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

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

DATE: 11/29/05

SUBJECT: Human Health Risk Assessment for Cloquintocet-mexyl for Uses on Wheat and Barley.

Chemical #:	700099	Class:	Safener
DP Barcode:	D313217	Trade Name:	Discover® Herbicide, Discover® NG Herbicide, Axial ™ Herbicide
		EPA Reg. #:	100-907, 100-1173, 100-XXX
Petition #	4E6831	40 CFR:	§180.560

TO: D. Rosenblatt/ T. Ward
MUIERB
Registration Division (7505C)

FROM: W. Cutchin, Chemist
Alternative Risk Integration Assessment (ARIA)
Registration Division (7505C)

THRU: Stephen Dapson, Branch Senior Scientist
Registration Action Branch 3
Health Effects Division (7509C)

1.0 EXECUTIVE SUMMARY

Background

As a result of a previous Syngenta proposal in PP#7E4920, tolerances were established for residues of the safener cloquintocet-mexyl in pesticide formulations (Discover® Herbicide/Discover NG® Herbicide) in wheat commodities. Additional data were required before a permanent registration for cloquintocet-mexyl in/on wheat commodities could be established . Additional data and/or information were required for plant and livestock metabolism, plant analytical methods, multiresidue methods, storage stability, crop field trials, processing studies, and rotational crops. In the present submission, Syngenta submitted data in response to the previous risk assessment for the use on wheat and proposed to revise the established tolerances for cloquintocet-mexyl residues in/on wheat commodities and proposed tolerances on barley commodities.

In petition PP#4E6831, Syngenta petitioned for amended tolerances to support additional use of cloquintocet-mexyl as a safener in a pesticide formulation (Axial™ Herbicide) for use on both wheat and barley.

Assessments of human exposures and risks were conducted for acute and chronic dietary risk, exposure and risk to cloquintocet-mexyl residues in water, residential exposure and risk, aggregate risk, and exposure and risk to workers.

Cloquintocet-mexyl is a safener needed in formulations to prevent damage to target crops due to phytotoxic effects.

Proposed Uses

The clodinafop-propargyl products Discover® Herbicide (EPA Reg. No. 100-907) and Discover® NG Herbicide (EPA Reg. No. 100-1173) are presently conditionally registered for foliar application to all varieties of wheat (including durum) grown in Montana, Minnesota, North Dakota, and South Dakota. The safener, cloquintocet-mexyl, is included for use as a component of Discover® Herbicide. The petitioner is now proposing to expand use of Discover® Herbicide and Discover® NG Herbicide to wheat grown in all areas of the U.S. The petitioner is also requesting registration of the pinoxaden product Axial™ Herbicide which also includes the safener cloquintocet-mexyl for foliar application to wheat and barley. Both proposed uses are for a single application of the products during postemergence or 2-leaf stage to pre-boot stage which would include cloquintocet-mexyl at 0.016 lb a.i./A with a 60 days PHI.

The proposed use directions are adequate except for the Axial™ label. The proposed Axial™ Herbicide label is adequate to allow evaluation of the residue data submitted in support of this petition provided that the following label restriction, which is already on the Discover®/Discover® NG labels, is added to the Axial label: "Do not apply to winter wheat in the fall."

Toxicology and Dose-Response

On June 17, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database of cloquintocet-mexyl (CGA 185072), established Reference Doses (RfDs), and selected toxicological endpoints for acute and chronic dietary as well as occupational and residential exposure risk assessments. The endpoint selected for acute dietary risk assessment was based on increased incidence of skeletal variants and decreased fetal body weight from a developmental toxicity in rats. An acute reference dose (RfD) of 1 mg/kg/day is based on the no-observable-adverse-effect-level (NOAEL) was selected for the subpopulation of females 13-50 years old. An acute RfD for the general population was not selected by the HIARC. Based on the available toxicology data, toxic effects observed in oral toxicity studies could not be attributed to a single dose (exposure) for population subgroups other than females 13-50 years old. The endpoint selected for chronic dietary risk assessment was based on increased incidence of thyroid follicular epithelial hyperplasia in a two year combined chronic/oncogenicity study in rats. This study is considered an appropriate study for assessment of chronic dietary risk because the endpoint is based on chronic effects observed in thyroid pathology. A chronic RfD of 0.04 mg/kg/day is based on the lowest-observable-adverse-effect-level (LOAEL).

Short- and intermediate-term dermal endpoints of 200 mg/kg/day (NOAEL) were selected from a 28-day dermal toxicity study based on mottled or reddish livers accompanied by histopathological changes including necrosis and fibrosis observed at the LOAEL of 1000 mg/kg/day. This study is selected because its duration and route of exposure are appropriate for short- and intermediate-term dermal exposure.

There were no inhalation toxicity studies appropriate for risk assessment in the toxicology database; only an acute inhalation toxicity study has been submitted to the Agency. A short-term inhalation endpoint of 100 mg/kg/day (NOAEL) was selected from a developmental toxicity study in rats based on an increased incidence of skeletal variants and decrease in fetal body weights at a LOAEL. A intermediate-term inhalation endpoint of 4.3 mg/kg/day (NOAEL) was selected from a two-year chronic toxicity/carcinogenicity in rats based on an increased incidence of thyroid follicular epithelial hyperplasia in females observed at a LOAEL. Since only an acute inhalation toxicity study has been submitted to the Agency, the oral values should be used for inhalation exposure risk assessment using a the route-to-route extrapolation.

Based on the proposed use patterns, no long-term dermal or inhalation exposure is expected to occur. Therefore, no endpoints were selected. A margin of exposure (MOE) of 100 is required for occupational exposure risk assessment.

The acute toxicity data indicates that cloquintocet-mexyl has low acute oral, dermal, and inhalation toxicity (Acute Toxicity Category III) and is slightly irritating to eyes. It is not a skin irritant. However, it is a skin sensitizer.

Carcinogenicity studies in rats and mice did not show increased incidence of

spontaneous tumor formation. With negative mutagenic test battery, it is suggested that cloquintocet-mexyl (CGA 185072) is not likely to be a human carcinogen. In 1999, the HIARC classified cloquintocet-mexyl as "not likely to be a human carcinogen."

The FQPA Safety Factor Committee (SFC) met on March 6, 2000 to evaluate the hazard and exposure data for cloquintocet-mexyl and recommended that the FQPA safety factor be reduced to 1x.

Dietary Risk from Drinking Water Sources

The mobility of cloquintocet-mexyl (as measured by its binding to soils) varies from low in a moderate organic soil to essentially immobile in a high organic soil. The persistence of cloquintocet-mexyl in soil is also very low. Therefore, based upon the its low persistence and low mobility, the leaching potential of cloquintocet-mexyl should be negligible. The major degradate is CGA-153433, 5-chloro-8-quinolinoxyacetic acid, described below. Surface and ground water EEC's have also been provided by EFED for CGA-153433.

The Agency currently lacks sufficient water-related exposure data from monitoring to complete a *quantitative* drinking water exposure analysis and risk assessment for cloquintocet-mexyl. Therefore, the Agency is presently relying on computer-generated estimated environmental concentrations (EECs). These EECs are provided by the Environmental Fate and Effects Division (EFED). GENEEC is a model used to generate EECs for *surface* water based on estimates of safener concentration in a farm pond. SCI-GROW is an empirical model based upon actual monitoring data collected for a number of pesticides which serve as benchmarks and has been used to predict EECs in *ground* water. Based on the environmental fate properties of cloquintocet-mexyl and the rapid degradation of the parent compound (i.e., hours to days) to the major degradate, CGA-153433 (5-chloro-8-quinolinoxyacetic acid), EFED provided HED with EECs for combined residues of cloquintocet-mexyl and CGA-153433. EFED reported that the highest EECs from the current and proposed uses were the GENEEC estimates acute (peak) and chronic (56-year mean) concentrations of cloquintocet-mexyl and CGA-153433 in water at 0.186 ppb and 0.005 ppb, respectively.

Dietary Risk

Residue Chemistry In PP#7E04920, Syngenta Crop Protection, Inc. proposed the establishment of tolerances for residues of the safener cloquintocet-mexyl (CGA-185072) in or on wheat grain at 0.02 ppm and wheat straw at 0.05 ppm. The safener is contained in the formulation Discover™ Herbicide, which contains the herbicide clodinafop-propargyl (CGA-184927). Cloquintocet-mexyl is needed in the formulation to prevent damage to the wheat due to phytotoxic effects of clodinafop-propargyl.

HED reviewed the data submitted in conjunction with the petition and concluded that, provided revised Sections B and F were submitted and the method validation was satisfactory, the submitted data were adequate to support a conditional registration for use of cloquintocet-

mexyl on wheat. Tolerances were subsequently established for the combined residues of cloquintocet-mexyl (acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester) and its acid metabolite (5-chloro-8-quinolinoxyacetic acid), when used as an inert ingredient (safener) in pesticide formulations containing the herbicide clodinafop-propargyl in a 1:4 ratio of safener to active ingredient, in/on the following raw agricultural commodities [40 CFR §180.560(a)]:

Wheat, forage	0.1 ppm
Wheat, grain	0.1 ppm
Wheat, hay	0.1 ppm
Wheat, straw	0.1 ppm

In the previous residue chemistry review, HED concluded that prior to granting full registration, additional data and/or information were required regarding plant and livestock metabolism, plant analytical methods, multiresidue methods, storage stability, crop field trials, processing studies, and confined rotational crops. Syngenta has now submitted data to address the requirements of conditional registration for cloquintocet-mexyl. (Data for the active ingredient clodinafop-propargyl are reviewed separately in D295198.)

In petition PP#4E6831, Syngenta has also petitioned for amended tolerances to support additional use of cloquintocet-mexyl as a safener in pesticide formulations containing the new active ingredient pinoxaden for use on both wheat and barley. In connection with the pinoxaden petition, Syngenta proposed to revise the established tolerances for cloquintocet-mexyl residues in/on wheat commodities and proposed tolerances on barley commodities.

Syngenta now proposes the following tolerances for the combined residues of cloquintocet-mexyl (acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester) and its acid metabolite (5-chloro-8-quinlinoxyacetic acid) when used as an inert ingredient (safener) in pesticide formulations containing either the herbicide clodinafop-propargyl or pinoxaden in a 1:4 ratio of safener to active ingredient in or on wheat and barley commodities as follows:

Wheat, forage	0.2 ppm
Wheat, straw	0.1 ppm
Wheat, hay	0.5 ppm
Wheat, grain	0.01 ppm
Barley, hay	0.1 ppm
Barley, straw	0.1 ppm
Barley, grain	0.01 ppm

Clodinafop-propargyl is a systemic herbicide that belongs to the oxyphenoxy acid ester chemical class. Two clodinafop-propargyl end-use products are conditionally registered for use on wheat: the 2 lb/gal emulsifiable concentrate (EC) formulation (Discover® Herbicide; EPA Reg. No. 100-907) and the 0.5 lb/gal EC formulation (Discover® NG Herbicide; EPA Reg. No. 100-1173). Currently, use of these products is restricted to Montana, Minnesota, North Dakota, and South Dakota. The petitioner wishes to expand use to wheat grown in all areas of the U.S.

Pinoxaden is a systemic herbicide. One pinoxaden end-use product is proposed for use on barley and wheat: Axial™ Herbicide (EPA Reg. No. 100-XXX), an EC formulation which contains 0.83 lb pinoxaden/gal.

The ratio of 1:4 safener to active ingredient applies to all three formulations (Discover® Herbicide, Discover® NG Herbicide, and Axial ™ Herbicide).

The nature of the residue in wheat, barley, livestock, and rotational crops is adequately understood. The HED Metabolism Assessment Review Committee (MARC) previously determined for the purpose of the conditional registration that the residues of concern for the tolerance expression and risk assessment for plants, livestock, and rotational crops are cloquintocet-mexyl and its metabolite CGA-153433. HED concludes that the residues of concern for the tolerance expression and risk assessment in wheat, barley, livestock, and rotational crops are cloquintocet-mexyl and its metabolite CGA-153433, the residues that are currently regulated**.**

Adequate enforcement methods are available for enforcement of the proposed/existing tolerances on wheat and barley. The two enforcement methods are the HPLC/UV method REM 138.01 for determination of cloquintocet-mexyl (parent) and the HPLC/UV Method REM 138.10 for determination of the metabolite CGA-153433. Adequate EPA petition method validations have been conducted on wheat grain, straw, and forage for the two enforcement methods. Both methods have been forwarded to FDA for publication in PAM, Vol. II. The validated limits of quantitation (LOQ) for Method REM 138.01 are 0.05 ppm for wheat forage, hay, and straw, and 0.02 ppm for wheat grain, processed commodities, and aspirated grain fractions. The validated LOQ for Method REM 138.10 is 0.05 ppm for all wheat commodities.

Because of the low levels of total radioactive residues found in livestock commodities in the ruminant and poultry metabolism studies and the corresponding low radioactive residues calculated for the 1X feeding levels, ruminant and poultry feeding studies are not needed and tolerances on livestock commodities are not needed. This use falls under 40 CFR §180.6(a)(3) since no secondary residues are expected to occur in livestock commodities.

The submitted wheat field trials are adequate for a conditional registration. Samples of wheat forage, hay, grain, and straw were analyzed. Most of the wheat samples were analyzed by the HPLC/UV enforcement methods REM 138.01 (for parent) and REM 183.10 (for the metabolite CGA-153433). The validated LOQs for Method REM 138.01 are 0.05 ppm for wheat forage, hay, and straw, and 0.02 ppm for wheat grain, processed commodities, and aspirated grain fractions. The validated LOQ for Method REM 138.10 is 0.05 ppm for all wheat commodities. Residues in spring wheat and winter wheat planted in the spring will not exceed 0.1 ppm in wheat grain, forage, hay, and straw.

The submitted barley field trials are adequate in number and geographic representation. The data collection methods for barley determined combined residues of cloquintocet-mexyl and its metabolite CGA-153433 as CGA-153433, using an oxidation step to convert cloquintocet-mexyl to CGA-153433. Based on these residue data, residues are not expected to exceed 0.01

ppm in barley grain (LOQ) and 0.05 ppm in barley hay and straw. Because the EPA-validated enforcement methods determine parent and metabolite separately at LOQs of 0.05 for each analyte on each commodity except for an LOQ of 0.02 ppm for parent in grain, the tolerances for the combined residues of cloquintocet-mexyl and its metabolite CGA-1532433 should be 0.1 ppm for barley, hay; 0.1 ppm for barley, grain; and 0.1 ppm for barley, straw.

The submitted processing data for wheat are tentatively adequate to satisfy data requirements, pending submission of additional information requested for Study 300/91 regarding the storage stability data for grain. The processing data indicate that residues of cloquintocet-mexyl and CGA-153433, determined as CGA-153433, do not concentrate in wheat processed commodities (bran, flour, middlings, shorts, and germ). Residues may concentrate in aspirated grain fractions (AGF) but residues in AGF are not likely to exceed the recommended tolerance of 0.10 ppm for grain. Therefore, tolerances are not needed for the wheat processed commodities (bran, flour, middlings, shorts, and germ) or for aspirated grain fractions.

Pending submission of additional information regarding storage stability of grain requested for Study 300/91 (MRID 44399210), HED tentatively concludes that the submitted barley processing study is adequate. Residues were <LOQ (<0.01 ppm) in barley grain treated at 5X and <LOQ (<0.01 ppm) in the processed fractions pearled barley, flour, and bran. Residues do not concentrate on processing and tolerances on the processed commodities pearled barley, flour, and bran are not needed.

Based on the available confined rotational crop data, the proposed rotational crop restrictions are appropriate. No field rotational crop data have been submitted but none are needed to support the requested uses on wheat and barley.

There are currently no Codex, Canadian, or Mexican MRLs/tolerances established for cloquintocet-mexyl on wheat. Therefore, no compatibility questions exist.

Dietary Exposure Analysis The acute dietary exposure analysis for cloquintocet-mexyl is a Tier 1 assessment (assuming 100% crop treated and tolerance level residues), because no additional data were used to refine the analysis. The acute dietary endpoint is applicable to the population subgroup females 13- 49 years old only. An acute dietary endpoint for the general population including infants and children was not identified. The Agency used FIRST and SCI-GROW screening models to determine the EECs of cloquintocet-mexyl in surface and ground water, respectively. The highest estimate for acute exposure, 0.186 ppb, was used in the analysis. The estimated dietary exposure (food and water) for females 13-49 years old occupies less than 1% of the aPAD and does not exceed HED's level of concern.

Similarly, the chronic dietary exposure analysis for cloquintocet-mexyl is a Tier 1 assessment. The chronic dietary endpoint applies to all population subgroups including infants and children. The Agency used FIRST and SCI-GROW screening models to determine the EECs of cloquintocet-mexyl in surface and ground water, respectively. The highest estimate for chronic exposure, 0.005 ppb, was used in the analysis. The estimated dietary exposure (food and water)

from cloquintocet-mexyl does not exceed HED's level of concern for any population subgroup. Food and water exposure occupies <1% of the cPAD for the US population and 1% of the cPAD for children 3-5 years old, the subgroup with the highest exposure.

Residential Risk

Residential uses are not proposed in this petition and there are no residential uses registered for products in which cloquintocet-mexyl serves as a safener, and therefore, a residential exposure assessment is not required.

Aggregate Risk

Acute, short-term, intermediate-term, and chronic aggregate risk estimates resulting from aggregate exposure to cloquintocet-mexyl, in food and drinking water are below HED's level of concern.

For the acute aggregate risk scenario, food and drinking water exposures were taken into account in the dietary exposure assessment. The estimated dietary exposure (food and water) for females 13-49 years old occupies <1% of the aPAD. Therefore, acute aggregate risk is below HED's level of concern.

For the short- and intermediate-term aggregate risk scenario, food, drinking water and residential exposures are taken into account. Since there is no residential uses of cloquintocet-mexyl, these aggregate risk assessments are not required.

For the chronic aggregate risk scenario, food , drinking water, and residential exposures were taken into account. In this case, there is no exposure in residential settings and the aggregate chronic assessment included food and drinking water only. Since the dietary exposure assessment already includes the highest chronic exposure from the drinking water modeling data, no further calculations are necessary. The general U.S. population and all population subgroups have exposure and risk estimates which are below HED's level of concern (i.e., the percentages of the chronic population adjusted doses (cPADs) are all below 100%). The aggregate chronic exposure to the U.S. population was <1% cPAD and the most highly exposed subgroup, children 3-5 yrs old, at 1% cPAD. Therefore, chronic aggregate risk is below HED's level of concern.

Occupational Exposure and Risk

Occupational exposure is expected from the use of cloquintocet-mexyl. The dermal toxicity endpoint (NOAEL = 200 mg/kg/day) was chosen for both short-and intermediate-term occupational exposure, based on the results of a 28-day dermal toxicity study in rats. The effects seen were mottled or reddish livers accompanied by histopathological changes including necrosis and fibrosis. There were no inhalation toxicity studies available for risk assessment. For short-term inhalation toxicity, the inhalation exposure is converted to an oral-equivalent dose (100%

absorption) and compared to the oral endpoint (NOAEL = 100 mg/kg/day) from a developmental study in rats. This endpoint is applicable to females 13+ years old, and therefore uses a 60-kg body weight in the calculations. For intermediate-term inhalation toxicity, the inhalation exposure is converted to an oral-equivalent dose and compared to the oral endpoint (NOAEL = 4.3 mg/kg/day) from a 2-year chronic toxicity/carcinogenicity study. These calculations result in MOEs which are compared to the level of concern (LOC) of 100 to determine any risk concerns.

Chemical-specific handler exposure data were submitted in support of this Section 3 registration. Handlers of cloquintocet-mexyl (in formulation with pinoxaden) were assessed for exposure during open mixing/loading to support aerial and groundboom application, using unit exposure values from the PHED Surrogate Table. Aerial and groundboom operators, as well as flaggers for aerial application, were assessed separately, using PHED unit exposure values for closed cockpit, open-cab tractor, and baseline clothing, respectively. The MOEs, under all the above circumstances, range from 250 to 4,500,000 for handlers. These MOEs are greater than 100, and do not exceed HED's level of concern.

Postapplication risk assessment uses the same dermal toxicity endpoints as for handlers above. However, because inhalation is not regarded as a significant route of exposure for post application activities, these postapplication risks are not assessed. Postapplication risks were assessed for workers entering wheat or barley fields to scout and irrigate. Wheat and barley are assumed to be mechanically harvested. The Agency acknowledges that there is some potential for exposure during harvesting because individuals engaged in fully mechanized activities have short-term excursions from the protected area for various reasons (e.g., unclogging machinery or equipment inspection for breakage). In these cases, the WPS § 170.112(c) Exception for short-term activities applies. Because the application being made relatively early in the growth cycle (i.e., 1 to 6 leaf stage on main stem), dislodgeable residues are expected to be significantly reduced by the time of harvest, due to degradation, growth of the plant, and absorption by the plant material. The MOE resulting from postapplication exposure is 490,000 on the day of application. This MOE is greater than 100, and therefore, does not exceed HED's level of concern.

The acute toxicity of technical cloquintocet-mexyl would require an interim restricted entry interval (REI) of 12 hours under the requirements of the Worker Protection Standard (WPS). However, the label for the pinoxaden product in which cloquintocet-mexyl serves as a safener lists a 48-hour interim restricted entry interval (REI) under requirements of the Worker Protection Standard, and therefore, this requirement will restrict the cloquintocet-mexyl component as well.

Recommendation for Tolerances

The available data indicate that no revisions to the current tolerance levels of 0.1 ppm on wheat, grain; wheat, forage, wheat, hay, and wheat, straw are needed. Pending the resolution of the Residue Chemistry Deficiencies (Section 8.2), the Agency recommends establishing permanent tolerances for the combined residues of cloquintocet-mexyl (acetic acid, [(5-chloro-8-

quniolinyl)oxy]-, 1-methylhexyl ester)(CAS Reg. No. 99607-70-2) and its acid metabolite (5-chloro-8-quinlinoxyacetic acid), in/on the following commodities be established:

Commodity	Proposed Tolerance, ppm
Barley, straw	0.1
Barley, hay	0.1
Barley, grain	0.1

Note to PM: The wording should changed in 40 CFR: §180.560 to: ".. when used as an inert ingredient (safener) in pesticide formulations containing either the herbicide clodinafop-propargyl or pinoxaden in a 1:4 ratio of safener to active ingredient..."

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

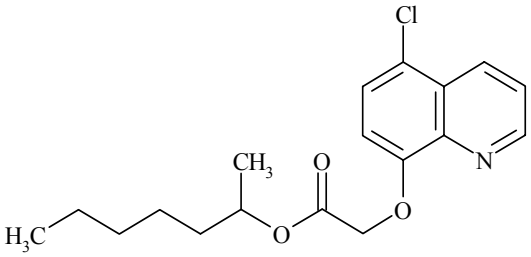
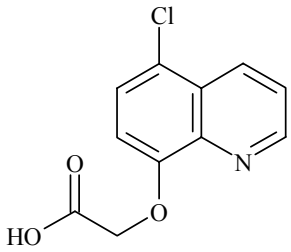
Table 1. Cloquintocet-mexyl Nomenclature.	
Chemical structure	
Common name	Cloquintocet-mexyl
Company experimental name	CGA-185072
IUPAC name	(5-chloroquinolin-8-yloxy)acetic acid 1-methylhexyl ester
CAS name	acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester
CAS registry number	99607-70-2
End-use products (EPs)	Discover Herbicide (EPA Reg. No. 100-907) Discover NG Herbicide (EPA Reg. No. 100-1173) Axial™ Herbicide (EPA Reg. No. 100-XXX)
Chemical structure of cloquintocet-mexyl acid metabolite (CGA-153433)	 [(5-chloro-8-quinolinyl)oxy]acetic acid

Table 2. Physicochemical Properties of the Technical Grade Test Compound		
Parameter	Value	Reference
Melting range	61.4 to 69˚C	MRID 44387401
pH	5.4 at 25˚C (1% w/v aqueous disp.)	MRID 44387401
Density	1.05 g/cm^3 at 22˚C	MRID 44387401
Water solubility (25˚C)	0.59 mg/L at pH 7.0 (PAI)*	MRID 44387401
Solvent solubility (g/L) (25˚C)	ethanol - 190 acetone - 340 toluene - 360 n -hexane - 0.140 n-octanol - 11	MRID 44387401
Vapor pressure at 25˚C	3.98 x10^{-8} mm Hg (PAI)*	MRID 44387401
Dissociation constant (pK$_a$)	3.55 (PAI)*	MRID 44387401
Octanol/water partition coefficient log P$_{ow}$	5.03 (at 25°C) (PAI)*	MRID 44387401
UV/visible absorption spectrum	Two absorbance maxima occur at 243.8-255.8 nm and 317.6-364.0 nm. No absorbance maxima occur between 370 nm and 750 nm.	MRID 44387401

*PAI = pure active ingredient

3.0 HAZARD CHARACTERIZATION

All toxicological data requirements for cloquintocet-mexyl technical have been satisfied. HED has a high degree of confidence in the toxicology database. Acute data requirements for all end-use products have been satisfied.

3.1 Hazard Profile

3.1.2 Acute Toxicity

The acute toxicity data (see Table 3) indicated that cloquintocet-mexyl (CGA 185072) has low acute oral, dermal, and inhalation toxicity (Acute Toxicity Category III) and is slightly irritating to eyes. It is not a skin irritant. However, it is a skin sensitizer.

Table 3. Acute Toxicity Data on Cloquintocet-mexyl				
GDLN	**Study Type**	**MRID nos.**	**Results**	**Tox. Cat.**
81-1	Acute Oral- Rat	44387414	LD$_{50}$ >2000 mg/kg (M&F)	3
81-1	Acute Oral- Mouse	44387415	LD$_{50}$ >2000 mg/kg (M&F)	3
81-2	Acute Dermal -Rat	44387416	LD$_{50}$ > 2000 mg/kg	3

GDLN	Study Type	MRID nos.	Results	Tox. Cat.
81-3	Acute Inhalation-Rat	44387417	LC_{50} >0.935 mg/L	3
81-4	Primary Eye Irritation-Rabbit	44387418	Slightly eye irritant	3
81-5	Primary Skin Irritation-Rabbit	44387419	Non-irritant	4
81-6	Dermal Sensitization-Guinea pig	44387420	Skin sensitizer	NA

3.1.2 Subchronic and Chronic Toxicity

Available toxicity studies are described in Table 4 below.

Systemic Toxicity
The primary target organs for subchronic exposure of cloquintocet-mexyl (CGA 185072) are the liver and the renal system. In a 90-day feeding study in rats, increased incidence of urinary bladder hyperplasia and increased serum bilirubin were observed in males at doses ≥1000 ppm (equivalent to 64 mg/kg/day). This observation was supported by a 28-day oral gavage study in rats where renal papillary necrosis and inflammation with fibrosis were observed at doses ≥100 mg/kg/day. In a 28-day dermal toxicity study in rats, mottled or reddish livers accompanied by histopathological changes including necrosis and fibrosis were observed in two of five females exposed to 1000 mg/kg/day of cloquintocet-mexyl (CGA 185072). In a 90-day feeding study in dogs, liver toxicity was evidenced by observations of liver necrosis and perivascular inflammatory cell infiltration. In the one-year dog study, increased relative liver weight and increased chronic interstitial nephritis were observed. It is to notable that in the two-year chronic toxicity study in rats, no renal or liver toxicity was reported; however, there was an increase in lymphoid hyperplasia of the thymus in male rats and an increase in thyroid follicular epithelial hyperplasia in female rats at 73 mg/kg/day.

Developmental/Reproductive Toxicity
There was no evidence of developmental or reproductive toxicity for cloquintocet-mexyl**.** The data demonstrate no increased sensitivity of rats or rabbits to *in utero* or early post-natal exposure to cloquintocet-mexyl (CGA 185072). NOAELs for maternal/parental toxicity were either less than or equal to the NOAELs for fetal or reproductive toxicity.

Carcinogenicity
In accordance with the EPA *Proposed EPA Weight-of-the-Evidence Categories*, August 1999, the HIARC classified cloquintocet-mexyl as **"not likely to be a human carcinogen."**
Carcinogenicity studies in rats and mice did not show increased incidence of spontaneous tumor formation. With negative mutagenic test battery, it is suggested that cloquintocet-mexyl (CGA

185072) is not likely to be a human carcinogen.

Mutagenicity
Studies indicate that cloquintocet-mexyl is not mutagenic in bacteria (*Salmonella typhimurium* or *Escherichia coli*) or cultured mammalian cells (Chinese hamster V79 lung fibroblasts). There is also no evidence of clastogenicity either *in vitro* or *in vivo*. Similarly, cloquintocet-mexyl did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes.

Neurotoxicity
There is no evidence of neurotoxicity based on observations in toxicity studies. Acute and subchronic neurotoxicity studies are not available for cloquintocet-mexyl; additional neurotoxicity testing is not being required at this time.

Metabolism
Metabolism studies in rats indicated that approximately 40% of the administered dose of cloquintocet-mexyl was absorbed through the gastrointestinal tract and subsequently excreted via the urine. Fecal excretion accounted for approximately 60% of the administered dose. The chemical was rapidly eliminated (more than 80% of the administered dose) via feces and urine within 48 hours post-dosing. Sex, dosing regime, and dose levels had little effect on the excretion pattern. Excretion patterns were similar between the biliary cannulated and non-cannulated animals indicating that there was no enterohepatic circulation of the chemical. Three days after administration, tissue radioactivity accounted for less than 0.3% of the administered dose (or was non-detectable) and was not detectable in the expired air. At day three post-dosing, most tissue residues of radioactivity were below the limit of detection. The major metabolic pathway of cloquintocet-mexyl was ester hydrolysis to yield 5-chloro-8-quinolinoxy acetic acid, the major metabolite in the fecal and urinary pools.

Other/Special Studies
None available.

Table 4. Toxicity Profile Summary Table for Cloquintocet-mexyl

Guideline No./ Study Type	MRID No. (year)/ Doses/ Classification	Results
870.3100/ 28-Day oral in rodents	44387421 (1988)/ 0, 10, 100, 1000 mg/kg Acceptable-Guideline	**NOAEL = 10 mg/kg/day** **LOAEL = 100 mg/kg/day** based on microscopic kidney lesions
870.3100/ 28-Day oral in rodents.	44387422 (1993)/ 0, 10, 400 mg/kg, females only Acceptable, Non Guideline	**NOAEL = 10 mg/kg/day (females only)** **LOAEL = 400 mg/kg/day** based on transient decrease in body weight gain, microscopic alterations of the pituitary and thyroid and possibly increased SGPT.

Table 4. Toxicity Profile Summary Table for Cloquintocet-mexyl		
Guideline No./ Study Type	**MRID No. (year)/ Doses/ Classification**	**Results**
870.3100/ 13 week oral in rodents	44387423 (1989)/ 0, 30, 150, 1000, 6000 ppm. M: 0, 2.0, 9.7, 63.9, 424 mg/kg, F: 0, 2.0, 10.2, 68.5, 407 mg/kg Acceptable-Guideline	**NOAEL = M: 150 ppm (9.7 mg/kg), F= 6000 ppm (=407 mg/kg/day).** **LOAEL = M - 1000 ppm (63.9 mg/kg); F ≥ 6000 ppm (≥ 407 mg/kg/day),** based on urinary bladder hyperplasia, kidney hydronephrosis and increased serum bilirubin in males.
870.3150 90-Day oral in non-rodent	44387424 (1989)/ 0, 100, 1000 or (40,000 to 15,000- decr. over time) ppm: M: 0, 2.9, 30.2, 446.4 mg/kg/day, F: 0, 3.3, 30.2, 472.7 mg/kg/day. Acceptable-Guideline	**NOAEL = 100 ppm (M: 2.9 mg/kg/day; F: 3.3 mg/kg/day).** **LOAEL = 1000 ppm (M and F: 30.2 mg /kg/day)** based on perivascular mixed inflammatory cell infiltrates and multicellular multifocal necrosis of the liver and thymic atrophy
870.3200 28-Day dermal toxicity	44387425 (1988)/ 0, 50, 200, 1000 mg/kg/day. Acceptable-Guideline	**NOAEL = 200 mg/kg/day** **LOAEL = 1000 mg/kg/day** based on mottled or reddish livers accompanied by histopathological changes including necrosis and fibrosis
870.3700a Prenatal developmental in rodent	44387429 (1989)/ 0, 10, 100, 400 mg/kg/day Acceptable-Guideline	**Maternal NOAEL = 100 mg/kg/day** **LOAEL = 400 mg/kg/day** based on clinical signs and decrease in body weight gain and food consumption. **Developmental NOAEL = 100 mg/kg/day** **LOAEL = 400 mg/kg/day** based on the higher incidence of skeletal variants and decrease in fetal body weights in the high dose group.
870.3700b Prenatal developmental in nonrodent	44387428 (1989)/ 0, 10, 60, 300 mg/kg/day Acceptable-Guideline	**Maternal NOAEL = 60 mg/kg/day** **Maternal LOAEL = 300 mg/kg/day** based on maternal toxicity (death) in the high dose group only. **Developmental NOAEL = 300 mg/kg/day** **Developmental LOAEL ≥ 300 mg/kg/day**

Table 4. Toxicity Profile Summary Table for Cloquintocet-mexyl		
Guideline No./ Study Type	**MRID No. (year)/ Doses/ Classification**	**Results**
870.3800 2 Generation Reproduction	44387430 (1991) 0, 50, 500, 5000, and 10,000 ppm M: 0, 3.5, 35.3, 370.7, 721.7 mg/kg/day F: 0, 4.2, 40.7, 422.8, 846.9 mg/kg/day Acceptable-Guideline	**Parental/Systemic NOAEL = 5000 ppm (M: 370.7; F: 442.8 mg/kg/day)** **Parental/Systemic LOAEL =10,000 ppm (M: 721.7 ; F: 846.9 mg/kg/day),** based on decreased body weight, deceased food consumption, and pathological changes in the kidney (dilated renal pelvis, nephrolith, hydronephrosis, urethral constrictions) and urinary bladder (cytoliths, hyperemia, cystitis and urothelial hyperplasia). **Reproductive NOAEL = 10,000 ppm (721.7 mg/kg/day).** **Reproductive LOAEL ≥ 10,000 ppm (721.7 mg/kg/day)** **Developmental NOAEL = 5000 ppm (442.8 mg/kg/day)** **Developmental LOAEL = 10,000 (846.9 mg/kg/day)** based on decreased pup weight and dilated renal pelvis.
870.4100b Chronic toxicity in nonrodent	44387426 (1991)/ 0, 75, 1500 and 15,000/10,000 ppm M: 0, 2.1, 43, 196/280 mg/kg/day F: 0, 2.4, 45, 216/301 mg/kg/day Acceptable-Guideline	**NOAEL = 1500 ppm (M: 43, F: 45 mg/kg/day)** **LOAEL = 15000/10,000 ppm (M: 196 F:216 mg/kg/day)** based on decreased body weight/weight gain and food consumption, anemia, increased serum iron, protein alterations, bone marrow hypoplasia and possibly decreased testes/prostate weights and interstitial nephritis.
870.4200b Carcinogenicity in mice	44387427 (1992)/ 0, 10, 100, 1000, and 5000 ppm. M: 0, 1.1, 11.1, 111, 583 mg/kg/day F: 0, 1.1, 10.8, 102, 520 mg/kg/day Acceptable-Guideline	**NOAEL = 1000 ppm (M: 111; F: 102 mg/kg/day)** **LOAEL = 5000 ppm (M: 583; F: 520 mg/kg/day) based on decreased body weight/weight gain in both sexes, urinary bladder lesions (chronic inflammation, ulceration, calculus and submucosa edema) in males and possibly slightly increased water consumption in both sexes. Negative for oncogenicity.**
870.4300 Combined chronic/ oncogenicity in rat	44387431 (1992)/ 0, 10, 100, 1000, 2000 ppm. M: 0, 0.36, 3.8, 36.4, 73.4 mg/kg/day F: :0, 0.42, 4.3, 41.2, 81.5 mg/kg/day Acceptable-Guideline	**NOAEL = F: 100 ppm (4.3 mg/kg/day) M: 1000 ppm (36.4 mg/kg/day)** **LOAEL = F: 1000 ppm (41.2 mg/kg/day); M: 2000 ppm (81.5 mg/kg/day)** based on increased incidence of thyroid follicular epithelial hyperplasia in females and based on lymphoid hyperplasia of the thymus in males.
870.5100 Gene Mutation	44387434 (1990)/ Acceptable-Guideline	Testing up to 5000 ug/plate with or without S9 microsomes produced no evidence that CGA 185072 technical induced a mutagenic effect in any strain. Negative mutagen

Table 4. Toxicity Profile Summary Table for Cloquintocet-mexyl		
Guideline No./ Study Type	**MRID No. (year)/ Doses/ Classification**	**Results**
870.5200 Gene Mutation	44387433 (1987)/ Chinese Hamster cells V70; Acceptable-Guideline	There was no evidence mutagenic effect at any dose (up to 500 ug/plate) with or without S9 activation. Negative mutagen.
870.5315 Human Lymphocytes in vitro	44387435 (1987)/ Acceptable-Guideline	Human lymphocytes were exposed in vitro up to 75 ug/mL with or without S9 activation showed no evidence that CGA 185072 induced a cytogenetic effects. at any dose. Negative mutagen.
870.5395 Micronucleus Test	44387432 (1978)/ (Chinese Hamster) Acceptable-Guideline	Chinese hamsters dosed from 625 to 2500 mg/kg showed no evidence that CGA 185072 induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time. Negative mutagen.
870.5550 DNA Repair Human Fibroblasts	4438736 (1987)/ Unacceptable-Guideline	Cultured human fibrocytes were exposed in vitro to up to 60 ug/mL for 5 hrs. and scored for silver grains in the nucleus. There was no evidence that CGA 185072 technical in the absence of S9 activation induced a genotoxic response.
870.5550 DNA Repair Rat Hepatocytes	4438737 (1987)/ Acceptable-Guideline	Primary rat hepatocytes expose to 200 ug/mL for 16-18 hour and scored for nuclear grains showed no evidence that CGA 185072 technical induced a genotoxic response. Negative mutagen.
870.7485 Metabolism and pharmacokinetics	44387438 (1989) Acceptable-Guideline	Absorption after a single low oral dose (50 mg/kg bw), was between 40.2% (males) and 35.6% (females). The major metabolite in the 0 to 24 hour fecal and urinary pools was determined to be quinolinoxy acetic acid, reference material CGA 153433, accounting for approximately 95% of the recovered radioactivity.
870.7485 Metabolism and pharmacokinetics	44387439/40 (1990)/ Acceptable-Guideline	The major metabolic pathway of CGA 185072 was determined to be hydrolysis of the ester group, resulting in the formation of 5-chloro-8-quinolinoxy acetic acid. The major metabolic pathway was not significantly affected by sex, dose level or dosing regime.

3.2 Dose-Response Assessment

On June 17, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database of cloquintocet-mexyl (CGA 185072), established Reference Doses (RfDs), and selected toxicological endpoints for acute and chronic dietary as well as occupational and residential exposure risk assessments. The doses and toxicological endpoints selected are summarized in a Table 5.

A. Food Exposure:

Acute Dietary Exposure: An acute reference dose (RfD) was selected for the subpopulation of females 13-50 years old. This acute RfD of **1 mg/kg/day** is based on the no-observable-adverse-effect-level (NOAEL) of 100 mg/kg/day selected from a developmental toxicity in rats (MRID 44387429) where an increased incidence of skeletal variants and decreased fetal body weight was observed at 400 mg/kg/day. [The NOAEL of 100 mg/kg/day is divided by uncertainty factors (UF) for inter-species extrapolation (10x) and intra-species variability (10x).] Based on the conservative assumption that developmental toxicity could occur following a single exposure to a pregnant female, this endpoint is appropriate for acute risk assessment for females 13-50 years old.

An acute RfD for the general population was not selected by the HIARC. Based on the available toxicology data, toxic effects observed in oral toxicity studies could not be attributed to a single dose (exposure) for population subgroups other than females 13-50 years old. No acute or subchronic neurotoxicity studies are available for cloquintocet-mexyl at this time. No other neurotoxic effects were observed in available toxicity studies. It is also noteworthy that the acute oral LD_{50} for male and female rats for technical grade cloquintocet-mexyl (98% a.i.) is >2000 mg/kg (Toxicity Category III).

Chronic Dietary Exposure: The HIARC selected a **chronic RfD of 0.04 mg/kg/day** (NOAEL = 4.3 mg/kg/day; Uncertainty Factor = 100). This chronic RfD is based on a two year combined chronic/oncogenicity study in rats (MRID 44387431). In this study, the NOAEL of 4.3 mg/kg/day was based on increased incidence of thyroid follicular epithelial hyperplasia in females at 41.2 mg/kg/day (lowest-observable-adverse-effect-level; LOAEL). The Uncertainty Factor accounts for both interspecies extrapolation (10X) and intraspecies variability (10X). This study is considered an appropriate study for assessment of chronic dietary risk because the endpoint is based on chronic effects observed in thyroid pathology.

B. Occupational/Residential Exposure

There are no residential uses; however, there is potential for residential exposure to spray drift resulting from aerial application. Based on the use pattern, there is potential for short-term exposures (private- one field) and intermediate-term exposure (commercial-several fields) during mixing, loading, application, and post-application activities. Long-term exposure is not expected to occur. A margin of exposure (MOE) of 100 is required for occupational exposure risk assessment.

Short- and Intermediate-Term Dermal Endpoints: Short- and intermediate-term dermal endpoints of 200 mg/kg/day (NOAEL) were selected from a 28-day dermal toxicity study (MRID 44387425) where mottled or reddish livers accompanied by histopathological changes including necrosis and fibrosis were observed at the LOAEL of 1000 mg/kg/day This study is selected because its duration and route of exposure are

appropriate for short- and intermediate-term dermal exposure.

It is important to note that a comparison of the NOAELs from the subchronic oral toxicity study in rat (LOAEL = 64 mg/kg/day) and the 28-day dermal toxicity study (LOAEL = 1000 mg/kg/day) in rat yields an estimated dermal absorption of 6.4%. As noted above, the acute RfD is based on a developmental endpoint. Application of this dermal absorption factor to the endpoint selected for the acute RfD (100 mg/kg/day from the developmental rat study), generates an estimated dermal dose of 1562 mg/kg/day. This estimated dermal dose is greater than the observed LOAEL from the 28-day dermal toxicity study (1000 mg/kg/day). Selection of the endpoint from the above noted dermal study is more conservative than using the developmental endpoint and is also more appropriate because it is route specific.

Short-Term Inhalation Risk Assessment: A short-term inhalation endpoint of 100 mg/kg/day (NOAEL) was selected from a developmental toxicity study in rats (MRID 4438749) where an increased incidence of skeletal variants and decrease in fetal body weights at a LOAEL of 400 mg/kg/day. Only an acute inhalation toxicity study has been submitted to the Agency. There were no inhalation toxicity studies appropriate for risk assessment in the toxicology database. Consequently, the oral values should be used for inhalation exposure risk assessment; the route-to-route extrapolation should be done as follows:

> Convert the inhalation exposure component (i.e. µg a.i./day) using a 100% absorption rate (default value) and an application rate to an equivalent oral dose (mg/kg/day) and compare it to the oral value of 100 mg/kg/day and 4.3 mg/kg/day for short- and intermediate-term exposures, respectively, to calculate the MOEs.

Intermediate-Term Inhalation Risk Assessment: A intermediate-term inhalation endpoint of 4.3 mg/kg/day (NOAEL) was selected from a two-year chronic toxicity/carcinogenicity in rats (MRID 44387431) where an increased incidence of thyroid follicular epithelial hyperplasia in females was observed at a LOAEL of 41.2 mg/kg/day. Only an acute inhalation toxicity study has been submitted to the Agency. There were no inhalation toxicity studies appropriate for risk assessment in the toxicology database. Consequently, the oral values should be used for inhalation exposure risk assessment; the route-to-route extrapolation should be done as shown above.

Long-Term Dermal and Inhalation Risk Assessments: Based on the proposed use patterns, no long-term dermal or inhalation exposure is expected to occur. Therefore, no endpoints were selected.

3. Application of Toxicology Endpoints for Aggregate Risk and Occupational Exposure Assessment:

For short and intermediate-term aggregate exposure risk assessment, oral and dermal exposures can not be combined due to differences in the toxicological endpoints via these routes. Oral and inhalation exposure can be combined since inhalation exposure is corrected to oral equivalent doses. Based on the current use pattern, long-term aggregate exposure risk assessment is not required.

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

Table 5. Summary of Toxicology Endpoint Selections for Cloquintocet-mexyl

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (For females 13+)	NOAEL=100 (UF=100)	Higher incidence of skeletal variants and decrease in fetal body weights in the high dose group at 400 mg/kg/day (LOAEL).	Developmental toxicity study in rats MRID 44387429
	Acute RfD (females 13+) = 1.0 mg/kg/day		
Acute Dietary (For general population)	Based on available data, a suitable endpoint was not identified for general population because there were no effects observed in oral toxicity studies appropriate to this population that could be attributed to a single dose exposure. **Acute RfD (general population) = Not applicable**		
Chronic Dietary	NOAEL=4.3 (UF=100)	Observation of thyroid hyperplasia in females at 41.2 mg/kg/day (LOAEL).	Chronic/Oncogenicity Toxicity -Rat MRID 44387431
		Chronic RfD = Chronic PAD = 0.04 mg/kg/day	
Short-term (Dermal)	Dermal NOAEL=200 acceptable MOE ≥ 100	Mottled or reddish livers accompanied by histopathological changes including necrosis and fibrosis in two of five female rats at 1000 mg/kg/day (LOAEL).	28-Day Dermal Toxicity- Rats MRID 44387425
Intermediate-Term (Dermal)			
Long-term (Dermal)	Not Applicable	Based on the current use pattern, no long-term dermal exposure is expected to occur.	
Short-term (Inhalation)	Oral NOAEL= 100[a] acceptable MOE ≥ 100	Higher incidence of skeletal variants and decrease in fetal body weights in the high dose group at 400 mg/kg/day (LOAEL).	Developmental toxicity study in rats MRID 44387429

Table 5. Summary of Toxicology Endpoint Selections for Cloquintocet-mexyl			
EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Intermediate-Term (Inhalation)	Oral NOAEL=4.3 [a] acceptable MOE ≥ 100	Observation of thyroid hyperplasia in females at 41.2 mg/kg/day (LOAEL).	Chronic/Oncogenicity Toxicity -Rat MRID 44387431
Long-term (Inhalation)	Not Applicable	Based on the current use pattern, no long-term inhalation exposure is expected to occur.	

[a] use route to route extrapolation

3.3 FQPA Considerations

The FQPA Safety Factor Committee (SFC) met on March 6, 2000 to evaluate the hazard and exposure data for cloquintocet-mexyl. The Committee recommended that the FQPA safety factor be **reduced to 1x.** The Committee concluded that the safety factor could be removed for cloquintocet-mexyl because:

1. The toxicology database (i.e., developmental toxicity studies in rats and rabbits; 2-generation reproduction study in rats) is complete for the assessment of the effects following *in utero* and/or postnatal exposure to cloquintocet-mexyl;

2. There is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to cloquintocet-mexyl in the available toxicity data;

3. The HIARC determined that a developmental neurotoxicity study is not required for cloquintocet-mexyl;

4. The dietary (food and drinking water) exposure assessments will not underestimate the potential exposures for infants and children from the use of cloquintocet-mexyl (currently there are no proposed residential uses and therefore non-occupational exposure is not expected).

3.4 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following 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 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, cloquintocet-mexyl may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Proposed Uses

Details for the use of cloquintocet-mexyl are presented in Table 6.

Table 6. Summary of Directions for Use of Cloquintocet-mexyl.

Trade Name	Applic. Timing; Type; and Equip.	Applic. Rate (lb ai A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Wheat (including Durum)						
Discover® Herbicide (EPA Reg. No. 100-907)[1] Discover® NG Herbicide (EPA Reg. No. 100-1173)	Postemergence, 2-leaf stage to pre-boot stage. Broadcast foliar Ground or aerial	0.050-0.062 clodinafop-propargyl 0.012-0.016 cloquintocet-mexyl	1	0.062 clodinafop-propargyl 0.016 cloquintocet-mexyl	60	Do not treat wheat underseeded to forages. Do not apply to winter wheat in the fall. Do not graze or feed forage or hay for 30 days after application. For rotational crops, the plantback intervals are 0 days for wheat (inclulding Duram) and 30 days for all other crops. Applications are to be made in a minimum spray volume of 3 gal/A for aerial equipment or 5 gal/A for ground equipment. Applications must always be made with DSV Adjuvant. Application through any type of irrigation system is prohibited. The restricted-entry interval (REI) is 12 hours.
Barley and Wheat (including Durum)						

Table 6. Summary of Directions for Use of Cloquintocet-mexyl.						
Trade Name	Applic. Timing; Type; and Equip.	Applic. Rate (lb ai A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Axial ™ Herbicide (EPA Reg. No. 100-XXX)	Postemergence, 2-leaf stage to pre-boot stage. Broadcast foliar Ground or aerial	0.036 - 0.062 pinoxaden 0.009-0.016 cloquintocet-mexyl	1	0.062 pinoxaden 0.016 cloquintocet-mexyl	60	Do not graze livestock or feed forage or hay for 30 days after application. Do not treat wheat or barley underseeded to forages. For rotational crops, the plantback intervals are 0 days for barley and wheat (including Duram),30 days for leafy crops and root crops, and 120 days for other cereal grains and all other crops. Applications are to be made in a minimum spray volume of 3 gal/A for aerial equipment or 5 gal/A for ground equipment. Add the correct amount of Adigor Adjuvant to the spray tank. Application through any type of irrigation system is prohibited. The restricted-entry interval (REI) is 48 hours.

[1] The Discover® Herbicide label is dated 5/29/03.

The proposed use directions are adequate except for the Axial™ label. The proposed Axial™ Herbicide label is adequate to allow evaluation of the residue data submitted in support of this petition provided that the following label restriction, which is already on the Discover®/Discover® NG labels, is added to the Axial label: "Do not apply to winter wheat in the fall."

Residential uses are not proposed in this petition and there are no residential uses registered for products in which cloquintocet-mexyl serves as a safener.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Metabolism in Plants, Livestock, and Rotational Crops

The nature of the residue in wheat, barley, livestock, and rotational crops is adequately understood. The HED Metabolism Assessment Review Committee (MARC) previously determined for the purpose of the conditional registration that the residues of concern for the tolerance expression and risk assessment for plants, livestock, and rotational crops are cloquintocet-mexyl and its metabolite CGA-153433. HED concludes that the residues of concern

for the tolerance expression and risk assessment in wheat, barley, livestock, and rotational crops are cloquintocet-mexyl and its metabolite CGA-153433, the residues that are currently regulated**.**

Residue Analytical Methods

Adequate enforcement methods are available for enforcement of the proposed/existing tolerances on wheat and barley. The two enforcement methods are the HPLC/UV method REM 138.01 for determination of cloquintocet-mexyl (parent) and the HPLC/UV Method REM 138.10 for determination of the metabolite CGA-153433. Adequate EPA petition method validations have been conducted on wheat grain, straw, and forage for the two enforcement methods. Both methods have been forwarded to FDA for publication in PAM, Vol. II. The validated LOQs for Method REM 138.01 are 0.05 ppm for wheat forage, hay, and straw, and 0.02 ppm for wheat grain, processed commodities, and aspirated grain fractions. The validated LOQ for Method REM 138.10 is 0.05 ppm for all wheat commodities.

Syngenta submitted analytical Methods REM 199.02, REM 199.03, and 117-01 for analysis of residues of CGA-153433, the metabolite of cloquintocet-mexyl, in cereal grain matrices. Method REM 199.02 was used to determine residues of CGA-153433 in barley grain, hay, and straw in one barley field trial study (MRID 46203205) and in wheat field trials conducted in Canada (MRID 46302206). Method 117-01 was used to determine residues of CGA-153433 in barley grain, hay, and straw in one barley field trial study (MRID 46203204) and in the barley grain and processed commodities in the processing study (MRID 46203204). All three methods possessed the same extraction procedure consisting of acid hydrolysis (1N HCl) by boiling under reflux for two hours. The acid hydrolysis is intended to convert the parent cloquintocet-mexyl (CGA-185072) to the acid metabolite, CGA-153433; however, validation/recovery data for CGA-185072 was not provided. The three methods are adequate for data gathering methods for cloquintocet-mexyl in cereal grain commodities.

Method REM 117-01 (MRID 46203138) is also proposed as an enforcement method. To be an enforcement method for cloquintocet-mexyl, EPA's analytical chemistry laboratory (ACB/BEAD) would have to validate the Method 117-01 for cloquintocet-mexyl (CGA-185072) and its metabolite CGA-153433 in cereal matrices and radiovalidation data for the method would have to be submitted. This is not a deficiency for these actions.

Multiresidue Methods

Cloquintocet-mexyl and CGA-153433 were tested through the FDA multiresidue methods according to the decision tree and protocols in the Pesticide Analytical Manual, Volume I, Appendix II. Cloquintocet-mexyl was tested per Protocols C, D, and E; recovery was variable using protocol D, and the test substance was not recovered using Protocol E. CGA-153433 was tested per Protocols B and C; the compound was not recovered using Protocol B, and based on the results of Protocol C testing, no further testing was required for this compound. The submitted multiresidue methods data have been forwarded to FDA.

Storage Stability Data

The available storage stability data are adequate to support the storage conditions and storage intervals for all wheat commodities except wheat grain. The petitioner must submit the following additional data to support the storage stability study (Study 300/91; MRID 44399210) for CGA-153433 in wheat grain: (1) raw data, including residues (ppm) found and representative chromatograms (for standards, controls, freshly fortified samples, and stored samples); (2) description of storage containers; and (3) submission or identification by number of the method used to analyze the storage stability samples.

Magnitude of the Residue

Wheat

Table 7. Summary of Residues from the Crop Field Trials with Cloquintocet-mexyl.

Commodity	Total Applic. Rate (lb ai/A) [g ai/A]	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
Wheat (proposed use = 0.016 lb safener/A total application rate, 30-day PHI for forage and hay, 60-day PHI for grain and straw)										
Spring wheat (MRID 46012904)										
Wheat, forage	0.016 [7.1]	29-32	CGA-185072	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	12	<0.10	<0.10	<0.10	<0.10	<0.10	0.0
Wheat, hay	0.016 [7.1]	29-47	CGA-185072	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	12	<0.10	<0.10	<0.10	<0.10	<0.10	0.0
Wheat, straw	0.016 [7.1]	57-61	CGA-185072	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	12	<0.10	<0.10	<0.10	<0.10	<0.10	0.0
Wheat, grain	0.016 [7.1]	57-61	CGA-185072	12	<0.02	<0.02	<0.02	<0.02	<0.02	0.0
			CGA-153433	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	12	<0.07	<0.07	<0.07	<0.07	<0.07	0.0
Winter wheat treated in the spring (MRID 46012904)										
Wheat, forage	0.016 [7.1]	29-32	CGA-185072	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	12	<0.10	<0.10	<0.10	<0.10	<0.10	0.0
Wheat, hay	0.016 [7.1]	29-32	CGA-185072	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	12	<0.10	<0.10	<0.10	<0.10	<0.10	0.0

Table 7. Summary of Residues from the Crop Field Trials with Cloquintocet-mexyl.										
Commodity	Total Applic. Rate (lb ai/A) [g ai/A]	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
Wheat, straw	0.016 [2] [7.1]	58-69	CGA-185072	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	12	<0.10	<0.10	<0.10	<0.10	<0.10	0.0
Wheat, grain	0.016 [2] [7.1]	58-69	CGA-185072	12	<0.02	<0.02	<0.02	<0.02	<0.02	0.0
			CGA-153433	12	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	12	<0.07	<0.07	<0.07	<0.07	<0.07	0.0
Winter wheat treated in the fall (MRID 46012904) *										
Wheat, forage	0.016 [7.1]	27-33	CGA-185072	16	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	16	<0.05	0.07	0.07	<0.05	<0.05	0.0
			Total	16	<0.10	<0.12	<0.12	<0.10	<0.10	0.0
Wheat, hay	0.016 [7.1]	27-33	CGA-185072	16	<0.05	0.06	0.06	<0.05	<0.05	0.0
			CGA-153433	16	<0.05	0.13	0.13	<0.05	<0.05	0.0
			Total	16	<0.10	0.19	0.19	<0.10	<0.10	0.0
Wheat, straw	0.016 [7.1]	58-63	CGA-185072	16	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	16	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	16	<0.10	<0.10	<0.10	<0.10	<0.10	0.0
Wheat, grain	0.016 [7.1]	58-63	CGA-185072	16	<0.02	<0.02	<0.02	<0.02	<0.02	0.0
			CGA-153433	16	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	16	<0.07	<0.07	<0.07	<0.07	<0.07	0.0
Winter wheat treated in the spring (MRID 46012905)										
Wheat, forage	0.016 [7.1]	29-30	CGA-185072	16	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	16	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	16	<0.10	<0.10	<0.10	<0.10	<0.10	0.0
Wheat, hay	0.016 [7.1]	29-30	CGA-185072	16	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	16	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	16	<0.10	<0.10	<0.10	<0.10	<0.10	0.0
Spring and winter wheat grown in the Pacific Northwest (MRID 46012918)										
Wheat, forage	0.016 [7.1]	29-30	CGA-185072	6	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	6	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	6	<0.10	<0.10	<0.10	<0.10	<0.10	0.0
Wheat, hay	0.016 [7.1]	29-30	CGA-185072	6	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	6	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	6	<0.10	<0.10	<0.10	<0.10	<0.10	0.0

Table 7. Summary of Residues from the Crop Field Trials with Cloquintocet-mexyl.										
Commodity	Total Applic. Rate (lb ai/A) [g ai/A]	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
Wheat, straw	0.016 [7.1]	56-60	CGA-185072	8	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			CGA-153433	8	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	8	<0.10	<0.10	<0.10	<0.10	<0.10	0.0
Wheat, grain	0.016 [7.1]	56-60	CGA-185072	8	<0.02	<0.02	<0.02	<0.02	<0.02	0.0
			CGA-153433	8	<0.05	<0.05	<0.05	<0.05	<0.05	0.0
			Total	8	<0.07	<0.07	<0.07	<0.07	<0.07	0.0

[1] HAFT = Highest Average Field Trial.
[2] In one trial, wheat plants inadvertently received both an early season and late season application, yielding an application rate of 0.032 lb ai/A (14.2 g ai/A).
* These studies on winter wheat treated in the fall should be disregarded because the labels will prohibit use on wheat in the fall.

Table 8. Summary of Residues from the Crop Field Trials with Cloquintocet-mexyl conducted in Canada (MRID 46302206)										
Commodity	Total Applic. Rate (lb ai/A) [g ai/A]	PHI (days)	Analyte [2]	Residue Levels (ppm) [3]						
				n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
Wheat (proposed use = 0.016 lb safener/A total application rate, 30-day PHI for forage and hay, 60-day PHI for grain and straw)										
Wheat (MRID 46203206)										
Wheat, forage	0.016 [7.1]å	22-31	CGA-153433	8	<0.02	<0.02	<0.02	<0.02	<0.02	0.0
Wheat, hay	0.016 [7.1]Ä	28-35	CGA-153433	29	<0.02	<0.02	<0.02	<0.02	<0.02	0.0
Wheat, straw	0.016 [7.1]	58-62	CGA-153433	23	<0.02	<0.02	<0.02	<0.02	<0.02	0.0
Wheat, grain	[7.1]ã	58-62	CGA-153433	23	<0.01	<0.01	<0.01	<0.01	<0.01	0.0

[1] HAFT = Highest Average Field Trial.
[2] The method (REM 199.02) determines parent and the metabolite CGA-153433 as CGA-153433.
[3] All values are reported as <LOQ in the table above. The LOD is ½ LOQ. Values were also <LOD in most cases.

In a previous residue chemistry review, HED stated:

> "Adequate geographic representation was not provided. To support a 30-day PHI in forage (as currently on the label), an additional 14 field trials are required, in Region 2 (1 trial), Region 4 (1 trial), Region 5 (3 trials), Region 6 (1 trial), Region 7 (1 trial), Region 8 (6 trials), and Region 11 (1 trial). Spring wheat (including hard red spring, duram and

white spring varieties) and winter wheat (including hard red winter, soft red winter, and white winter varieties) should be included. (If the petitioner could not analyze the spring wheat straw samples (included in the interim report) for residues of CGA-153433 and support the reanalyses with storage stability data, then additional crop field trial data would be required.) Each study should include DSV Adjuvant or similar adjuvant. Raw data and representative chromatograms of standards, controls, fortified samples, and treated samples should be included. Storage information including types of storage containers and dates of extraction (as well as dates of storage and analysis) should be included."

This deficiency has not been resolved. The wheat field trials are not adequate in number or geographic representation. A total of 20 wheat field trials (6 spring wheat trials and 14 winter wheat trials) were conducted during the 1998-1999 growing seasons. Spring wheat field trials were conducted in Regions 5 (MN and ND; 2 trials) and 7 (MT, ND, and SD; 4 trials). Winter wheat field trials were conducted in Regions 2 (NC; 1 trial), 4 (AR; 1 trial), 5 (IL, KS, and MO; 3 trials), 6 (OK; 1 trial), 8 (CO, KS, NM, OK, and TX; 6 trials), and 11 (WA; 1 trial). In addition, one trial was conducted in Region 5 (NE) close enough to the border with Region 7 to support geographic representation requirements for Region 7. The winter wheat field trials were conducted with two types of early season application: application in the fall or application in the spring. Of the 14 winter wheat trials, a total of 8 trials were conducted reflecting application in the fall, in Regions 2 (NC; 1 trial), 4 (AR; 1 trial), 5 (KS; 1 trial), 6 (OK; 1 trial), and 8 (KS, OK, and TX; 4 trials). The remaining 6 trials were conducted reflecting early season application in the spring, in Regions 5 (IL and MO; 2 trials), 7 (NE; 1 trial), 8 (CO and NM; 2 trials), and 11 (WA; 1 trial). The petitioner has stated that they will not be supporting application of Discover/Discover NG to winter wheat in the fall; application to winter wheat will be restricted to a spring postemergence foliar application. Because application to winter wheat in the fall is restricted, the data can be disregarded for Discover/Discover NG; however, not using these studies as part of the database means that geographic representation of the residue trials is not adequate.

Because the data for the winter wheat treated in the spring will not be used, the number and geographic representation for the wheat field trials are not adequate. For Discover/Discover NG, an additional 8 field trials are needed for adequate geographic representation as follows: 1 trial in Region 2, 1 trial in Region 4, 1 trial in Region 5, 1 trial in Region 6, and 4 trials in Region 8. For Axial, the petitioner should add the restriction "Do not apply to winter wheat in the fall" to the label; this restriction is already on the Discover®/Discover® NG Herbicide labels.

Alternatively, the winter wheat data could be used but the higher tolerances then needed on wheat commodities would mean that a ruminant feeding study would be needed or a livestock method for meat, fat, and milk including radiovalidation data and an independent laboratory validation would be needed. A validation of the livestock method by EPA's ACB/BEAD would also be needed. If a validated livestock enforcement method could be made available, tolerances for ruminant commodities, pending ChemSAC approval, could be set at the limit of quantitation

of the method.

The submitted wheat field trials are adequate for a conditional registration. Samples of wheat forage, hay, grain, and straw were analyzed. Most of the wheat samples were analyzed by the HPLC/UV enforcement methods REM 138.01 (for parent) and REM 183.10 (for the metabolite CGA-153433). The validated LOQs for Method REM 138.01 are 0.05 ppm for wheat forage, hay, and straw, and 0.02 ppm for wheat grain, processed commodities, and aspirated grain fractions. The validated LOQ for Method REM 138.10 is 0.05 ppm for all wheat commodities. Residues in spring wheat and winter wheat planted in the spring will not exceed 0.1 ppm in wheat grain, forage, hay, and straw.

Barley

Table 9. Summary of Residue Data from Barley Field Trials with Cloquintocet-mexyl,

Commodity	Total Applic. Rate, (lb a.i./A)	PHI (days)	Residue Levels of CGA-153433 (ppm)[1]						
			n	Min.	Max.	HAFT[2]	Median (STMdR)	Mean (STMR)	Std. Dev.
CGA-153433 (metabolite of safener Cloquintocet-mexyl) in herbicide NOA-407855 (MRIDs 46203204 and 46203205)									
Barley hay	0.016	26-35	48	<LOQ[3]	0.048	0.029	<LOQ	<LOQ	N/A[4]
Barley straw	0.016	57-66	44	<LOQ	0.050	0.036	<LOQ	<LOQ	N/A
Barley grain	0.016	57-66	44	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	N/A
CGA-153433 (metabolite of safener Cloquintocet-mexyl) in herbicide NOA-407855 (MRID 46203204)									
Barley hay	0.016	30	24	<LOQ	0.048	0.029	<LOQ	<LOQ	N/A
Barley straw	0.016	60	24	<LOQ	0.050	0.036	<LOQ	<LOQ	N/A
Barley grain	0.016	60	24	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	N/A
CGA-153433 (metabolite of safener cloquintocet-mexyl)in herbicide NOA-407855 (MRID 46203205)									
Barley hay	0.016	26-35[5]	24	<LOQ	0.02	0.02	<LOQ	<LOQ	N/A
Barley straw	0.016	57-66[5]	20	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	N/A
Barley grain	0.016	57-66[5]	20	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	N/A

[1] The method determines parent cloquintocet-mexyl and its metabolite CGA-153433 as CGA-153433.
[2] HAFT = Highest Average Field Trial.
[3] LOQ =0.01 ppm for grain and 0.02 ppm for hay and straw.
[4] N/A = not applicable.
[5] Studies from MRID 46203205 with hay at PHIs of 26-35 days include Region 5B (1 study), Regiion 5 (1), Region 7 (1), and Region 14 (9). Studies with straw and grain at PHIs of 57-66 days include Region 7 (1) and Region 14 (7).

The submitted barley field trials are adequate in number and geographic representation. The data collection methods for barley determined combined residues of cloquintocet-mexyl and its metabolite CGA-153433 as CGA-153433, using an oxidation step to convert cloquintocet-mexyl to CGA-153433. Based on these residue data, residues are not expected to exceed 0.010 ppm in barley grain (LOQ) and 0.050 ppm in barley hay and straw. Because the EPA-validated enforcement methods determine parent and metabolite separately at LOQs of 0.05 for each

analyte on each commodity except for an LOQ of 0.02 ppm for parent in grain, the tolerances for the combined residues of cloquintocet-mexyl and its metabolite CGA-1532433 should be 0.10 ppm for barley, hay; 0.10 ppm for barley, grain; and 0.10 ppm for barley, straw.

Processed Food and Feed

Wheat

A deficiency remains outstanding pending submission of additional information requested for Study 300/91 (MRID 44399210) regarding the storage stability data for grain. The additional information requested for Study 300/91 (MRID 44399210) are as follows: Raw data, including residues (ppm) found and representative chromatograms (for standards, controls, freshly fortified samples, and stored samples) should be submitted. Storage containers should be described. The method used to analyze the storage samples should be submitted or identified by number as a submitted method.

The submitted processing data for wheat are tentatively adequate to satisfy data requirements, pending submission of additional information requested for Study 300/91 (MRID 44399210) regarding the storage stability data for grain. The processing data indicate that residues of cloquintocet-mexyl and CGA-153433, determined as CGA-153433, do not concentrate in wheat processed commodities (bran, flour, middlings, shorts, and germ). Residues may concentrate in aspirated grain fractions (AGF) but residues in AGF are not likely to exceed the recommended tolerance of 0.10 ppm for grain. Therefore, tolerances are not needed for the wheat processed commodities (bran, flour, middlings, shorts, and germ) or for aspirated grain fractions.

Barley

Pending submission of additional information regarding storage stability of grain, HED tentatively concludes that the submitted barley processing study is adequate. Residues were <LOQ (<0.01 ppm) in barley grain treated at 5X and <LOQ (<0.01 ppm) in the processed fractions pearled barley, flour, and bran. Residues do not concentrate on processing and tolerances on the processed commodities pearled barley, flour, and bran are not needed.

Magnitude of the Residue in Meat, Milk, Poultry and Eggs

Because of the low levels of total radioactive residues found in livestock commodities in the ruminant and poultry metabolism studies and the corresponding low radioactive residues calculated for the 1X feeding levels, ruminant and poultry feeding studies are not needed and tolerances on livestock commodities are not needed. This use falls under 40 CFR §180.6(a)(3) since no secondary residues are expected to occur in livestock commodities.

Confined/Field Accumulation in Rotational Crops

The nature of the residue in rotational crops is adequately understood. No additional data are needed for rotational crops. The HED Metabolism Assessment Review Committee (MARC) previously determined for the purpose of the conditional registration that the residues of concern for the tolerance expression and risk assessment for rotational crops are cloquintocet-mexyl and its metabolite CGA-153433. HED concludes that the residues of concern for the tolerance expression and risk assessment in rotational crops are cloquintocet-mexyl and its metabolite CGA-153433, the residues that are currently regulated. A 30-day plantback interval is appropriate for cloquintocet-mexyl for all crops not on the label. This 30-day plantback restriction is included on the Discover®/Discover® NG Herbicide and Axial™ Herbicide labels.

4.2.2 Dietary Analysis

Acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.02), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, and 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, and 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

Established and recommended tolerances were used in acute and chronic dietary assessments. Percent crop treated data were not applied. DEEM™ default concentration factors were used.

4.2.2.1 Acute Dietary

The acute dietary exposure analysis for cloquintocet-mexyl is a Tier 1 assessment because no additional data were used to refine the analysis. One hundred percent of proposed and registered crops are assumed treated with cloquintocet-mexyl (100% CT) and tolerance-level residues were used in the analysis. The acute dietary endpoint (incidence of skeletal variants and decrease in fetal body weights) is only applicable to the population subgroup females 13-49 years old. An acute dietary endpoint for the general population including infants and children was not identified. The highest estimate for acute drinking water exposure, 0.186 ppb, was used in the analysis (see Section 4.3, below). The estimated dietary exposure for females 13-49 years old occupies less than 1% of the aPAD and does not exceed HED's level of concern.

Table 10. Results of Acute Dietary Exposure Analysis			
Population Subgroup	aPAD (mg/kg/day)	95th Percentile	
		Exposure (mg/kg/day)	% aPAD
Females 13-49 years old	1	0.000347	<1

4.2.2.2 Chronic Dietary

The chronic dietary exposure analysis for cloquintocet-mexyl is a Tier 1 assessment because no additional data were used to refine the analysis. One hundred percent of proposed and registered crops are assumed treated with cloquintocet-mexyl (100% CT) and tolerance-level residues were used in the analysis. The chronic dietary endpoint applies to all population subgroups including infants and children. The highest estimate for chronic drinking water exposure, 0.005 ppb, was used in the analysis (see Section 4.3, below). A listing of the subgroups are reported below in Table 11.

The results of the chronic dietary analysis show that risk ranges from <1% of the cPAD for adults (50+ years) to 1% of the cPAD for children (3-5 years). Risk estimates for all population subgroups are below HED's level of concern (100% of the cPAD).

Table 11. Results of Chronic Dietary Exposure Analysis			
Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.04	0.000180	<1
All Infants (< 1 year old)	0.04	0.000077	<1
Children 1-2 years old	0.04	0.000403	1
Children 3-5 years old	0.04	0.000411	1
Children 6-12 years old	0.04	0.000289	<1
Youth 13-19 years old	0.04	0.000176	<1
Adults 20-49 years old	0.04	0.000153	<1
Adults 50+ years old	0.04	0.000120	<1
Females 13-49 years old	0.04	0.000137	<1

4.2.2.3 Cancer Dietary

In August 1999, the HIARC classified cloquintocet-mexyl as "not likely to be a human

carcinogen." Due to the classification, no cancer risk assessment was performed.

4.3 Water Exposure/Risk Pathway

The mobility of cloquintocet-mexyl (as measured by its binding to soils) varies from low in a moderate organic soil to essentially immobile in a high organic soil. The persistence of cloquintocet-mexyl in soil is also very low. Therefore, based upon the its low persistence and low mobility, the leaching potential of cloquintocet-mexyl should be negligible. The results of the aerobic aquatic metabolism studies indicate that cloquintocet-mexyl will rapidly degrade in aerobic ground and surface waters that have adequate microbial activity. The results of the direct photolysis (DT50 of several hours) indicate that cloquintocet-mexyl is also susceptible to rapid rates of direct photolysis in clear shallow water. However, based on the results of the abiotic hydrolysis study (half-lives of 4.4 yr. at pH 5, 134 days at pH 7 and 6.6 days at pH 9), it may be substantially more persistent in aerobic waters with low microbial activity. Data are not currently available to assess its persistence in anaerobic waters.

The Agency currently lacks sufficient water-related exposure data from monitoring to complete a *quantitative* drinking water exposure analysis and risk assessment for cloquintocet-mexyl. Therefore, the Agency is presently relying on computer-generated estimated environmental concentrations (EECs). These EECs are provided by the Environmental Fate and Effects Division (EFED). GENEEC is a model used to generate EECs for *surface* water based on estimates of safener concentration in a farm pond. SCI-GROW is an empirical model based upon actual monitoring data collected for a number of pesticides which serve as benchmarks and has been used to predict EECs in *ground* water. Based on the environmental fate properties of cloquintocet-mexyl and the rapid degradation of the parent compound (i.e., hours to days) to the major degradate, CGA-153433 (5-chloro-8-quinolinoxyacetic acid), EFED provided HED with EECs for combined residues of cloquintocet-mexyl and CGA-153433. EFED reported that the highest EECs from the current and proposed uses were the GENEEC estimates acute (peak) and chronic (56-year mean) concentrations of cloquintocet-mexyl and CGA-153433 in water at 0.186 ppb and 0.005 ppb, respectively.

4.4 Residential Exposure/Risk Pathway

Residential uses are not proposed in this petition and there are no residential uses registered for products in which cloquintocet-mexyl serves as a safener, and therefore, a residential exposure assessment is not required.

4.4.1 Other Exposure Sources

There are no existing or proposed residential uses for this product. However, spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the groundboom application. The 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

5.1 Acute Aggregate Risk (food + drinking water)

The aggregate acute risk estimates include exposure to residues of cloquintocet-mexyl in food and water, and does not include dermal, inhalation or incidental oral exposure. Since the dietary exposure assessment already includes the highest acute exposure from the drinking water modeling data, no further calculations are necessary. The food and water exposure estimates for females 13-49 yrs old is <1% aPAD. **The acute risk estimate for females 13-49 years, resulting from aggregate exposure to cloquintocet-mexyl in food and drinking water is below HED's level of concern.**

5.2 Short- and Intermediate-Term Aggregate Risk (food + drinking water + residential)

These aggregate risk assessments take into account chronic dietary exposure from food and water (considered to be a background exposure level) plus (short- and/or intermediate-term, as applicable) indoor and outdoor residential exposures.

The HIARC selected doses and toxicological endpoints (Table 5) for assessments of short- and intermediate-term dermal and inhalation risk. However, since there are no residential uses for cloquintocet-mexyl (either established or pending) **at this time, these risk assessments are not currently required.**

5.3 Chronic Aggregate Risk

The aggregate chronic risk assessment takes into account average exposure estimates from dietary consumption of cloquintocet-mexyl (food and drinking water) and residential uses. Since since there are no residential uses for cloquintocet-mexyl (either established or pending) at this time, the aggregate chronic assessment included food and drinking water only. Since the dietary exposure assessment already includes the highest chronic exposure from the drinking water modeling data, no further calculations are necessary. The general U.S. population and all population subgroups have exposure and risk estimates which are below HED's level of concern (i.e., the percentages of the chronic population adjusted doses

(cPADs) are all below 100%). The exposure to the U.S. population was <1% cPAD and the most highly exposed subgroup, children 3-5 yrs old, at 1% cPAD. Therefore, **chronic risk estimates resulting from aggregate exposure to cloquintocet-mexyl in food and drinking water are below HED's level of concern from all population subgroups.**

5.5 Cancer Aggregate Risk

In August 1999, the HIARC classified cloquintocet-mexyl as "not likely to be a human carcinogen." Due to the classification, **no cancer risk assessment was performed**.

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.

HED did not perform a cumulative risk assessment as part of this tolerance action for cloquintocet-mexyl, because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of cloquintocet-mexyl. For purposes of this tolerance action, EPA has assumed that cloquintocet-mexyl does not have a common mechanism of toxicity with other substances.

7.0 OCCUPATIONAL EXPOSURE

Workers may be exposed to cloquintocet-mexyl during mixing, loading, application, and postapplication activities. Based on the proposed use pattern, short-, and intermediate-term exposures may occur. Chronic exposures (more than 6 months of continuous exposure) are not expected.

7.1 Occupational Handler

There is a potential for exposure to cloquintocet-mexyl during mixing, loading, and application activities. An exposure/risk assessment using applicable endpoints selected by the HIARC was performed. Handler's exposure and risk were estimated for the following scenarios: 1) mixing/loading liquid to support aerial application; 2) aerial application 3) mixing/loading liquid to support groundboom application; 4) groundboom application; 5) mixing, loading and

applying by groundboom; and, (6) flagging for aerial application. Flaggers for aerial application are assessed for 350 acres per day application, because a larger number of acres treated would likely require pilot-activated mechanical flagging or Global Positioning Systems, and not human flaggers.

It is the policy of the HED to use data from the PHED Version 1.1, as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft Policy # 7, dated 1/28/99). HED believes the use of the Surrogate Exposure Guide provides a more reliable exposure estimate than individual subsets because of the larger number of replicates in the pooled data. Because no chemical-specific handler exposure data were submitted in support of this action, and in accordance with HED's Exposure Science Advisory Council (SAC) SOP, exposure data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) was used with other HED standard values for acres treated per day, body weight, and the level of personal protective equipment to assess handler exposures. The unit exposure values from PHED are considered to be central tendency. The application rates, treatment variables, etc used in this assessment are upper percentile values. Therefore, the potential dose is characterized as central to high-end.

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

Exposure assumptions and estimates for occupational handlers are summarized in Table 12. The MOEs range from 250 to 4,500,000 for handlers. **These MOEs are greater than 100, and therefore, do not exceed HED's level of concern.**

Table 12. Exposure and Risk Assessment for Occupational Handlers

PHED Scenarios for Cloquintocet-mexyl Uses	PHED Unit Exposure[1] (mg/lb safener)	Maximum Application Rate	Area/Amount Treated	Daily Dose[2] (mg/kg/day) [70 kg BW]	Short/Intermediate Term Dermal Risk (MOE)[3]	Short-term Inhalation Risk (MOE)[4]	Intermediate-term Inhalation Risk (MOE)[5]
(1) Mix/load : liquid to support aerial (open)	Dermal: 2.9	0.016 lb ai/A	1200	0.80	250	260,000	13,000
	Inhalation: 0.0012			0.00033			
(2) Apply: aerial (closed cab)	Dermal: 0.0050	0.016 lb ai/A	1200	0.0014	140,000	4,500,000	230,000
	Inhalation: 0.000068			0.000019			
(3) Mix/load : liquid to support groundboom (open)	Dermal: 2.9	0.016 lb ai/A	200	0.13	1500	1,600,000	78,000
	Inhalation: 0.0012			0.000055			
(4) Apply: groundboom (open cab)	Dermal: 0.014	0.016 lb ai/A	200	0.00064	310,000	2,500,000	130,000
	Inhalation: 0.00074			0.000034			
(5) Flaggers for aerial application	Dermal: 0.011	0.016 lb ai/A	350	0.00088	220,000	3,000,000	170,000
	Inhalation: 0.00035			0.000028			

[1] PHED Unit Exposure values are for baseline protection (long-sleeved shirt, long pants, shoes plus socks) unless otherwise indicted.
[2] Daily Dose =(Unit Exposure x Application Rate x Area Treated)/Body Weight [Body weight of 60 kg used for short-term inhalation; 70 kg used for other endpoints]
[3] MOE = NOAEL/ Daily Dose. Short- and Intermediate-term dermal NOAEL= 200 mg/kg/day.
[4] MOE = NOAEL/ Daily Dose. Short-term inhalation NOAEL=100 mg/kg/day.
[5] MOE = NOAEL/ Daily Dose. Intermediate-term inhalation NOAEL= 4.3 mg/kg/day.

7.2 Occupational Postapplication

Postapplication occupational risks from working in wheat fields treated with cloquitocet-mexyl were assessed for scouting and irrigation. Wheat and barley are assumed to be mechanically harvested. The Agency acknowledges that there is some potential for exposure during harvesting because individuals engaged in fully mechanized activities have short-term excursions from the protected area for various reasons (e.g., unclogging machinery or equipment inspection for breakage). In these cases, the WPS § 170.112(c) Exception for short-term activities applies. Because the application being made relatively early in the growth cycle, dislodgeable residues are expected to be significantly reduced by the time of harvest, due to degradation, growth of the plant, and absorption by the plant material.

Because chemical-specific postapplication exposure data were not provided, an appropriate default transfer coefficient was chosen from those established by the HED Exposure SAC (5/7/98, policy #3). Likewise, because chemical-specific dissipation data were not submitted, it is the HED policy to assume that 20% of the application rate is available to dislodge on the day of treatment, and that this residue dissipates at a rate of 10% per day, thereafter, for calculating postapplication exposure and risk. The application rate, transfer coefficient, and dislodgeable residue dissipation variables used in this assessment are upper percentile values. Therefore, the daily dose is characterized as high-end.

Inputs and calculated postapplication risk can be seen in Table 13. Risk calculations for postapplication workers result in an MOE = 490,000 on the day of application. Because this MOE well exceeds 100, this risk does not trigger HED concern for postapplication workers in wheat or barley fields treated with cloquintocet-mexyl (in formulation with pinoxaden).

Table 13. Exposure and Risk Assessment for Occupational Postapplication Activities

Crop Group	Application Rate (lb safener/A)	Dermal Transfer Coefficient (cm^2/hr)	Dislodgeable Foliar Residue (ug/cm^2)	Post-application Day (t)	Daily Dose[2] (mg/kg/day)	Short-/Intermed. Term Dermal MOE[3]
Wheat & Barley	0.016	100[1]	0.036	0	0.00041	490,000

[1] Transfer Coefficient for scouting and irrigating.
[2] Daily Dose = (Dislodgeable Foliar Residue x Dermal Transfer Coefficient x Exposure Time) / (CF: 1000 ug/mg) x Body weight
[3] MOE = NOAEL/Daily Dose. Short-/Intermediate-Term Dermal NOAEL = 200 mg/kg/day

The acute toxicity of technical cloquintocet-mexyl would require an interim restricted entry interval (REI) of 12 hours under the requirements of the Worker Protection Standard (WPS). However, the label for the pinoxadem product in which cloquintocet-mexyl serves as a safener lists a 48-hour interim WPS REI, and therefore, this requirement restricts the cloquintocet-mexyl

component as well.

8.0 DATA NEEDS

8.1 Toxicology

None

8.2 Residue Chemistry

860.1200 Directions for Use

1. The proposed Axial™ Herbicide label is adequate to allow evaluation of the residue data submitted in support of this petition provided that the following label restriction, which is already on the Discover®/Discover® NG labels, is added to the Axial label: "Do not apply to winter wheat in the fall."

2. Since residue data support one application per season, the Discover®/Discover®NG Herbicide labels and the Axial™ Herbicide labels should all contain the statement "Do not apply both Discover® and Axial™ products to the same crop in the same season."

860.1380 Storage Stability

3. The requirement from the 4/7/00 review for additional information to support Study 300/91 reported in MRID 44399210 (storage stability study for CGA-153433 in wheat grain) has not been addressed by the petitioner. The petitioner must submit the following additional data to support the storage stability study in MRID 44399210 for CGA-153433 in wheat grain: (1) raw data, including residues (ppm) found and representative chromatograms (for standards, controls, freshly fortified samples, and stored samples); (2) description of storage containers; and (3) submission or identification by number of the method used to analyze the storage stability samples.

860.1500 Crop Field Trials

4. The wheat field trials are not adequate in number or geographic representation. Because the data for the winter wheat treated in the fall will not be used, the number and geographic representation for the wheat field trials are not adequate. An additional 8 field trials are needed for adequate geographic representation as follows: 1 trial in Region 2, 1 trial in Region 4, 1 trial in Region 5, 1 trial in Region 6, and 4 trials in Region 8. For Axial, the petitioner should add the restriction "Do not apply to winter wheat in the fall" to the label; this restriction is already on the Discover®/Discover® NG Herbicide labels.

Alternatively, the winter wheat data could be used but the higher tolerances then needed on wheat commodities would mean that a ruminant feeding study would be needed or a livestock method

for meat, fat, and milk including radiovalidation data and an independent laboratory validation would be needed. A validation of the livestock method by EPA's ACB/BEAD would also be needed. If a validated livestock enforcement method could be made available, tolerances for ruminant commodities, pending ChemSAC approval, could be set at the limit of quantitation of the method.

860.1520 Processed Food/Feed

5. The submitted processing data for barley and wheat are tentatively adequate to satisfy data requirements, pending submission of additional information requested for Study 300/91 (MRID 44399210) regarding the storage stability data for grain (requested under 860.1380 Storage Stability).

860.1550 Proposed Tolerances

6. A revised Section F must be submitted to propose retention of the tolerance of 0.1 ppm for wheat, forage; wheat, grain; wheat, hay; and wheat, straw and to propose a tolerance of 0.1 ppm for barley, grain; barley, hay; and barley, straw.

8.3 Occupational/Residential

None

References:
PP#7E4920, DP Barcode: D264559, A. Lowit, 5/8/00.
PP#7E4920, DP Barcode: D257181, N. Dodd, 4/7/00.
HIARC cloquintocet-mexyl, Y. Yang, 6/17/99.
PP #7E04920, S. Gross, 4/20/2000.
CLOQUINTOCET-MEXYL - Report of the FQPA Safety Factor Committee, B. Tarplee, 3/20/99.
PP#'s 7E04920 and 4E06831, DP Barcode: D308470, MRID: 46012904, 46012905, 46012909, 46012910, 46012911, 46012912, 46012913, 46012914, 46012915, 46012916, 46012917, 46012918, 46203138, 46203139,46203140, 46203142, 46203143, 46203203, 46203204, 46203205, 46203206, 46373301, & 46373302, N. Dodd, in process.
PP# 4E6831, DP Barcode: D322951, W. Cutchin, in process.
PP# 7E4920, DP Barcode: D263289, N. Dodd, 2/25/00.
DP Barcode: D262416, E. Hayes, ACB, 6/22/00.
DP Barcode: D267870, N. Dodd, 8/8/00.
DP Barcode: D255566, N. Dodd, 5/12/99.
DP Barcode: D322950, J. Arthur, in process.
DP Barcode: D323526, L. Shanaman, 11/17/05.