levels ≥0.01 ppm in the following rotational crop commodities of soybeans and wheat 30 days after treatment (DAT) with uniformly ring-labeled phenyl (PH) or cyclohexane-labeled (CY) [^{14}C]mesotrione at 0.274 lb a.i./A (1.1x the maximum proposed preemergence rate for corn): soybean forage, hay, and soybeans, and wheat forage, hay, straw, and grain. TRR in PH samples ranged from 0.038 ppm in wheat grain to 2.58 ppm in wheat straw; in CY samples TRR were lower, ranging from 0.010 ppm in wheat grain to 0.059 ppm in wheat straw. Results of both labels show that there was cleavage between the two rings. Based on the components identified, the results suggest that PH-labeled mesotrione is metabolized in rotational crops via a route similar to that demonstrated in primary crops and that CY-labeled mesotrione was incorporated mainly into natural products. The MARC concluded that for the proposed PBI of 120 days, the residue of concern in/on rotational crops is mesotrione *per se*.

Field Accumulation in Rotational Crops

The petitioner submitted an acceptable limited field rotational crop study. Residues of mesotrione were less than the method LOQ (<0.01 ppm) in/on all rotational crop matrices (radish, roots and tops; soybean forage, hay, and seed; millet forage, hay, straw, and grain; and sorghum forage) from the 29- to 30-day PBI following single preplant incorporated application made to field corn at 0.30 lb a.i./A/application (~0.7x maximum proposed seasonal rate). Residues of mesotrione were less than the method LOQ (<0.01 ppm) in/on all rotational crop matrices (radish, roots and tops; endive leaves; and wheat forage, hay, straw, and grain) from the 74- to 100-day PBI following two applications (preplant incorporated and postemergence) made to field corn at a total rate of 0.50 lb a.i./A (~1.2x maximum proposed seasonal rate).

These data support a 30-day PBI for all crops and thus support the PBI proposed on the specimen label. Note that the proposed label specifies that corn may be replanted immediately, following any crop failure and that soybeans, small grains, alfalfa, and clover may be planted 120 days after application. All other rotational crops may be planted the spring following application of mesotrione. Shorter PBIs were not proposed because the petitioner noted that planting at shorter than recommended intervals may result in injury to the rotational crop.

International Harmonization of Tolerances

There are no CODEX, Canadian, or Mexican tolerances/MRLs for mesotrione residues. Thus, harmonization is not an issue at this time.

4.2.2 Dietary Exposure Analyses

HED conducts dietary (food only) risk assessments using DEEM™, ver 7.72, which incorporates consumption data generated in USDA's CSFII, 1989-1992. For chronic risk assessments, residue estimates for foods or food-forms of interest are multiplied by the average consumption estimate of each food/food-form of each population subgroup. Chronic exposure estimates are expressed in mg/kg bw/day and as a percent of the cPAD.

4.2.2.1 Acute Dietary Exposure Analysis

Acute doses and endpoints were not selected for the general U.S. population (including infants and children) or the females 13-50 years old population subgroup for mesotrione; therefore, an acute dietary exposure analysis was **not** performed.

4.2.2.2 Chronic Dietary Exposure Analysis

A conservative chronic analysis was performed using the HED-recommended tolerance level residues for field corn RACs, DEEM™ default processing factors, and assuming all crops were 100% treated with mesotrione. For chronic dietary risk, HED's level of concern is >100% cPAD. Dietary exposure estimates for representative population subgroups are presented in Table 4. The results of the chronic analysis indicate that the estimated chronic dietary risk associated with the HED-recommended uses of mesotrione is below HED's level of concern.

Table 4. Summary of Results from Chronic DEEM™ Analysis of Mesotrione.

Subgroup	Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	0.000013	1.8
All Infants (< 1 year old)	0.000030	4.3
Children 1-6 years old	0.000030	4.2
Children 7-12 years old	0.000023	3.3
Females 13-50 years old	0.000009	1.4
Males 13-19 years old	0.000016	2.3
Males 20+ years old	0.000009	1.3
Seniors 55+ years old	0.000007	1.0

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups that may not be sufficiently represented in the consumption surveys, (e.g., nursing and non-nursing infants). However, risk estimates for these subpopulations are included in representative populations having sufficient numbers of survey respondents (e.g., all infants). The population subgroups listed in Table 4 are subgroups having a sufficient number of respondents in the USDA 1989-92 CSFII food consumption survey to be considered statistically reliable.

4.2.2.3 Cancer Dietary Exposure Analysis

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the HIARC classified mesotrione as "not likely to be carcinogenic to humans" by all routes of exposure based upon lack of evidence of carcinogenicity in rats and mice. Therefore, a cancer dietary exposure analysis was **not** performed.

4.3 Water Exposure/Risk Pathway

Environmental Fate Assessment

The following information concerning the environmental fate and drinking water assessment of mesotrione was provided by EFED (electronic correspondence, A. Clem, 15-MAR-2001). At the present time, surface and ground water monitoring data are not available. However, the registrant has submitted (without request from the Agency) two *interim* reports on a prospective ground water monitoring (PGM) study at a site in Michigan. Superficial indications are that no leaching of *parent* was occurring. Until the registrant submits a final report to the Agency with study details and actual laboratory sequences for parent *and metabolites* in the PGM study, EFED cannot project general leaching conclusions. The following is an excerpt from the DRAFT EFED memorandum dated 9-MAR-20001:

The herbicide mesotrione and its major metabolites MNBA and AMBA are distinctly acidic compounds. This acidic/ionic property has a major influence on their behavior in environmental media at different pHs. As a suite, these compounds had low to virtually no sorption to tested soils/sediments at the more neutral pHs typical of agriculture, indicating high potential for leaching and runoff. Tending to offset the opportunity for leaching and runoff, parent was relatively short-lived. Generally, MNBA and AMBA were also relatively short-lived under aerobic conditions. However, as indicated further below, there is greater uncertainty about the persistence of MNBA and AMBA under suboxic conditions, such as would be found in subsoil and ground water. These metabolites would be more likely candidates for leaching and runoff than parent. Based on physicochemical properties, bioconcentration of mesotrione, MNBA and AMBA is not expected. Likewise, volatilization of mesotrione and its transformation products (except for carbon dioxide) is not indicated.

Based on laboratory studies, the primary routes of environmental transformation for parent mesotrione are aerobic and suboxic metabolism in soil and water. Numerous laboratory "half-lives" (more than 17) ranged from around four days to one month, depending on ambient conditions, especially pH (see main text). In relative, practical terms, photolysis is a minor degradative route. Mesotrione was stable against simple hydrolysis.

Sorption of mesotrione to soil organic matter and its aerobic soil metabolism half-lives (paired values for sorption and half-life for 17 soils) each correlate inversely with pH–the higher the pH, the lower the apparent sorption to soil organic matter and the shorter the half-life (see main text). Lower sorption to soil acts to increase available concentrations, while shorter half-lives act to decrease them. For mesotrione, the overall quantitative effect tended to normalize estimated environmental concentrations to a central value, regardless of pH.

Only three compounds, MNBA, AMBA, and carbon dioxide, were identified specifically as by-products in laboratory studies. Depending on conditions and time after application of parent, MNBA and AMBA can comprise up to approximately 60% of applied parent equivalent. Aerobic conditions favor MNBA, suboxic conditions favor AMBA. Half-lives for MNBA can only be crudely estimated from the available data and are highly uncertain. In at least two aerobic soils, MNBA half-lives appeared to be measured in one to several months, but seemed to be much shorter in others. Although, as for parent, metabolism rates for MNBA may show correlation with pH, this has not been pursued because of lack of sufficient, amenable data.

In a separate aerobic soil metabolism study with AMBA as the test substance in three soils, AMBA half-lives averaged 21 $\pm$ 5 days with an upper 90% confidence interval on the mean of 31 days. Data are insufficient to determine the range of variation of half-life with pH. Under suboxic conditions, half-lives for AMBA cannot be reliably established because of study deficiencies; a crude, reviewer-estimated first-order half-life for AMBA under the existing study conditions is 110 days, but may be longer with greater restriction of oxygen.

Under aerobic conditions, carbon dioxide was a ubiquitous product which issued from key positions in both rings of the mesotrione molecule. The cyclohexanedione ring was much more reactive in yielding carbon dioxide than the benzene ring. In some cases, carbon dioxide comprised up to about 80% of the radioactive dose after about six months. Increasingly difficult to extract soil residues tended to increase with time up to roughly15 to 50% of the dose, and then tended to decrease in roughly complementary fashion with increasing levels of carbon dioxide. This pattern clearly indicates progression to ultimate degradation/mineralization when there is sufficient aeration. However, when aeration was limited (suboxic conditions), carbon dioxide was only sparingly evolved from either ring. Under such conditions, as stated above, AMBA was a prominent metabolite which may be persistent when oxygen is in short supply.

Three terrestrial field dissipation studies on bare ground did not adequately account for the dissipation of mesotrione. They did, however, provide supplemental aspects which are consistent with the laboratory findings of a relatively short residency time for mesotrione in soil. The registrant failed to identify any degradates in the field, or to clearly determine leaching potential.

Ground and Surface Water EECs

The HED MARC determined that for risk assessment purposes, the residue of concern in drinking water is mesotrione *per se* (D274111, S. Levy and D. Nixon, 26-APR-2001). Data provided by the EFED showed that the acidic/ionic nature of mesotrione, MNBA, and AMBA has a major influence on the behavior of these compounds in the environment, indicating that these compounds are relatively short-lived under aerobic conditions. EFED provided coarse screens of potential surface and ground water concentrations that are based on the EFED GENEEC (version 1.2) surface water simulation model, which is a provisional, ecological (field edge) model, and the SCI-GROW (version 1.0) groundwater regression model, which was developed from studies with different hydrology and study conditions. Both models assumed a maximum seasonal application rate of 0.43 lb a.i./A.

The following are the surface and ground water EECs provided by EFED:

surface water EEC:	20 ppb; peak concentration (acute) 13 ppb; 56-day average (chronic)
ground water EEC:	0.15 ppb (acute and chronic)

4.4 Residential Exposure/Risk Pathway

There are no registered or proposed residential uses of mesotrione; therefore, there are no residential exposure risks from this chemical.

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 groundboom application methods. 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. 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 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 and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Aggregate exposure risk assessments were performed only for the following: chronic aggregate exposure (food + drinking water). Acute, short- and intermediate-term and cancer aggregate risk assessments were not performed because an acute dietary endpoint was not selected, there are no registered or proposed residential non-food uses, and mesotrione is not carcinogenic, respectively. Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, DWLOCs were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

To calculate the chronic DWLOCs, the chronic dietary food estimates (from DEEM™) were subtracted from the cPAD value to obtain the maximum water exposure level. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70kg/2L (adult male and US Population), 60 kg/2L (adult female), and 10kg/1L (infant & children).

5.1 Chronic Aggregate Risk (food + drinking water)

The chronic dietary exposure analysis assumed tolerance level residues, DEEM™ default processing factors, and 100% crop treated for all proposed commodities (Tier 1). The EECs generated by EFED are less than HED's DWLOCs. **Thus, chronic aggregate risk estimates are below HED's level of concern.** Table 5 summarizes the chronic aggregate exposure estimates to mesotrione residues.

Table 5. Chronic Aggregate Exposures to Mesotrione Residues.

Population Subgroup	cPAD, mg/kg/day	Chronic Food Exposure, mg/kg/day	Maximum Chronic Water Exposure[1], mg/kg/day	Ground Water EEC[2], ppb	Surface Water EEC[2], ppb	Chronic DWLOC[3], (μg/L)
U.S. Population	0.0007	0.000013	0.000687	0.15	4.3	24
All infants (< 1 year old)	0.0007	0.000030	0.00067	0.15	4.3	6.7
Children (1-6 years old)	0.0007	0.000030	0.00067	0.15	4.3	6.7
Children (7-12 years old)	0.0007	0.000023	0.000677	0.15	4.3	6.8
Females (13-50 years old)	0.0007	0.000009	0.000691	0.15	4.3	21
Males (13-19 years old)	0.0007	0.000016	0.000684	0.15	4.3	24
Males (20+ years old)	0.0007	0.000009	0.000691	0.15	4.3	24
Seniors (55+ years old)	0.0007	0.000007	0.000693	0.15	4.3	24

1 Maximum chronic water exposure (mg/kg/day) = cPAD (mg/kg/day) - chronic food exposure from DEEM™ (mg/kg/day).

2 EECs resulting from the maximum proposed application rate (0.43 lbs a.i./A/season); 56-day surface water average/3 (HED SOP 99.5).

3 Because there are no residential uses, the chronic DWLOCs were calculated as follows:

$$DWLOC\ (\mu g/L) = \frac{maximum\ water\ exposure\ (mg/kg/day)\ x\ body\ weight\ (kg)}{consumption\ (L/day)\ x\ 0.001\ mg/\mu g}$$

6.0 CUMULATIVE RISK

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

EPA does not have, at this time, available data to determine whether mesotrione has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that mesotrione has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether mesotrione shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for mesotrione need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with mesotrione, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment once the final guidance HED will use for conducting cumulative risk assessments is available.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on June 30, 2000 (65 FR 40644-40650) and is available from the OPP Website at: http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-30/6049.pdf
In the dràft guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed. The proposed guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity is expected to be finalized by the summer of 2001.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

7.0 OCCUPATIONAL EXPOSURE

Syngenta has proposed the registration of the herbicide Callisto™, a SC formulation containing 40% of the (a.i.) mesotrione. The proposed use is for pre- and post-emergence selective contact and residual control of broadleaf weeds in field corn, (including production seed corn, and silage corn; use is prohibited on sweet corn, popcorn, and ornamental (Indian) corn). According to the label, this product is absorbed through the soil or by the foliage of emerged weeds, and should be applied to actively growing weeds. Mesotrione may be applied either by ground sprayers or by aerial application up to corn height of 30 inches (or up to the V8 leaf corn growth stage for field corn). Application using irrigation equipment is prohibited. A maximum of two applications per season totaling 0.43 a.i./A/season is proposed. For preemergence application, Callisto™ is proposed for use at 0.188-0.24 lbs a.i./A by groundboom. In a single postemergence application, 0.094 lbs a.i./A should not be exceeded. The petitioner did not propose a PHI, however, the residue chemistry data support a PHI of 45 days (Memo, S. Levy, 6-JUN-2001, D245477). Table 6 summarizes the use pattern of mesotrione for the proposed use. Currently, there are no registered or proposed residential uses of mesotrione.

Table 6. Use Pattern Summary of Mesotrione on Field Corn.

Crop	field corn
Formulation	liquid SC
Pests	broadleaf weeds
Application methods	groundboom sprayer and aerial application
Maximum application rate (AR)	0.24 lbs a.i./Acre
Maximum seasonal AR	0.43 lbs a.i./A/season
Number of applications per season	2
Manufacturer	Syngenta

The exposure estimates are based on toxicological endpoints identified in HED's HIARC document dated 21-APR-2001. The acute toxicity of mesotrione and the doses and toxicological endpoints selected for various occupational exposure scenarios are in Tables 1 and 3.

7.1 Handler

In the case of mesotrione, the short-term dermal endpoint [rat developmental endpoint (LOAEL = 100 mg/kg/day)] is appropriate for the 0 to 30 day exposure period since it provides protection for developmental effects seen below maternally toxic doses (Personal Communication, S. Makris to D. Nixon, 9-MAY-2001). For the proposed use of mesotrione, no longer than 30 days of exposure is expected for both private and commercial handlers.

Based on the proposed use patterns, short-term dermal and inhalation exposures are expected for private applicators (farmers treating their own crops) and commercial applicators. Since mesotrione may be applied only twice per year, long-term exposures are not expected from the proposed uses.

Since no chemical-specific data are available to assess potential exposure to workers, the exposure and risk assessment presented in this document are based on the PHED Version 1.1 (Surrogate Exposure Guide, August 1998). PHED was designed by a task force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association (ACPA). PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates).

Users select criteria to subset the PHED database to reflect the exposure scenario being evaluated. The subsetting algorithms in PHED are based on the central assumption that the magnitude of handler exposures to pesticides are primarily a function of activity (e.g., mixing/loading, applying), formulation type (e.g., wettable powders, granulars), application method (e.g., aerial, groundboom), and clothing scenarios (e.g., gloves, double layer clothing).

Once the data for a given exposure scenario have been selected, the data are normalized (i.e., divided) by the amount of pesticide handled resulting in standard unit exposures (milligrams of exposure per pound of active ingredient handled). Following normalization, the data are statistically summarized. The distribution of exposure values for each body part (e.g., chest upper arm) is categorized as normal, lognormal, or "other" (i.e., neither normal nor lognormal). A central tendency value is then selected from the distribution of the exposure values for each body part. These values are the arithmetic mean for normal distributions, the geometric mean for lognormal distributions, and the median for all "other" distributions. Once selected, the central tendency values for each body part are composited into a "best fit" exposure value representing the entire body.

The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has developed a set of grading criteria to characterize the quality of the original study data. The assessment of data quality is based on the number of observations and the available quality control data. While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. HED has developed a series of tables of standard unit exposure values for many occupational scenarios that can be utilized to ensure consistency in exposure assessments (Exposure SAC, Policy #007).

PHED does not contain exposure scenarios for the SC formulation. However, HED believes that the data for mixer/loaders and applicators using "liquid" formulations are adequate to confidently estimate exposures for these job functions. Table 8 provides exposure estimates for workers wearing a single layer of clothing, with or without gloves. It should be noted that the label requires a single layer of clothing and chemical resistant gloves as the necessary personal protective equipment (PPE). All data is rated medium to high confidence.

Currently, HED recommends that the exposure and risk estimates for mixer/loaders and applicators of tractor drawn equipment remain separate unless specific chemical and/or crop information exists to warrant the combining of the two estimates (HED Exposure SAC, Draft Policy, 29-MAR-2000). Therefore, scenarios applicable to mixing/loading SCs and applying by groundboom were not included in the handler exposure assessment for the proposed uses of mesotrione.

The maximum application rate listed on the label was used for all calculations. The standard values for acreage were taken from the HED Exposure SAC Policy #09, effective 5-JUL-2000. Both the low and high number of acres treated per day were used to demonstrate a range of potential exposure. Table 8 lists what is considered to be typical to high-end worker exposure and risk assessment for handlers of mesotrione.

Table 7. Assumptions Used in Mesotrione Occupational Handler Exposure Calculations.

Exposure Scenario	Application Rate [1] (lb ai/acre)	Surrogate Unit Exposures [2] (mg/lb ai)				Amount Treated [3] (acres/ day)
		Baseline		With Gloves		
		Dermal	Inhalation	Dermal	Inhalation	
Mixer/Loader						
Open Mixing/ Loading Liquids for Aerial Application	0.24	2.9	0.0012	0.023	0.0012	350
						1200
Open Mixing/ Loading Liquids for Groundboom Application	0.24	2.9	0.0012	0.023	0.0012	80
						200
Flagger						
Flagging	0.24	0.011	0.00035	-NA-[4]	-NA-[4]	350
Applicator						
Aerial Application (Enclosed Cockpit)	0.24	0.005	0.000068	-NA-[4]	-NA-[4]	350
						1200
Groundboom Application (Open Cab)	0.24	0.014	0.00074	0.014	0.00074	80
						200

[1] Maximum application rates which are based on the proposed Callisto™ label.

[2] Surrogate unit exposures are from the PHED as presented in the PHED Surrogate Exposure Guide (AUG-1998). mitigation levels: **baseline** (long pants, a long-sleeved shirt, no chemical-resistant gloves, and no respirator), **plus gloves** (baseline clothing, and chemical-resistant gloves).

[3] The number of acres treated per day were based on Exposure SAC Policy #09 (dated 5-JUL-2000).

[4] Only engineering controls are available.

Table 8. Mesotrione Exposure and Risk Estimates for Handler Exposure to Mesotrione.

Exposure Scenario	Acres/Day	Baseline [1]		With Gloves [2]	
		Total ADD[3] (mg/kg/d)	Combined Short-term MOE [4]	Total ADD [3] (mg/kg/d)	Combined Short-term MOE [4]
Mixer/Loader					
Mixing/Loading Liquids for Aerial application	low	1.0	**100**	0.010	10000
	high	3.5	**30**	0.29	3000
Mixing/Loading for Groundboom application	low	0.23	420	0.0022	45000
	high	0.58	**170**	0.0056	18000
Flagger					
Flagging		0.0044	23000		
Applicator					
Aerial application	low	0.0019	54000		
	high	0.0063	16000		
Groundboom application	low	0.0013	72000	0.0013	72000
	high	0.0034	29000	0.0034	29000

[1] Baseline = long pants, a long-sleeved shirt, no chemical-resistant gloves, and no respirator.
[2] Plus Gloves = Baseline clothing plus chemical-resistant gloves.
[3] Total Average Daily Dose (mg/kg/day) = Average Dermal Daily Dose (mg/kg/day) + Average Inhalation Daily Dose (mg/kg/day)
where: Average Daily Dose (ADD) (mg/kg/day) = Unit Exposure (mg/lb ai) x (lb ai/acre) x (acres/day) x Absorption Factor (25% and 100% used to convert dermal and inhalation, respectively to an oral equivalent dose) / Body Weight (60 kg)
[4] Combined MOE = LOAEL/Total ADD, LOAEL = 100 mg/kg/day for short-term.
level of concern is for MOEs below 300.

With the addition of gloves, all MOEs are greater than 300. Since the label required PPE is a single layer of clothing and gloves, the MOEs for all scenarios do not exceed HED's level of concern.

7.2 Post-Application

Most cultural practices related to field corn are mechanized, having low potential for dermal contact. According to information from the *USDA OPMP & PIAP Crop Profiles* website (http://pestdata.ncsu.edu/cropprofiles/Detail.CFM?FactSheets__RecordID=62), field corn is planted mechanically with a row crop planter or grain drill. Corn may be grown using till or non-till methods. Tillage is mainly accomplished by use of a rotary hoe and harvest is done by

combine. Scouting and irrigation may be performed throughout the season.

Workers having potential exposure to mesotrione from the proposed use include scouts and workers re-entering treated fields to perform irrigation tasks. Since mesotrione will be applied at the early stages of crop growth (or up to the V8 leaf corn growth stage) and up to corn height of 30 inches, limited potential for post-application exposure is expected. Therefore, short- term post-application exposures are assessed for scouting activities occurring around the time of application. This assessment is considered to be screening level, demonstrating that there are minimal potential risks to workers re-entering fields treated with mesotrione.

There are no chemical-specific data available to determine the potential risks from post-application activities associated with the proposed use of mesotrione. To provide an screening level estimate of the potential risks and exposures, a risk assessment was conducted using the following assumptions:

- Maximum application rate of 0.24 lb a.i./A
- HED standard transfer coefficients (TC) of **400** cm^2/hour for scouting
- 20% of the application rate available as dislodgeable residues
- Work day of 8 hours
- Reentry on day 0
- 25% dermal absorption (considered an upper bound assumption)

The TC used in this assessment are from an interim TC policy developed by HED's Exposure SAC for using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (Policy # 3.1). It is the intention of HED's Exposure SAC that this policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on TC. 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.

Exposure estimates for scouting activities are listed in Table 9 and are expected to represent high-end estimates of potential post-application exposure resulting from the proposed uses of mesotrione.

Table 9. Post-application Exposure Assessment for Mesotrione.

Post-application Activity	TC[1] cm^2/hr	DFR [2] ug/cm^2 DAT = 0	ADD[3] mg/kg/day	Short-term MOE[4]
Early season scouting of field corn	400	0.54	0.0072	14000

[1]TC(Standard TC for Agricultural Activities, field corn scouting (minimum foliage), HED Exposure SAC, 3-AUG-2000, taken from ARTF009 for sweet corn)
[2]Surrogate DFR_0 = application rate X 20% available as dislodgeable residue X 4.54E8 ug/lb X 2.47E-8 A/cm^2
[3]ADD = DFR X TC X Duration X 0.001 mg/ug /BW (60 kg) X 25%DA
[4]MOE = LOAEL/ADD; Short-term dermal LOAEL = 100 mg/kg/day
level of concern is for MOEs below 300.

HED's level of concern for mesotrione is for MOEs below 300. The calculated MOE is 14,000 for scouting activities related to the proposed use of mesotrione on field corn. This screening level assessment demonstrates that potential post-application exposures for workers contacting mesotrione treated surfaces are not expected to exceed HED's level of concern.

REI

Mesotrione is in toxicity category III for the dermal route of exposure. Based on the Worker Protection Standard (WPS), an interim REI of 12 hours is sufficient to protect workers performing re-entry activities for the proposed use of mesotrione.

7.3 Incidents

Since mesotrione is a new a.i., no incident data are available.

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Chemistry

- Successful PMV of the analytical enforcement method.
- Adequate storage stability data in the plant and livestock metabolism studies.
- Revised interference study.
- Revised Section B.
- Revised Section F.

8.2 Toxicology

- DNT study in the mouse. (A DNT study is required in the mouse in order to better characterize the effects of tyrosinemia on the developing nervous system and to correlate plasma tyrosine levels to neurotoxic effects.)
- 28-day inhalation study.

8.3 Occupational Exposure

- None.

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