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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: May 8, 2000

MEMORANDUM

Subject: **PP #7E04920.** Human Health Risk Assessment for the Use of the New Safener, Cloquintocet-mexyl, on Wheat.

DP Barcode	D264559	Submission	S533228
PC Code	999999	Case	289237
40 CFR	None (New Inert)	Class	Safener
Trade Name	See Confidential Appendix		

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The Health Effects Division (HED) has conducted a human health risk assessment for cloquintocet-mexyl for the purpose of making a tolerance eligibility decision for use on wheat as requested by Novartis Crop Protection, Inc, the petitioner. Novartis Crop Protection, Inc has submitted a petition (PP#7E04920) proposing to establish permanent tolerances for residues of cloquintocet-mexyl (acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester) in/on wheat. Cloquintocet-mexyl is the safener in the formulation described in the confidential appendix. HED is recommending for the establishment of a **time-limited registration, conditional upon submission of data/information to satisfy the outstanding deficiences** for the formulation. Tolerances should be established for the combined residues of cloquintocet-

mexyl and its acid metabolite (5-chloro-8-quinolinoxyacetic acid) at 0.10 ppm for wheat grain, forage, hay and straw.

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1.0 EXECUTIVE SUMMARY

♦ **For a LIST of the ATTACHMENTS to this review, see Section 7.0.**

Cloquintocet-mexyl (acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester) is a new safener for use in/on wheat (PP#7E04920). The subject petition proposes **the first food use in the US** for this safener. There are no proposed non-food uses in the US. There are no Codex, Canadian, or Mexican tolerances for cloquintocet-mexyl on wheat. Novartis Crop Protection, Inc. (formerly Ciba Crop Protection), the petitioner, has submitted a petition for the establishment of permanent tolerances for residues of the safener cloquintocet-mexyl (also referred to as CGA-185072) in/or on wheat. The safener cloquintocet-mexyl prevents damage to wheat due to phytotoxic effects of the active ingredient contained in the end-use product. The petitioner is also requesting a Section 3 registration for the end-use product; the end-use product is described in the Confidential Appendix.

Specifically, the petitioner proposed the establishment of tolerances for residues of the safener cloquintocet-mexyl (acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester), in or on wheat grain at 0.02 ppm and wheat straw at 0.05 ppm. HED is recommending for the establishment of a **time-limited registration, conditional upon submission of data/information to satisfy the outstanding deficiences** for the formulation described in the Confidential Appendix. Tolerances should be established for the combined residues of cloquintocet-mexyl and its acid metabolite (5-chloro-8-quinolinoxyacetic acid) at 0.10 ppm for wheat grain, forage, hay and straw.

For wheat, the formulation is to be applied broadcast by ground or air to all types of spring and winter wheat (including Durum) grown in Montana, Minnesota, North Dakota, and South Dakota. The formulation is to be applied postemergence to wheat from the 2-leaf stage to emergence of the 4th tiller (see Confidential Appendix for the use rate of the safener). It should not be used to treat wheat underseeded to forages and should not be applied through any type of irrigation system. Grazing of livestock or feeding of forage from treated areas should not be done for a minimum of 7 days following application. Hay should not be fed for 30 days following application. (Note: HED is recommending that the Section B/label be revised to change the feeding/grazing restriction on forage to 30 days since limited residue data are available at a 7-day PHI.) Wheat (grain and straw) should not be harvested for 60 days following application. It is proposed for only one application to be made per crop season.

The toxicity database for cloquintocet-mexyl is considered complete for risk assessment. Cloquintocet-mexyl is not carcinogenic or mutagenic, does not cause neurotoxicity, developmental toxicity, or reproductive toxicity. The primary target organs for subchronic exposure of cloquintocet-mexyl (CGA 185072) are the liver and the renal system. The acute toxicity data 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.

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.

Acute Dietary Exposure: An acute reference dose (RfD) was selected for the subpopulation of females 13-50 years old. This acute RfD of **1.0 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 no. 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).]

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.

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 no. 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).

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 no. 44387425) where mottled or reddish livers accompanied by histopathological changes including necrosis and fibrosis were observed at the LOAEL of 1000 mg/kg/day.

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 no. 4438749) where an increased incidence of skeletal variants and decrease in fetal body weights were observed at a LOAEL of 400 mg/kg/day. Route-to-route extrapolation has been performed assuming 100% absorption.

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 study in rats (MRID no. 44387431) where an increased incidence of thyroid follicular epithelial hyperplasia in females was observed at a LOAEL of 41.2 mg/kg/day. Route-to-route extrapolation has been performed assuming 100% absorption.

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.

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 **removed (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; and 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). With the removal of the FQPA safety factor (i.e., 1x), the chronic RfD (0.04 mg/kg/day) is equal to the chronic population adjusted dose (cPAD; 0.04 mg/kg/day)

HED is recommending that the Section B/label be revised to change the feeding/grazing restriction on forage to 30 days since limited residue data are available at a 7-day PHI. Provided the above revision to the Section B/label is made, the proposed use of cloquintocet-mexyl on wheat will be adequately described.

At the time of this risk assessment, Registration Division was reviewing the product chemistry data for this safener.

HED has evaluated (4/7/00) the residue chemistry database from residue field trials and processing studies. There are residue chemistry data gaps. Provided that revised Sections B (proposed label) and F (tolerance proposal) are submitted and the analytical method validation by ACL/BEAD is successful, the residue chemistry data gaps do not preclude the establishment of a time-limited registration.

Issues remain to be resolved or deficiencies exist concerning the following topics:
1. Proposed Use/Revised Section B/label
2. Nature of the Residue in Wheat
3. Nature of the Residue in Ruminants
4. Nature of the Residue in Poultry
5. Plant Analytical Methods
6. Multiresidue Methods
7. Storage Stability
8. Magnitude of the Residue in Wheat
9. Magnitude of the Residue in Processed Food/Feed
10. Rotational Crop Data
11. Revised Section F

Although the noted residue chemistry issues exist, this assessment is considered conservative and health protective. Except for the submission of revised Sections B and F

and the availability of adequate EPA method validations, noted issues will not preclude the establishment of a time-limited registration.

The HED Metabolism Assessment Review Committee (MARC) has determined (2/15/00) for this time-limited registration that the residues of concern for risk assessment and tolerance setting purposes in the primary crop are the parent and the acid metabolite 5-chloro-8-quinolinoxyacetic acid (CGA-153433). Transfer of finite residues of cloquintocet-mexyl to meat, milk, poultry, and eggs is not expected (40 CFR §180.6(a)(3) category). An EPA (ACL/BEAD) method validation of methods REM 138.01, REM 138.06, and REM 138.10 has been requested and is now underway. The validation by ACL/BEAD must be successfully completed prior to the establishment of the proposed tolerances.

HED has conducted Tier 1 acute and chronic food exposure assessments for cloquintocet-mexyl (M. Xue, 3/27/2000, DP Barcode D263506) using the Dietary Exposure Evaluation Model (DEEM™). The acute risk estimate for food exposure associated with cloquintocet-mexyl use on wheat is below HED's level of concern (100% acute PAD). Based on tolerance level residues and assuming 100% crop treated, the 95th percentile of exposure is predicted to be **< 1.0%** of the acute PAD for the all subgroups of females ages 13-50 years old. For a Tier 1 analysis, HED considers exposure at the 95th percentile of exposure.

The chronic food risk estimate associated with cloquintocet-mexyl use in/on wheat is below HED's level of concern (100% of chronic PAD). The Tier 1 analysis estimates are **<1.0%** of the chronic PAD for the **total U.S. population** and **1.0%** of the chronic PAD for the most highly exposed population, **children 1-6 years old.**

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 both cloquintocet-mexyl and CGA-153433. SCI-GROW estimates the concentration of cloquintocet-mexyl and CGA-153433 in groundwater to be **0.0060 µg/L and 0.00017 µg/L**. GENEEC estimates acute (peak) and chronic (56-year mean) concentrations of cloquintocet-mexyl in water to be **0.038 and 0.0053 µg/L**, respectively. GENEEC estimates acute (peak) and chronic (56-year mean) concentrations of CGA-153433 in water to be **0.031 and 0.017 µg/L**, respectively.

A drinking water level of comparison (DWLOC) is the concentration of the safener in drinking water that would be acceptable as a theoretical upper limit in light of total aggregate exposure to

the safener from food, water, and residential uses. (No residential uses are proposed or established for cloquintocet-mexyl.) HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with cloquintocet-mexyl exposure through drinking water. For acute and chronic (non-cancer) dietary exposure scenarios, the DWLOC values are all in excess of the modeled EEC values reported by EFED. DWLOCs calculated for acute dietary exposure are **3.0×10^4 µg/L** for subgroups of females 13-50 years old. DWLOCs calculated for chronic dietary exposure range from **4.0×10^2 µg/L** to **1.4×10^3 µg/L** for the most highly exposed population, **children 1-6 years old**, and the **total U.S. population**, respectively. All calculated DWLOCs exceed EEC's provided by EFED. **Residues of cloquintocet-mexyl and its major degradate, CGA-15343, in drinking water are not of concern for acute or chronic exposure.** This risk assessment is considered high confidence, conservative, and very protective of human health.

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 Margins of Exposure (MOE) which are compared to the target MOE of 100 to determine any risk concerns.

There are no residential uses registered for cloquintocet-mexyl.

Handlers of cloquintocet-mexyl (in formulation with clodinafop-propargyl) were assessed for exposure during open mixing/loading to support aerial and groundboom application, using PHED unit exposure values. 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. Also, handlers who mix, load and apply by groundboom were assessed together, using unit exposure values obtained from a registrant-sponsored study. The MOEs, under all the above circumstances, range from **2.5×10^2 to 4.5×10^6** for handlers. **These MOEs are greater than the target (100) and do not exceed HED's level of concern.**

The proposed label for cloquintocet-mexyl (in formulation with clodinafop-propargyl) has a 12-hour restricted entry interval (REI). The technical material has a Toxicity Category IV for Primary Skin Irritation; all other acute effects are Category III. Per the Worker Protection Standard(WPS), a 12-hour restricted entry interval (REI) is required for chemicals classified under Toxicity Category III. Therefore, the REI of 12 hours is in compliance with the WPS.

Postappication 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 postapplication activities, these postapplication risks are not assessed. Postapplication risks were assessed for workers entering wheat fields to scout and irrigate. Wheat is 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 **4.9×10^5** as early as the day of application. **This MOE is greater than the target (100) and does not exceed HED's level of concern.**

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.

Based on the data gaps outlined in Section 6.0, HED is recommending for the establishment of a *time-limited registration* for the formulation. Tolerances should be established for the combined residues of cloquintocet-mexyl and its acid metabolite (5-chloro-8-quinolinoxyacetic acid) in or on the following commodities:

wheat, grain	0.10 ppm
wheat, forage	0.10 ppm
wheat, hay	0.10 ppm
wheat, straw	0.10 ppm.

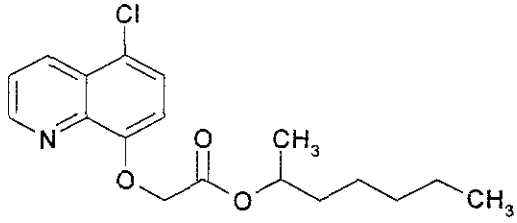
Prior to the establishment of these tolerances, revised Sections B and F along with adequate validation of the proposed analytical enforcement methods are required.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Chemical Name:	acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester
Chemical Group:	safener
Chemical Type:	herbicide (grass weeds)
CAS Registry No.:	99607-70-2
Common Name:	cloquintocet-mexyl
Other Names:	CGA-185072
Trade Names:	See Confidential Appendix
PC Code Number:	999999
Mode of Action:	not reported
Empirical Formula:	$C_{18}H_{22}Cl_1N_1O_3$
Molecular Weight:	335
Appearance:	review pending[a]
Melting Point:	review pending[a]
Vapor Pressure:	review pending[a]
Partition Coefficient:	review pending[a]
Solubility in Water:	review pending[a]
Hydrolysis:	review pending[a]
Half-Life:	review pending[a]
Toxic Impurities:	review pending[a]

[a] At the time of this risk assessment, Registration Division was reviewing product chemistry data.

Chemical Structure of Cloquintocet-mexyl:



3.0 HAZARD CHARACTERIZATION

- **References**:
  Attachment 1: Cloquintocet-mexyl - Report of the Hazard Identification Assessment Review Committee (Y. Yang, 6/17/99).

  Attachment 2: PP #7E04920 Cloquintocet-mexyl (CGA 185072) (PC Code: 999999/inert) Toxicology Disciplinary Chapter for Registration Support Document (S. Gross, 4/20/2000).

3.1 Hazard Profile

3.1.2 Acute Toxicity

The acute toxicity data (see Table 1) 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 1. 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
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 2 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 2. 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.
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**

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

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 3.

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 no. 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 no. 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 no. 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 no. 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 no. 44387431) where an increased incidence of thyroid follicular epithelial hyperplasia in females at 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.

C. 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 3. 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 no. 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 no. 44387431
		Chronic RfD = Chronic PAD = 0.04 mg/kg/day	
Short-term (Dermal) Intermediate-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 no. 44387425
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 no. 44387429
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 no. 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

- **Reference:**
  Attachment 3:*CLOQUINTOCET-MEXYL* - Report of the FQPA Safety Factor Committee (B. Tarplee, 3/20/99).

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 **removed (1x).** The Committee concluded that the safety factor could be removed for cloquintocet-mexyl because:

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

Table 4. Determinations of the FQPA Safety Factor Committee

Exposure Scenario	FQPA Safety Factor To Be Applied	Calculation of PAD[1]	Populations to Which PAD[1] Should be Applied
Acute dietary	1x	1.0/1x = 1.0 acute RfD = acute PAD	Females 13-50 years old
Chronic dietary	1x	0.04/1x = 0.04 chronic RfD = chronic PAD	ALL population subgroups

[1] PAD = Population Adjusted Dose; RfD (acute or chronic) ÷ FQPA Safety Factor = Population Adjusted Dose

4.0 EXPOSURE ASSESSMENT

♦ **References:**

Attachment 4: Acute and Chronic Dietary Exposure Analyses for Proposed Tolerances for Cloquintocet-mexyl in/on Wheat Commodities. (M. Xue, 3/27/2000).

Attachment 5: PP#7E04920. Cloquintocet-mexyl (Safener) in/on Wheat. Review of Analytical Methods and Residue Data. First Food Use Review. (4/7/2000, N. Dodd).

Attachment 6: Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration (New Inert) of Cloquintocet-Mexyl on Wheat. (J. Arthur, 5/8/2000).

Attachment 7: Tier I Estimated Environmental Concentrations of Cloquintocet-mexyl (Chemical: 700099) (H. Nelson, 11/7/1999).

Attachment 8: Cloquintocet-mexyl. Metabolism Assessment Review Committee (MARC) Decision Document for Meeting Held on 2/15/00. Chemical # 999999. DP Barcodes: D263289 and D263319.

Attachment 9: Names and Structures of Cloquintocet-mexyl and its Metabolite; Proposed Wheat, Goat, and Hen Metabolism Pathway of Cloquintocet-mexyl

4.1 Summary of Proposed Uses

Formulation.
The formulation containing cloquintocet-mexyl is an emulsifiable concentrate and is described in the Confidential Appendix.

Proposed Use.
For wheat, the formulation is to be applied broadcast by ground or air to all types of spring and winter wheat (including Durum) grown in Montana, Minnesota, North Dakota, and South Dakota. The formulation is to be applied postemergence to wheat from the 2-leaf stage to emergence of the 4th tiller. It should not be used to treat wheat underseeded to forages and should not be applied through any type of irrigation system. Grazing of livestock or feeding of forage from treated areas should not be done for a minimum of 7 days following application. Hay should not be fed for 30 days following application. (Note: HED is recommending that the Section B/label be revised to change the feeding/grazing restriction on forage to 30 days since limited residue data are available at a 7-day PHI.) Wheat (grain and straw) should not be harvested for 60 days following application. It is proposed for only one application to be made per crop season.

The Section B/label should be revised to change the feeding/grazing restriction on forage to 30 days since limited residue data are available at a 7-day PHI. Provided the above revision to the Section B/label is made, the proposed use directions will be adequate to allow an assessment of whether the residue data reflect the maximum residues likely to occur in food/feed.

4.2 Dietary Exposure

A very brief summary of information from the residue chemistry review (Attachment 5) is given below. Data gaps exist in the residue chemistry database (see Section 6.0 of this review). **Although the noted residue chemistry issues exist, this assessment is considered conservative and health protective. Except for the submission of revised Sections B and F and the availability of adequate EPA method validations, noted issues will not preclude the establishment of a time-limited registration.**

Metabolism in Plants. The fate of [3-^{14}C-quinoline]CGA-185072 (i.e., [3-^{14}C]5-chloro-8-quinolinoxyacetic acid, 1-methylhexyl ester) was studied in field grown spring wheat in Klus, Switzerland after postemergence foliar spray application at the 2X rate (See the Confidential Appendix). Samples were extracted with 80% aqueous acetonitrile. Samples were further extracted with 100% acetonitrile by Soxhlet extraction overnight. CGA-185072 was readily absorbed by the leaves and quickly degraded to the acid CGA-153433, which amounted to 19.1% of the total radioactive residues (TRR) in/on leaves at 1.5 hours after treatment. CGA-153433 further degraded, decreasing to 1.8% of the TRR in/on leaves by 35 days after treatment. The only identified residues in leaves at ear emergence were CGA-185072 (14.2%) and CGA-153433 (1.8%). Nonextractable residues in leaves amounted to 41.1% and 58.3% of the TRR at 35 days and 56 days after treatment, respectively. An unknown (I_1) accounted for 25.6% of the TRR in leaves at 35 days. Total radioactive residues (expressed as parent equivalents) in field grown wheat at maturity (82 days after treatment) were 0.003 ppm in grains, 0.003 ppm in husks, and 0.083 ppm in straw. In straw, 78.2% remained as non-extractable radioactivity. The only identified residue in straw was CGA-153433 (4.4% of the TRR at 82 days after treatment). Residues in grains and husks (at 56 days and 82 days after treatment) were too low to identify.

A proposed plant metabolism scheme is outlined in Figure 1 (Attachment 9).

The nature of the residue in wheat is not adequately understood for the purposes of a <u>permanent</u> tolerance for the following reasons pertaining to the [3-^{14}C-quinoline]CGA-185072 study:

a.. Due to large amounts of the radioactivity being nonextractable with 80% aqueous acetonitrile and by Soxhlet extraction with 100% acetonitrile, only 16.0%, 0.9%, and 4.4%TRR were identified in leaves (ear emergence), leaves (milky stage), and straw (maturity), respectively. The petitioner should have attempted to extract more of the radioactivity using acid, base, and enzymes and then characterized/identified the residues.

b. Residues in grain were not identified in the field study. The identity of residues in grain resulting from application to the plant in a manner simulating expected field use are needed. The study should be conducted at a higher rate than the 2X study which was submitted.

c. The time from sampling to final analysis should be clarified for the wheat samples. If the time between sampling and final analysis of the field samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses should show that the basic profile of radiolabeled residues has not changed during that time.

The nature of the residue in wheat is adequately understood for the purposes of a time-limited registration. The residues of concern in wheat were determined by HED's Metabolism Assessment Review Committee (MARC) on 2/15/00 (D263289, N. Dodd, 2/25/00) to be CGA-185072 and its acid metabolite CGA-153433. HED may revisit the MARC after additional wheat metabolism data have been submitted.

Metabolism in Rotational Crops. Following one application of [3-^{14}C]quinoline CGA-185072 to spring wheat at the 2X rate in a confined rotational crop study (see the Confidential Appendix for the rate in lbs safener/acre), radioactivity levels in each of the rotational crops (lettuce, winter wheat, sugar beets, and corn) were ≤0.001 ppm at the rotational crop intervals tested (i.e., days between application of CGA-185072 and planting of the rotational crops: 85 days for lettuce, 146 days for winter wheat, 321 days for sugar beets, and 351 days for corn).

The submitted confined rotational crop data are adequate for a permanent tolerance provided that rotational crop restrictions are placed on the formulation label of at least 85 days (or 3 months) for lettuce and other leafy vegetables, 146 days (or 5 months) for small grains (barley, oats, and rye), and one year (or 12 months) for all other crops for which uses are not established.

If the petitioner wants shorter rotational crop restrictions, then a confined rotational crop study conducted at the soil aging intervals of 1, 4, and 12 months would be needed for three rotated crops (a small grain, a leafy vegetable, and a root crop) reflecting one application of CGA-185072 at the maximum label rate (1X).

No field accumulation in rotational crops studies were submitted. Pending results from the confined rotational crop study which may be conducted if the petitioner wants shorter rotational crop restrictions, the field accumulation in rotational crops studies may be required.

Metabolism in Animals.

Ruminants: A lactating goat was fed 5 ppm (3-^{14}C)quinoline-labeled cloquintocet-mexyl for ten days. (This is 18X the maximum theoretical residues in the diet of cattle.) Radioactivity levels in tissues and milk were low. The highest concentrations (expressed as CGA-185072 equivalents) were found in kidney (0.024 ppm) and liver (0.010 ppm). Residues were ≤0.003 ppm in muscle and ≤0.001 ppm in fat. Residues in milk peaked during the first day of the dosing period at 0.084 ppm but declined to 0.015 ppm by the second day and further declined to 0.008 ± 0.001 ppm for the remainder of the study. The majority of the radioactivity administered to the lactating goat was eliminated in urine (62%) and feces (21%).

The major residue in urine, milk, and kidney was CGA-153433. Residues in muscle and liver were not determined because of interferences and low radioactivity. No attempt was made to identify residues in fat because of low radioactivity (≤0.001 ppm).

The proposed ruminant metabolic pathway of 3-^{14}C-quinoline CGA-185072 is outlined in Figure 1 (Attachment 9).

The nature of the residue in ruminants is not adequately understood for the purpose of a permanent tolerance for the following reason: The time between sampling and final analysis should be clarified for milk and tissues. If the time between sampling and final analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

For this use on wheat, the nature of the residue in ruminants is adequately understood for the purposes of a time-limited registration. The major residue in urine, milk, and kidney was CGA-153433. Residues in muscle and liver were not determined because of interferences and low radioactivity. No attempt was made to identify residues in fat because of low radioactivity (≤0.001 ppm). The residues of concern in ruminants were determined by the MARC to be CGA-185072 and its acid metabolite CGA-153433.

Poultry: Three hens were orally fed 5 ppm of (3-^{14}C)quinoline-labeled cloquintocet-mexyl in a daily capsule for fourteen days. (This is 50X the maximum theoretical residues in the diet.) Total radioactivity (in ppm CGA-185072 equivalents) was determined in egg white (≤0.007 ppm), egg yolk (≤0.004 ppm), muscle (<0.001 ppm, i.e., <LOD), peritoneal fat (<0.002, i.e., <LOD), liver (≤0.01 ppm), and kidney (≤0.04 ppm). The major metabolite in liver, kidney, and egg white was identified by two-dimensional TLC and cochromatography as CGA-153433. Residues in egg yolk could not be identified due to low radioactivity. Because no detectable residues were found in lean meat (<0.001 ppm) and fat (<0.002 ppm), characterization/identification of residues in lean meat and fat was not attempted.

The proposed poultry metabolic pathway of 3-^{14}C-quinoline CGA-185072 is outlined in Figure 1 (Attachment 9).

The nature of the residue in poultry is not adequately understood for the purpose of a permanent tolerance for the following reason: The time between sampling and final analysis should be clarified for eggs and tissues. If the time between sampling and final analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

For this use on wheat, the nature of the residue in poultry is adequately understood for the purposes of a time-limited registration. The major metabolite in liver, kidney, and egg white was identified by two-dimensional TLC and cochromatography as CGA-153433. Residues in egg yolk could not be identified due to low radioactivity. Because no detectable residues were found in lean meat (<0.001 ppm) and fat (<0.002 ppm), characterization/identification of residues in lean meat and fat was not attempted. The residues of concern in ruminants were determined by HED's Metabolism Assessment Review Committee on 2/15/00 (D263289, N. Dodd, 2/25/00) to be CGA-185072 and its acid metabolite CGA-153433.

Enforcement Methods.

Wheat:

Analytical Method REM 138.01 was used to determine CGA-185072 in wheat in all of the residue/processing samples in the US and Canada and in some of the storage stability samples. CGA-185072 and CGA-184927 are determined separately by high performance liquid chromatography (HPLC) with UV-detection. The limits of quantitation of the method for CGA-185072 are 0.02 ppm for grain and 0.05 ppm for wheat forage, hay, and straw. A successful independent laboratory method validation, indicating adequate recovery of the residue, was conducted for Method REM 138.01 on wheat grain, forage, and straw. An EPA method validation of Method REM 138.01 has been requested (D254000, PP#7F04924, N. Dodd, 4/27/99).

Analytical method REM 138.06 was used to determine CGA-153433 in wheat in all of the residue studies in Canada and in some storage stability samples. CGA-153433 and CGA-193469 are independently determined by high performance liquid chromatography (HPLC) with UV-detection. The limit of quantitation of the method for CGA-153433 is 0.05 ppm for wheat forage, grain, hay, and straw. A successful independent laboratory method validation, indicating adequate recovery of the residue, was conducted for Method REM 138.06 on wheat grain, forage, and straw. An EPA method validation of Method REM 138.06 has been requested (D254000, PP#7F04924, N. Dodd, 4/27/99).

Analytical method REM 138.10 was used to determine CGA-153433 in wheat in some storage stability samples and in all the residue/processing studies in the US. CGA-193469 and CGA-153433 are separately determined by HPLC with UV-detection. The limits of quantitation for CGA-153433 are 0.02 ppm for wheat grain and 0.05 ppm for forage, hay, and straw. An EPA method validation of Method REM 138.10 has been requested (D254000, PP#7F04924, N. Dodd, 4/27/99).

To establish a permanent tolerance, the following additional information is needed regarding the analytical methods used to obtain the storage stability and residue data: a) Radiovalidation data for Methods REM 138.01, 138.06, 138.10, and 138.12 are needed to demonstrate the efficiency of the methods in extracting and quantifying aged or bound residues in samples; b) Method REM 138.12 should be submitted.

Before EPA can determine whether adequate analytical methods are available for enforcement of permanent tolerances on wheat, the following additional information is needed for the proposed enforcement methods: a) For REM 138.01 and REM 138.06, either an interference study must be submitted which determines whether other pesticides registered on wheat will interfere with the analysis of cloquintocet-mexyl residues by the enforcement method or a specific confirmatory method such as mass spectroscopy is needed as discussed in OPPTS GLN 860.1340. Provided that a specific confirmatory method is available, the Agency will not require that an interference study be conducted; b) Confirmatory methods are needed for REM 138.01 and 138.06; c) The GC/MS confirmatory method in Method REM 138.10 includes derivatization with diazomethane. The petitioner should investigate whether another methylating agent could be substituted for diazomethane. If an alternative methylating agent is not available, EPA requires that justification for the use of diazomethane be provided. An alternative confirmatory method for REM 138.10 would be LC/MS. REM 138.10 could be rewritten to include LC/MS as the confirmatory method instead of GC/MS; d) Adequate EPA petition method validations are needed for the proposed enforcement methods. RAB3 has requested EPA petition method validations for REM 138.01, 138.06, and 138.10. These EPA petition method validations are underway. Adequate independent laboratory method validations have been provided for methods REM 138.01 and 138.06.

Provided that the petition method validations which are being conducted by EPA are successful, adequate enforcement methods (MRID nos. 44399211, 44399213, and 44755302) are available to enforce time-limited registration on wheat.

Animals:

Analytical/enforcement methods for animal commodities are not needed for this use on wheat since secondary residues are not expected to occur in animal commodities and, therefore, tolerances on animal commodities are not needed.

Multiresidue Methods Testing. Multiresidue methods testing data for CGA-185072 and CGA-153433 in wheat grain have been submitted. CGA-185072 and CGA-153433 were tested through the FDA multiresidue methods according to the decision tree and protocols in the Pesticide Analytical Manual, Volume I (PAM I), Appendix II, Transmittal 96-1 (1/96). CGA-185072 was tested per Protocols C, D, and E. CGA-153433 was tested per Protocols B and C.

In Protocol C, CGA-185072 yielded adequate detector responses to Section 302 DG5, DG13, and DG18 gas-liquid chromatography (GLC) systems. In Protocol D, CGA-185072 was completely recovered through the complete method without Florisil cleanup (Section 302 E4), and no interference was observed; CGA-185072 was not recovered through Florisil cleanup (Section 302 C1) or the complete method with Florisil cleanup (Section 302 E4/C1). In Protocol E, CGA-185072 was not recovered through Section 303 C1 Florisil cleanup, partially (7%) recovered through Section 303 C2 Florisil cleanup, and not recovered through the complete method (Section 303 E3/C1 and E3/C2).

In Protocol C, CGA-153433 did not yield adequate detector responses to any of the Section 302 DG5, DG13, and DG18 systems; however, the methyl ester of CGA-153433 yielded adequate responses to the gas-liquid chromatography (GLC) systems. In Protocol B, the methyl ester of CGA-153433 was not recovered through Florisil cleanup (Section 402 C1c).

RAB3 (D255566, N. Dodd, 5/12/99) has forwarded the submitted multiresidue methods data to FDA for review to determine sufficiency. Multiresidue methods are not adequate for enforcement purposes; while parent is completely recovered through Protocol D, the acid metabolite is only partially recovered.

Freezer Storage Stability Data. Storage stability data were submitted for CGA-185072 in wheat grain and straw. CGA-185072 declined 17% in wheat grain stored at -18°C for 728 days. CGA-185072 declined 31% in wheat straw stored at -18°C for 731 days. The storage times for CGA-185072 in grain and straw in the storage stability studies are adequate to cover maximum storage times for CGA-185072 in grain and straw residue samples (62 days for grain and 70 days for straw in the US residue data and 574 days for grain and straw in the Canadian residue data). (Note: Since degradation was shown for CGA-185072 in wheat grain and straw, storage stability data will be required for any future uses on all crops/substrates for which tolerances are requested.)

Storage stability data were also submitted for CGA-153433 in wheat grain and straw. Residues of CGA-153433 were stable in wheat straw stored at -18°C for 380 days. Pending receipt of the additional information requested below for MRID no. 44399210, HED tentatively concludes that CGA-153433 is stable in wheat grain stored at -20°C for 727 days. The storage times for CGA-153433 in grain and straw in the storage stability studies are adequate to cover maximum storage times for CGA-153433 in grain and straw residue samples (i.e., 95 days for grain and 141 days for straw in US residue data and 341 days for grain and straw in the Canadian residue data).

Adequate storage stability data have not been submitted. The following additional storage stability data are needed:

a. Additional data are needed for Study 300/91 (MRID no. 44399210). 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 stability samples should be submitted or identified by number as a submitted method.

b. No storage stability data were submitted for forage. Storage stability data for forage are needed for the 105-day storage interval for CGA-185072 and the 218-day storage interval for CGA-153433 in US residue samples. If the Canadian residue studies could be used (i.e., upgraded to acceptable), storage stability data for forage would be needed for the 434-day storage interval for CGA-185072 and CGA-153433 in the Canadian residue samples so that the tolerance can be adjusted for any storage degradation; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies to an acceptable level.

c. No storage stability data were submitted for wheat processed commodities. The storage time between processing and analysis was ≤25 days for CGA-185072; storage stability data are not needed for CGA-185072 in processed commodities since they were analyzed within 30 days of their production (OPPTS 860.1520). The storage time between processing and analysis for CGA-153433 was 51 days for aspirated grain, 45 and 125 days for germ, 45 days for bran, 42 days for middlings and shorts, and 37 days for low grade flour and patent flour. Storage stability data for CGA-153433 in aspirated grain fractions are not needed since this is an early season use and residues are not expected to occur in aspirated grain fractions. Storage stability data are not needed for bran, flour, middlings, and shorts since these matrices are similar to grain and can be covered by the storage stability data on grain. Storage stability data are needed for CGA-153433 in wheat germ for up to 125 days.

Magnitude of the Residue in Wheat. In the US, six field trials on spring wheat to determine residues of CGA-185072 and CGA-153433 were conducted in the four states of ND (2), MN (1), MT (2), and SD(1) in crop year 1998. The US field trials were conducted in Region 5 (2 studies) and Region 7 (four studies), as defined in OPPTS 860.1500. A single foliar application of the the fomulation was applied. CGA-185072 was applied at the 1X rate (see the Confidential Appendix). The application was made with ground equipment. A 5X rate was also applied in one study (OW-HR-210-98/ND). Score, an adjuvant, was used at a concentration of 1% (v/v). Samples were frozen after collection, shipped frozen, and stored frozen (-20°C) at the analytical laboratory. Analytical Method REM 138.01, with modifications for some substrates, was used to determine residues of CGA-185072 by HPLC with ultraviolet detection. The limit of quantitation (based on the lowest acceptable recovery level) was 0.02 ppm for grain and 0.05 ppm for forage, hay, and straw. Recoveries of CGA-185072 were 65-129% (average 93%, n=10) for forage, 62-105% (average 78%, n=6) for hay, and 62-104% (average 81%, n= 6) for straw at fortifications of 0.05 ppm. Recoveries of CGA-185072 were 94-133% (average 107%, n=9) for

grain at fortifications of 0.02 ppm. Analytical Method REM 138.10, with modifications, was used to determine the metabolite CGA-153433 by HPLC with UV detection. The limit of quantitation for CGA-153433 (based on the lowest acceptable recovery level) was 0.05 ppm for forage, hay, straw, and grain. Recoveries of CGA-153433 were for 56-99% (average 73%, n= 13) for forage, 61-111% (average 86%, n=2) for hay, and 59-94% (average 67%, n=9) for grain at fortifications of 0.05 ppm; straw recoveries were not available. Selected samples were analyzed for CGA-153433 by HPLC with mass spectrometric detection (LC/MS). Residues in the US studies at 1X were <0.05 ppm CGA-185072 + <0.05 ppm CGA-153433 in wheat forage at a 7-day PHI (one study) and a 29-32 day PHI (6 studies); <0.05 ppm CGA-185072 + <0.05 ppm CGA-153433 in wheat hay at a 30-day PHI; <0.05 ppm CGA-185072 in wheat straw at a 60-day PHI; and <0.02 ppm CGA-185072 + <0.05 ppm CGA-153433 in wheat grain at a 60-day PHI. Residues at 5X and a 61-day PHI were <0.02 ppm CGA-185072 and <0.05 ppm CGA-153433 in wheat grain and <0.05 ppm CGA-185072 in wheat straw. Residues of CGA-153433 in wheat straw at 1X and 5X were not determined.

In Canada, fifteen field trials on spring wheat (hard red spring wheat and duram spring wheat) were conducted in Canada in 1989 (3), 1990 (3), 1991 (6), and 1992 (3). The locations of the 15 Canadian field trials relative to the overlapping US-Canadian zones defined in HED SOP 98.2 were reported. Four studies were conducted in extended Zone 5, seven studies were conducted in extended Zone 7, and four studies were conducted in extended Zone 14. An EC (emulsifiable concentrate) formulation was applied. CGA-185072 was applied at the 1X rate (see the Confidential Appendix). The application was made in 100 liters spray solution/ha (10.7 gal/A). In each study, one postemergence foliar application was made to each of 3 or 4 plots. Assist (1%, vol/vol) was included in 8 of the studies. The application was made by bicycle sprayer in all of the studies except MRID no. 44399228 (small plot sprayer). Samples were stored frozen until shipment, shipped frozen, and then stored frozen (at -20°C) in the laboratory until analysis. The analytical methods were REM 138.01 for CGA-185072 and REM 138.06 for CGA-153433. In MRID nos. 44399328, 44399329, and 44399330, CGA-153433 in grain and straw was not determined. The limits of quantitation were 0.02 ppm for CGA-185072 in grain and forage, 0.05 ppm for CGA-185072 in straw, 0.02 or 0.05 ppm for CGA-153433 in grain, and 0.05 ppm for CGA-153433 in forage and straw. Recoveries for CGA-185072 using REM 138.01 were 85-117% (average 95%, n=4) in wheat grain and 70-92% (average 82%, n=3) in wheat forage at a fortification level of 0.04 ppm, and 84-104% (average 92%, n=4) in wheat straw at a fortification level of 0.1 ppm. Recoveries for CGA-153433 at a fortification level of 0.1 ppm using REM 138.06 were 69-84% (average 76%, n=2) in wheat grain, 73-79% (average 77%, n=3) in wheat forage, and 65-88% (average 75%, n=3) in wheat straw. Residues in Canada were <0.02 ppm CGA-185072 + <0.05 ppm CGA-153433 in wheat grain at PHI's ranging from 60-105 days, <0.05 ppm CGA-185072 + <0.05 ppm CGA-153433 in straw at PHI's ranging from 60-105 days, and <0.02 ppm CGA-185072 + <0.05 ppm CGA-153433 in forage at PHI's ranging from 3 to 28 days.

The proposed use indicates that forage could be fed/grazed at a 7-day PHI, hay could be fed at a 30-day PHI, and grain and straw could be harvested at a 60-day PHI. Based on the available residue data, residues of parent or CGA-153433 were less than the limit of

quantitation (LOQ) in the grain, forage, hay, and straw commodities which were analyzed in the US and Canada at these PHI's. (Straw in the US was not analyzed for CGA-153433. Hay was not analyzed in Canada. For US data, the limits of quantitation for parent were 0.02 ppm for grain and 0.05 ppm for forage, hay, and straw; the limit of quantitation for CGA-153433 was 0.05 ppm for grain, forage, and hay; straw was not analyzed for CGA-153433. For Canadian data, the limits of quantitation for parent were 0.02 ppm for grain and forage and 0.05 ppm for straw; the limits of quantitation for CGA-153433 were 0.02 or 0.05 ppm for grain, and 0.05 ppm for forage and straw.) However, the field trial residue data are not adequate to support a permanent tolerance for the following reasons:

a. Adequate geographic representation is not provided. (Wheat is not a minor crop, for which a regional registration would be accepted.) According to OPPTS 860.1500, a minimum of 20 field trials are needed to support a tolerance on wheat. The suggested distribution of wheat field trials is one in Region 2, one in Region 4, five in Region 5, one in Region 6, five in Region 7, six in Region 8, and 1 in Region 11. The US field trials were conducted in Region 5 (2 studies) and Region 7 (four studies), as defined in OPPTS 860.1500; however, these US studies did not determine CGA-153433 in straw. Of the 15 Canadian field trials, four studies were conducted in extended Zone 5, seven studies were conducted in extended Zone 7, and four studies were conducted in extended Zone 14; however, the Canadian field trials have deficiencies which are not upgradeable (see below). Additional field trial residue studies are needed to support a permanent tolerance. If residues of CGA-153433 in straw samples in the US can be reanalyzed by an adequate method and the reanalysis can be supported by storage stability data, the following additional field trial studies would be needed: For a 30-day PHI in forage, the additional studies would be one in Region 2, one in Region 4, three in Region 5, one in Region 6, one in Region 7, six in Region 8, and 1 in Region 11. (If a 7-day PHI in forage is desired, then the additional studies would be one in Region 2, one in Region 4, five in Region 5, one in Region 6, four in Region 7, six in Region 8, and one in Region 11.) Otherwise (without US residue data for CGA-153433 in straw), the following additional field trial studies would be needed: one in Region 2, one in Region 4, five in Region 5, one in Region 6, five in Region 7, six in Region 8, and one in Region 11. Each study should include PHI's of 30 (or 7) days for forage, 30 days for hay, and 60 days for grain and straw. Spring (including hard red spring, duram, and white spring) and winter (including hard red winter, soft red winter, and white winter) varieties of wheat should be included in the studies. 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.

b. Only spring wheat was used in the US and Canadian studies. Winter wheat should be included in the residue studies.

c. Forage was sampled at the proposed preharvest interval (PHI) of 7 days in only one US study and three Canadian studies.

d. Based on the available residue data, the petitioner should submit a revised Section F which proposes tolerances of 0.10 ppm for the combined residues of cloquintocet-mexyl and its metabolite 5-chloro-8-quinolinoxyacetic acid on wheat grain, forage, hay, and straw. These levels were obtained by adding the limits of quantitation for CGA-185072 and CGA-153433.

For the Canadian field trial residue studies, the following data should have been included. (HED is not recommending that the petitioner attempt to upgrade these studies to an acceptable level.)

a. Grain, forage, hay, and straw should be analyzed in each of the wheat field trial residue studies. (For an early season use, data on aspirated grain fractions are not needed.) Of the 15 Canadian studies, only grain and straw were analyzed in most of the studies (i.e., in twelve studies for CGA-185072 and 9 studies for CGA-153433), and only forage was analyzed (for both CGA-185072 and CGA-153433) in three studies. Hay was not analyzed.

b. PHI's should reflect the proposed use. PHI's for grain and straw in the Canadian studies ranged from 55-105 days (with all but two studies with PHI's above 60 days) whereas the proposed PHI for grain and straw is 60 days.

c. Extraction dates were not provided for studies 44399217, 44399218, 44399219, 44399220, 44399221, 44399222, 44399223, 44399224, 44399225, 44399226, 44399227, and 44399231.

d. Storage containers were not described.

e. Raw data and representative chromatograms of standards, controls, fortified samples, and treated samples were not submitted.

Magnitude of the Residue in Wheat Processed Commodities. Wheat grain treated with a 240 EC formulation of CGA-184927 and CGA-185072 at 1X and 5X (see the Confidential Appendix for rate information) was processed. Residues of CGA-185072 and its metabolite CGA-153433 were <0.02 ppm and <0.05 ppm, respectively, in wheat grain and the following processed commodities: aspirated grain fractions, germ, bran, middlings, shorts, low grade flour, and patent flour.

Pending submission of storage stability data on CGA-153433 in processed commodities (see storage stability section of this review), HED concludes that no concentration of CGA-185072 or CGA-153433 occurred on processing.

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

Ruminants: Based on the goat metabolism study and the maximum theoretical dietary burden, maximum radioactive residues in goat tissues and milk resulting from the proposed use on wheat

would be 0.005 ppm in milk, 0.0002 ppm in muscle, 0.00006 ppm in fat, 0.001 ppm in kidney, and 0.0006 ppm in liver.

A ruminant feeding study is not needed and tolerances on milk and the meat, fat, liver, and kidney of cattle, goats, hogs, horses, and sheep are not needed because of the low residue levels found in milk, muscle, fat, liver, and kidney in the goat metabolism study and the corresponding low radioactive residues calculated for the 1X feeding level. This use falls under 40 CFR §180.6(a)(3) since no secondary residues are expected to occur in milk and in the meat, fat, liver, and kidney of cattle, goats, hogs, horses, and sheep.

Poultry: Based on the poultry metabolism study and the maximum theoretical dietary burden, maximum radioactive residues in poultry tissues and eggs resulting from the proposed use on wheat would be <0.000020 ppm in muscle, <0.000040 ppm in fat, 0.00020 ppm in liver, and 0.00012 ppm in eggs.

Because of the low residue levels found in muscle, fat, liver, and eggs in the poultry metabolism study and the corresponding low radioactive residues calculated for the 1X feeding level, a poultry feeding study is not needed and tolerances on poultry tissues and eggs are not needed. This use falls under 40 CFR §180.6(a)(3) since no secondary residues are expected to occur in poultry commodities.

International Harmonization. At this time, there are no Codex, Canadian, or Mexican tolerances for cloquintocet-mexyl on wheat. Therefore, no compatibility issues exist with regard to the proposed US tolerances discussed in this review.

4.2.1 Food Exposure

HED has conducted Tier 1 acute and chronic food exposure assessments for cloquintocet-mexyl (Attachment 4) using the Dietary Exposure Evaluation Model (DEEM™). This model incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For this acute food risk assessment, the entire distribution of single day food consumption events is combined with a single residue level (deterministic analysis) to obtain a distribution of exposure in mg/kg/day. For chronic food risk assessments, the three-day average of consumption for each sub-population is combined with residues in commodities to determine average exposure in mg/kg/day.

These are conservative food risk estimates consisting of tolerance-level residues and 100% crop treated assumptions. The proposed tolerance for the combined residues of cloquintocet-mexyl (acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester) and its metabolite 5-chloro-8-quinolinoxyacetic acid in/on wheat is 0.10 ppm.

4.2.1.1 Acute Assessment of Food Exposure

As shown in Table 3, the acute RfD is *only applicable to females 13-50 years old.* As shown below in Table 5, the acute risk estimate for food exposure associated with cloquintocet-mexyl use on wheat is **below** HED's level of concern (100% acute PAD). Based on tolerance level residues and assuming 100% crop treated, the 95th percentile of exposure is predicted to be **< 1.0%** of the acute PAD for all subgroups of females ages 13-50 years old. For a Tier 1 analysis, HED considers exposure at the 95th percentile of exposure. A complete listing of acute dietary exposure estimates for the 95th, 99th, and 99.9th percentile of food exposure is included as Attachment 4.

Table 5. Acute Tier 1 Exposure Estimates for Food for Cloquintocet-mexyl

Population Subgroup	95th Percentile	
	Exposure (mg/kg/day)	% acute PAD [2, 3]
Females (13-50 years)	0.00028	< 1.0

[1] Population subgroup shown include women of child-bearing age.

[2] acute PAD values incorporate the RfD and FQPA Safety Factor for the women of childbearing age, as listed in Table 4

[3] % acute PAD = Exposure (mg/kg) ÷ acute PAD (mg/kg) × 100

4.2.1.2 Chronic Assessment for Food Exposure

The chronic food risk estimate associated with cloquintocet-mexyl use in/on wheat is below HED's level of concern (100% of chronic PAD). The Tier 1 analysis estimates are **<1.0%** of the chronic PAD for the **total U.S. population** and **1.0%** of the chronic PAD for the most highly exposed population, **children 1-6 years old.** Exposure estimates and associated risk, as % chronic PAD, are shown in Table 6 for the selected population subgroups. A complete listing of chronic exposure estimates for all DEEM™ population subgroups is included as Attachment 3.

Table 6. Chronic Dietary Tier 1 Exposure Estimates

Population Subgroup [1]	Exposure (mg/kg/day)	% chronic PAD [2, 3]
U.S. Population (total)	0.00015	<1.0%
All infants (< 1 year)	0.000052	<1.0%
Children 1-6 yrs	0.00034	1.0%
Children 7-12 yrs	0.00024	1.0%
Females 13+ nursing	0.00012	<1.0%
Males 13-19	0.00017	<1.0%

[1] Population subgroups shown include the U.S. general population and the maximally exposed subpopulation of adults, infants and children, and women of child-bearing age.

[2] chronic PAD values incorporate the different FQPA Safety Factors for the various population subgroups, as listed in Table 4.

[3] % chronic PAD = Exposure (mg/kg) ÷ chronic PAD (mg/kg) × 100

4.2.1.3 Cancer Assessment for Food Exposure

In accordance with the *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 mutagenicicity test battery, it is suggested that cloquintocet-mexyl (CGA-185072) is not likely to be a human carcinogen.

4.2.2 Water Exposure

Because cloquintocet-mexyl is a new chemical, 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). 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. These models take into account the use patterns and the environmental profile of cloquintocet-mexyl, but do not include consideration of the impact that processing raw water for distribution as drinking water would likely have on the removal of safener from the source water. The primary use of these models by the Agency at this stage is to provide a coarse screen for assessing whether cloquintocet-mexyl is likely to be present in drinking water at concentrations which would exceed human health levels of concern. Ground and surface water exposure estimates for both cloquintocet-mexyl and it's major degradate, CGA-153433 (5-chloro-8-quinolinoxyacetic acid) were provided by the Environmental Fate and Effects Divisoin (EFED; Attachment 7).

The SCI-GROW model generates a single EEC value of safener concentration in *ground* water. That EEC is used in assessments of both acute and chronic dietary risk. The GENEEC model generates several time-based EECs of safener concentration in *surface* water, ranging from 0-days (peak) to 56-days (average). The GENEEC peak EEC is used in assessments of acute dietary risk; the GENEEC 56-day (average) EEC is used in assessments of chronic (non-cancer) dietary risk.

A drinking water level of comparison (DWLOC) is the concentration of the safener in drinking water that would be acceptable as a theoretical upper limit in light of total aggregate exposure to that chemical from food, water, and residential uses. HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with cloquintocet-mexyl exposure through drinking water. In the absence of monitoring data for cloquintocet-mexyl, the DWLOC is used as a point of comparison against the conservative EECs provided by computer modeling (SCI-GROW and GENEEC).

HED back-calculates DWLOCs by a two-step process: 1) exposure [food + (if applicable) residential] is subtracted from the PAD to obtain the maximum acceptable exposure allowed in

drinking water; 2) DWLOCs are then calculated using the above calculated value and HED default body weight and drinking water consumption figures. In assessing human health risk, DWLOCs are compared to EECs. When DWLOCs are greater than EECs, HED considers the aggregate risk [from food + water + (if applicable) residential exposures] to be acceptable. At the present time, cloquintocet-mexyl is only to be used on wheat; no residential exposures are expected. DWLOCs calculated for cloquintocet-mexyl are shown below in Section 4.2.2.4.

4.2.2.1 Environmental Fate Properties

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.

Nevertheless, initial **half-lives of < 1 day to 3.63 days** during the first week of the aerobic soil and aquatic metabolism studies indicate that microbial mediated hydrolysis could possibly contribute significantly to its foliar dissipation. In addition, a DT50 of several hours in the aqueous photolysis study indicates that photolysis may also play a major role in the foliar dissipation of cloquintocet-mexyl. The major degradate is CGA-153433, 5-chloro-8-quinolinoxyacetic acid, described below. Surface and ground water EEC's have been provided by EFED for CGA-153433 and have been included below in calculations of DWLOCs.

CGA-153433 rapidly formed during the first day post-application will be available for runoff and leaching for several months post-application. However, despite substantial persistence in soils, the leaching potential of CGA-153433 is probably low in most cases due to its low mobility. The relatively slow dissipation of CGA-153433 in surface soil indicates that significant fractions of any CGA-153443 reaching or formed in the soil may be available for runoff for several months. In some cases, runoff events could transport significant quantities of CGA-153443 to surface water via adsorption to eroding soil. High soil/water partitioning such as that exhibited by CGA-153433 does not preclude substantial runoff transport to surface water via adsorption to eroding soil. However, because runoff water masses are generally much greater than eroding soil masses, the mass of pesticide transported to surface water generally decreases with increasing soil/water partitioning. Therefore, the overall runoff potential of CGA-153433 should be relatively low in most cases.

The half-lives for CGA-153433 in aerobic aquatic metabolism for the water/sediment system combined indicate that CGA-193469 may be relatively persistent in aerobic surface water/sediment systems. EFED calculated a half-life of 105 days (for 28-238 days; n = 5; r2 = 0.981; Figure 12) for CGA-153433 in anaerobic aquatic metabolism study 443874-48 for the water/sediment system as a whole. That indicates any CGA-153433 reaching the more anaerobic portions of deep water columns or typically anaerobic sediment may also be relatively persistent. The persistence of CGA-153433 in ground water may generally be somewhat longer than in surface water due to generally lower microbial activity in ground water.

4.2.2.2 Ground Water Modeling

EFED used the SCI-GROW model to estimate environmental concentrations of cloquintocet-mexyl in ground water. 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. SCI-GROW appears to provide realistic estimates of safener concentrations in shallow, highly vulnerable ground water sites. SCI-GROW estimates the concentration of cloquintocet-mexyl and the metabolite, CGA-153433 in groundwater to be **0.0060 µg/L and 0.00017 µg/L**, respectively. As there is relatively little temporal variation in ground water, this estimate can be used for both acute and chronic exposure scenarios.

4.2.2.3 Surface Water Modeling

EFED used the Tier 1 GENEEC model to obtain EECs in surface water. GENEEC provides an upper-bound concentration value. GENEEC is a single runoff event model, but accounts for spray drift from single or multiple applications. GENEEC represents a 10-hectare field immediately adjacent to a 1-hectare pond that is 2-meter deep with no outlet. GENEEC estimates acute (peak) and chronic (56-year mean) concentrations of cloquintocet-mexyl in water to be **0.038 and 0.0053 µg/L**, respectively. GENEEC estimates acute (peak) and chronic (56-year mean) concentrations of CGA-153433 in water to be **0.031 and 0.017 µg/L**, respectively.

Table 7. EFED Estimated Environmental Concentrations (EECs) for Cloquintocet-mexyl an dCGA-153433			
	SCI-GROW[1] (μg/L)[2]	GENEEC[3] (μg/L)[2]	
Cloquintocet-mexyl	0.0060 μg/L	Peak	56-day average
		0.038 μg/L	0.0053 μg/L
CGA-153433	0.00017 μg/L	Peak	56-day average
		0.031 μg/L	0.017 μg/L

1 SCI-GROW (Screening Concentration in Ground Water) is an empirical model for predicting cloquintocet-mexyl levels in ground water. The value from SCI-GROW is considered an upper bound concentration estimate.
2 μg/L = parts per billion.
3 GENEEC is an empirical model for predicting cloquintocet-mexyl levels in surface water.

4.2.2.4 DWLOC Calculations

As stated above a DWLOC is the concentration of safener in drinking water that would be acceptable as a theoretical upper limit in light of total aggregate exposure to that safener from food, water, and residential uses. HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with safener exposure through drinking water. In the absence of monitoring data for cloquintocet-mexyl, the DWLOC is used as a point of comparison against the conservative EECs provided by computer modeling (SCI-GROW and GENEEC).

For acute and chronic (non-cancer) dietary exposure scenarios, the DWLOC values are all in excess of the modeled EEC values reported by EFED for both the parent safener and the major metabolite. DWLOCs calculated for acute dietary exposure are **3.0 x 10^4 µg/L** for subgroups of females 13-50 years old. DWLOCs calculated for chronic dietary exposure range from **4.0 x 10^2 µg/L** to **1.4 x 10^3 µg/L** for the most highly exposed population, **children 1-6 years old**, and the **total U.S. population**, respectively. HED does not have concern for residues of cloquintocet-mexyl and its metabolite in drinking water.

Table 8. Drinking Water Levels of Comparison for Aggregated Exposures for Cloquintocet-mexyl				
Scenario/Population Subgroup[a]	**Population-Adjusted Dose, mg/kg/day**	**Exposure, mg/kg/day**	**Maximum Water Exposure, mg/kg/day**	**DWLOC, µg/L[b]**
Acute			Cloquintocet GW EEC = 0.0060 Cloquintocet SW EEC = 0.038 CGA153433 GW EEC=0.00017 CGA153433 SW EEC=0.031	
Females (13+/nursing)	1.0	0.00037	1.0	3.0×10^4
Chronic			Cloquintocet GW EEC = 0.0060 Cloquintocet SW EEC = 0.0053 CGA153433 GW EEC=0.00017 CGA153433 SW EEC=0.017	
U.S. Population (total)	0.04	0.00015	0.04	1.4×10^3
Children 1-6 yrs	0.04	0.00034	0.04	4.0×10^2
Females 13+ nursing	0.04	0.00015	0.04	1.2×10^3
Males 13-19	0.04	0.00017	0.04	1.4×10^3

[a] Population subgroups shown include females of childbearing age for acute exposure; the U.S. general population and the maximally exposed subpopulation of adults, infants and children, and women of child-bearing age for chronic exposure.

[b] DWLOC = Maximum Water Exposure (mg/kg/day) × 1000 µg/mg × body weight (70 kg general population/males 13+, 60 kg females 13+, 10 kg infants and children) ÷ Water Consumption (2 L/day adults, 1 L/day infants and children).

4.3 Occupational Exposure

- **Reference**
  Attachment 6: Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration (New Inert) of Cloquintocet-Mexyl on Wheat. (5/8/2000, J. Arthur).

Cloquintocet-mexyl is being considered as a safener for the new active ingredient (ai), clodinafop-propargyl in a product to control grass weeds in wheat. In this memorandum, the name cloquintocet-mexyl will be used for the ingredient being assessed, and will be referred to as the "safener." It should be noted that the Canadian government has reviewed this same formulation for registration in Canada.

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 Margins of Exposure (MOE) which are compared to the target MOE of 100 to determine any risk concerns.

There are no residential uses registered for cloquintocet-mexyl.

Chemical-specific handler exposure data were submitted in support of this Section 3 registration.

Two of these submissions (MRID#s 443992-33 and -34) were surrogate exposure assessments for aerial applicators and groundboom mixer/loaders, based on an analysis of Pesticide Handlers Exposure Database (PHED) data sets. However, HED performed its own analysis of these scenarios using the PHED Surrogate Table for unit exposure values.

Data from the submission on Field Operator Exposure for mixing, loading and applying using a groundboom sprayer (MRID# 443992-35) was used in a modified form. The modification was based on poor recovery of spiked field samples and poor storage stability results, and is explained in more detail in a later section. The approach taken is in harmony with the Canadian risk assessment for the same formulation.

Handlers of cloquintocet-mexyl (in formulation with clodinafop-propargyl) were assessed for exposure during open mixing/loading to support aerial and groundboom application, using PHED unit exposure values. 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. Also, handlers who mix, load and apply by groundboom were assessed together, using unit exposure values obtained from a registrant-sponsored study. The MOEs, under all the above circumstances, range from **2.5×10^2 to 4.5×10^6** for handlers. **These MOEs are greater than the target (100) and do not exceed HED's level of concern.**

The proposed label for cloquintocet-mexyl (in formulation with clodinafop-propargyl) has a 12-hour restricted entry interval (REI). The technical material has a Toxicity Category IV for Primary Skin Irritation; all other acute effects are Category III. Per the Worker Protection Standard(WPS), a 12-hour restricted entry interval (REI) is required for chemicals classified under Toxicity Category III. Therefore, the REI of 12 hours is in compliance with the WPS.

Postappication 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 postapplication activities, these postapplication risks are not assessed. Postapplication risks were assessed for workers entering wheat fields to scout and irrigate. Wheat is 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 **4.9 x 10^5** as early as the day of application. **This MOE is greater than the target (100) and does not exceed HED's level of concern.**

4.4 Non-Occupational/Residential Exposure

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.

4.5 Cumulative Exposure

HED does not currently have data available to determine with certainty whether cloquintocet-mexyl has a common mechanism of toxicity with any other substances. For the purposes of this human health risk assessment, HED has not assumed that cloquintocet-mexyl has a common mechanism of toxicity with other chemicals.

4.6 Endocrine Disruption

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and

anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of cloquintocet-mexyl for endocrine effects may be required.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

5.1 Acute Aggregate Dietary Risk (Food + Water)

Acute (non-cancer) aggregate risk from food + drinking water exposures to cloquintocet-mexyl was described in detail in Section 4.2.1 (Food exposure) and 4.2.2 (Water exposure) of this document. Below is a summary of this aggregate risk analysis.

HED used Dietary Exposure Evaluation Model (DEEM™) software for conducting a Tier 1 acute food exposure analysis for females of childbearing age (13-50 years old). Tier 1 assumptions are tolerance level residues and 100% crop-treated.

As shown in Table 5, the resulting dietary food exposures occupy **< 1.0 %** of the Acute PAD for the **subgroups of females of childbearing age (13-50 years old).**

The EECs (Table 6) provided by EFED for assessing acute aggregate dietary risk are **0.0060 μg/L and 0.00017 μg/L** (in ground water for parent and metabolite, respectively, based on SCI-GROW) and **0.038 μg/L and 0.031 μg/L** (in surface water for parent and metabolite, respectively, peak value based on GENEEC). The back-calculated DWLOCs (Table 8) for assessing acute aggregate dietary risk are **3.0×10^4 μg/L** for women of childbearing age (13-50 years old)

The acute EECs generated by SCI-GROW and GENEEC are less than the Agency's level of comparison (the DWLOC value for each population subgroup) for cloquintocet-mexyl residues in drinking water as a contribution to acute aggregate exposure.

HED thus concludes with reasonable certainty:

- residues of cloquintocet-mexyl and CGA-153433 in drinking water will not contribute significantly to the aggregate acute human health risk

- the acute aggregate exposure from cloquintocet-mexyl residues in food and drinking water **will not exceed the Agency's level of concern** (100% of the acute PAD) for acute dietary aggregate exposure by *any* population subgroup.

EPA generally has no concern for exposures below 100% of the acute PAD, because it is a level at or below which aggregate dietary exposure over a single day or single dose will not pose appreciable risks to the health and safety of *any* population subgroup. This risk assessment is considered high confidence, conservative, and very protective of human health.

5.2 Chronic (Non-Cancer) Aggregate Dietary Risk (Food + Water)

Chronic (non-cancer) aggregate risk from food + drinking water exposures to cloquintocet-mexyl was described in detail in Section 4.2.1 (Food exposure) and 4.2.2 (Water exposure) of this document. Below is a summary of this risk analysis.

HED used Dietary Exposure Evaluation Model (DEEM™) software for conducting a Tier 1 chronic (non-cancer) food exposure analysis. Tier 1 assumptions are tolerance level residues and 100% crop-treated.

As shown in Table 6, the resulting food exposures occupy up to **1%** of the Chronic PAD for the most highly exposed population subgroup, **children (1-6 years old)** and **< 1%** of the Chronic PAD for the **total U.S. population (48 states, all seasons).**

The EECs (Table 7) provided by EFED for assessing chronic aggregate dietary risk are **0.0060 μg/L and 0.00017 μg/L** (in ground water for parent and metabolite, respectively, based on SCI-GROW) and **0.0053 μg/L and 0.017 μg/L** (in surface water for parent and major metabolite, respectively, based on the 56-day mean from the GENEEC). The back-calculated DWLOCs (Table 8) for assessing chronic aggregate dietary risk range from **4.0×10^2 µg/L** for the most highly exposed population subgroup **(children 1-6 years old)** to **1.4×10^3 µg/L** for the **total U.S. Population (48 states, all seasons).**

The chronic EECs generated by SCI-GROW and the GENEEC are less than the Agency's level of comparison (the DWLOC value for each population subgroup) for cloquintocet-mexyl and CGA-153433 residues in drinking water as a contribution to chronic aggregate exposure.

HED thus concludes with reasonable certainty:

- residues of cloquintocet-mexyl and CGA-153433, the major metabolite, in drinking water will not contribute significantly to the aggregate chronic human health risk
- the chronic aggregate exposure from cloquintocet-mexyl residues in food and drinking water **will not exceed the Agency's level of concern** (100% of the chronic PAD) for chronic dietary aggregate exposure by *any* population subgroup.

EPA generally has no concern for exposures below 100% of the chronic PAD, because it is a level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to the health and safety of *any* population subgroup. This risk assessment is considered high confidence, conservative, and very protective of human health.

5.3 Cancer Aggregate Dietary (Food + Water)

Cancer aggregate risk is the sum of exposures resulting from chronic food + chronic drinking water. Cloquintocet-mexyl is classified as "not likely" a human carcinogen. **This risk assessment is not required.**

5.4 Short- and Intermediate-Term Aggregate Dietary and Non-Dietary Risks (Food + 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 3) 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.

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.

5.5 Long-Term Aggregate Dietary and Non-Dietary Risks (Food + Water + Residential)

Based on the proposed use patterns, no long-term dermal or inhalation exposure is expected to occur. Therefore, no endpoints were selected by the HIARC. **Thus, long-term aggregate risk assessments are not required.**

6.0 DEFICIENCIES/DATA NEEDS

Although the noted residue chemistry issues exist, this assessment is considered conservative and health protective. Noted issues do not preclude the establishment of a time-limited registration for the formulation along with the establishment of tolerances for cloquintocet-mexyl and its acid metabolite once revised Sections B and F and adequate EPA method validations are available.

Toxicology

- None

Occupational/Residential Exposure

- None

Product Chemistry

- *Under review in Registration Division.*

Residue Chemistry

The data gaps in the residue chemistry database are listed below. The data gaps are discussed in detail in the review of 4/7/00 (Memo, N. Dodd, D257181), which is included as Attachment 5. **Although the noted residue chemistry issues exist, this assessment is considered conservative and health protective. Except for the submission of revised Sections B and F and the availability of adequate EPA method validations, noted issues will not preclude the establishment of a time-limited registration.**

OPPTS GLN 860.1200: PROPOSED USE

1. The Section B/label should be revised to change the feeding/grazing restriction on forage to 30 days since limited residue data are available at a 7-day PHI. Provided the above revision to the Section B/label is made, the proposed use of cloquintocet-mexyl on wheat will be adequately described. The proposed use directions will be adequate to allow an assessment of whether the residue data reflect the maximum residues likely to occur in food/feed.

OPPTS GLN 860.1300: NATURE OF THE RESIDUE IN PLANTS

2. The nature of the residue in wheat is not adequately understood for the purposes of a permanent tolerance for the following reasons pertaining to the [3-^{14}C-quinoline]CGA-185072 study:

a. Due to large amounts of the radioactivity being nonextractable with 80% aqueous acetonitrile and by Soxhlet extraction with 100% acetonitrile, only 16.0%, 0.9%, and 4.4%TRR were identified in leaves (ear emergence), leaves (milky stage), and straw (maturity), respectively. The petitioner should have attempted to extract more of the radioactivity using acid, base, and enzymes and then characterized/identified those residues.

b. Residues in grain were not identified in the field study. The identity of residues in grain resulting from application to the plant in a manner simulating expected field use are needed. The study should be conducted at a higher rate than the 2X study which was submitted.

c. The time from sampling to final analysis should be clarified for the wheat samples. If the time between sampling and final analysis of the field samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses should show that the basic profile of radiolabeled residues has not changed during that time.

3. The nature of the residue in wheat is adequately understood for the purposes of a time-limited registration. The residues of concern in wheat were determined by HED's Metabolism Assessment Review Committee (MARC) on 2/15/00 (D263289, N. Dodd, 2/25/00) to be CGA-185072 and its acid metabolite CGA-153433. HED may revisit the MARC after additional wheat metabolism data have been submitted.

OPPTS GLN 860.1300: NATURE OF THE RESIDUE IN LIVESTOCK

Ruminants

4. The nature of the residue in ruminants is not adequately understood for the purpose of a permanent tolerance for the following reason: The time between sampling and final analysis should be clarified for milk and tissues. If the time between sampling and final analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

Poultry

5. The nature of the residue in poultry is not adequately understood for the purpose of a permanent tolerance for the following reason: The time between sampling and final analysis should be clarified for eggs and tissues. If the time between sampling and final analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable,

such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

OPPTS GLN 860.1340: RESIDUE ANALYTICAL METHODS

Plants

6. To establish a permanent tolerance, the following additional information is needed regarding the analytical methods used to obtain the storage stability and residue data: a) Radiovalidation data for Methods REM 138.01, 138.06, 138.10, and 138.12 are needed to demonstrate the efficiency of the methods in extracting and quantifying aged or bound residues in samples; b) Method REM 138.12 should be submitted.

7. Before EPA can determine whether adequate analytical methods are available for enforcement of permanent tolerances on wheat, the following additional information is needed for the proposed enforcement methods: a) For REM 138.01 and REM 138.06, either an interference study must be submitted which determines whether other pesticides registered on wheat will interfere with the analysis of cloquintocet-mexyl residues by the enforcement method or a specific confirmatory method such as mass spectroscopy is needed as discussed in OPPTS GLN 860.1340. Provided that a specific confirmatory method is available, the Agency will not require that an interference study be conducted; b) Confirmatory methods are needed for REM 138.01 and 138.06; c) The GC/MS confirmatory method in Method REM 138.10 includes derivatization with diazomethane. The petitioner should investigate whether another methylating agent could be substituted for diazomethane. If an alternative methylating agent is not available, EPA requires that justification for the use of diazomethane be provided. An alternative confirmatory method for REM 138.10 would be LC/MS. REM 138.10 could be rewritten to include LC/MS as the confirmatory method instead of GC/MS; d) Adequate EPA petition method validations are needed for the proposed enforcement methods. RAB3 has requested EPA petition method validations for REM 138.01, 138.06, and 138.10. These EPA petition method validations are underway. Adequate independent laboratory validations have been provided for methods REM 138.01 and 138.06.

8. Provided that the petition method validations which are being conducted by EPA are successful, adequate enforcement methods (MRID nos. 44399211, 44399213, and 44755302) are available to enforce a time-limited registration on wheat.

OPPTS GLN 860.1380: STORAGE STABILITY DATA

9. Adequate storage stability data have not been submitted. The following additional storage stability data are needed:

a. Additional data are needed for Study 300/91 (MRID no. 44399210). 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 stability samples should be submitted or identified by number as a submitted method.

b. No storage stability data were submitted for forage. Storage stability data for forage are needed for the 105-day storage interval for CGA-185072 and the 218-day storage interval for CGA-153433 in US residue samples. If the Canadian residue studies could be used (i.e., upgraded to acceptable), storage stability data for forage would be needed for the 434-day storage interval for CGA-185072 and CGA-153433 in the Canadian residue samples so that the tolerance could be adjusted for any storage degradation; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies to an acceptable level.

c. No storage stability data were submitted for wheat processed commodities. The storage time between processing and analysis was ≤25 days for CGA-185072; storage stability data are not needed for CGA-185072 in processed commodities since they were analyzed within 30 days of their production (OPPTS 860.1520). The storage time between processing and analysis for CGA-153433 was 51 days for aspirated grain, 45 and 125 days for germ, 45 days for bran, 42 days for middlings and shorts, and 37 days for low grade flour and patent flour. Storage stability data for CGA-153433 in aspirated grain fractions are not needed since this is an early season use and residues are not expected to occur in aspirated grain fractions. Storage stability data are not needed for bran, flour, middlings, and shorts since these matrices are similar to grain and can be covered by the storage stability data on grain. Storage stability data are needed for CGA-153433 in wheat germ for 45 and 125 days.

OPPTS GLN 860.1500: MAGNITUDE OF THE RESIDUE IN PLANTS

10. The proposed use indicates that forage could be fed/grazed at a 7-day PHI, hay could be fed at a 30-day PHI, and grain and straw could be harvested at a 60-day PHI. Based on the available residue data, residues of parent or CGA-153433 were less than the limit of quantitation (LOQ) in the grain, forage, hay, and straw commodities which were analyzed in the US and Canada at these PHI's. (Straw in the US was not analyzed for CGA-153433. Hay was not analyzed in Canada. For US data, the limits of quantitation for parent were 0.02 ppm for grain and 0.05 ppm for forage, hay, and straw; the limit of quantitation for CGA-153433 was 0.05 ppm for grain, forage, and hay; straw was not analyzed for CGA-153433. For Canadian data, the limits of quantitation for parent were 0.02 ppm for grain and forage and 0.05 ppm for straw; the limits of quantitation for CGA-153433 were 0.02 or 0.05 ppm for grain, and 0.05 ppm for forage and straw.) However, the field trial residue data are not adequate to support a permanent tolerance for the following reasons:

a. Adequate geographic representation is not provided. (Wheat is not a minor crop, for which a regional registration would be accepted.) According to OPPTS 860.1500, a minimum of 20 field trials are needed to support a tolerance on wheat. The suggested distribution of wheat field trials is one in Region 2, one in Region 4, five in Region 5, one in Region 6, five in Region 7, six in Region 8, and 1 in Region 11. The US field trials were conducted in Region 5 (2 studies) and Region 7 (four studies), as defined in OPPTS 860.1500; however, these US studies did not

determine CGA-153433 in straw. Of the 15 Canadian field trials, four studies were conducted in extended Zone 5, seven studies were conducted in extended Zone 7, and four studies were conducted in extended Zone 14; however, the Canadian field trials have deficiencies which are not upgradeable (see Conclusion 11 below). Additional field trial residue studies are needed to support a permanent tolerance. If residues of CGA-153433 in straw samples in the US can be reanalyzed by an adequate method and the reanalysis can be supported by storage stability data, the following additional field trial studies would be needed: For a 30-day PHI in forage, the additional studies would be one in Region 2, one in Region 4, three in Region 5, one in Region 6, one in Region 7, six in Region 8, and 1 in Region 11. (If a 7-day PHI in forage is desired, then the additional studies would be one in Region 2, one in Region 4, five in Region 5, one in Region 6, four in Region 7, six in Region 8, and one in Region 11.) Otherwise (without US residue data for CGA-153433 in straw), the following additional field trial studies would be needed: one in Region 2, one in Region 4, five in Region 5, one in Region 6, five in Region 7, six in Region 8, and one in Region 11. Each study should include PHI's of 30 (or 7) days for forage, 30 days for hay, and 60 days for grain and straw. Spring (including hard red spring, duram, and white spring) and winter (including hard red winter, soft red winter, and white winter) varieties of wheat should be included in the studies. 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.

b. Only spring wheat was used in the US and Canadian studies. Winter wheat should be included in the residue studies.

c. Forage was sampled at the proposed preharvest interval (PHI) of 7 days in only one US study and three Canadian studies.

d. Based on the available residue data, the petitioner should submit a revised Section F which proposes tolerances of 0.10 ppm for the combined residues of cloquintocet-mexyl and its metabolite 5-chloro-8-quinolinoxyacetic acid on wheat grain, forage, hay, and straw. These levels were obtained by adding the limits of quantitation for CGA-185072 and CGA-153433.

11. For the Canadian field trial residue studies, the following data should have been included. (HED is not recommending that the petitioner attempt to upgrade these studies to an acceptable level.)

a. Grain, forage, hay, and straw should be analyzed in each of the wheat field trial residue studies. (For an early season use, data on aspirated grain fractions are not needed.) Of the 15 Canadian studies, only grain and straw were analyzed in most of the studies (i.e., in twelve studies for CGA-185072 and 9 studies for CGA-153433), and only forage was analyzed (for both CGA-185072 and CGA-153433) in three studies. Hay was not analyzed.

b. PHI's should reflect the proposed use. PHI's for grain and straw in the Canadian studies ranged from 55-105 days (with all but two studies with PHI's above 60 days) whereas the proposed PHI for grain and straw is 60 days.

c. Extraction dates were not provided for MRID nos. 44399217, 44399218, 44399219, 44399220, 44399221, 44399222, 44399223, 44399224, 44399225, 44399226, 44399227, and 44399231.

d. Storage containers were not described.

e. Raw data and representative chromatograms of standards, controls, fortified samples, and treated samples were not submitted.

OPPTS GLN 860.1520: MAGNITUDE OF THE RESIDUE IN PROCESSED FOOD/FEED

12. Pending submission of storage stability data on CGA-153433 in processed commodities (see storage stability section of this review), HED concludes that no concentration of CGA-185072 or CGA-153433 occurred on processing.

OPPTS GLN 860.1850: CONFINED ACCUMULATION IN ROTATIONAL CROPS

13. The submitted confined rotational crop data are adequate for a permanent tolerance provided that rotational crop restrictions are placed on the formulation label of at least 85 days (or 3 months) for lettuce and other leafy vegetables, 146 days (or 5 months) for small grains (except wheat), and one year (or 12 months) for all other crops.

14. If the petitioner wants shorter rotational crop restrictions, then a confined rotational crop study conducted at the soil aging intervals of 1, 4, and 12 months would be needed for three rotated crops (a small grain, a leafy vegetable, and a root crop).

OPPTS GLN 860.1900: FIELD ACCUMULATION IN ROTATIONAL CROPS

15. No field accumulation in rotational crop study was submitted. Pending results from the confined rotational crop study which may be conducted if the petitioner wants shorter rotational crop restrictions, this study may be required.

HED cannot recommend for the proposed permanent tolerances for cloquintocet-mexyl on wheat for the reasons given in the conclusions above.

Provided the petitioner submits a revised Section B/label and a revised Section F and EPA's method validation is satisfactory (see Conclusions 1, 8, and 10d above), there will be no residue chemistry data requirements that would preclude the establishment of a time-limited registration for the combined residues of cloquintocet-mexyl (acetic acid, [(5-chloro-8-quinolinyl)oxy]-, 1-methylhexyl ester) and its acid metabolite 5-chloro-8-

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quinolinoxyacetic acid in/on wheat grain, forage, hay, and straw at 0.10 ppm while the remaining concerns are addressed.

7.0 LIST OF ATTACHMENTS

Attachment 1:Cloquintocet-mexyl - Report of the Hazard Identification Assessment Review Committee (6/17/99, Y. Yang).

Attachment 2:PP #7E04920 Cloquintocet-mexyl (CGA 185072) (PC Code: 999999/inert)Toxicology Disciplinary Chapter for Registration Support Document (S. Gross, 4/20/2000).

Attachment 3:*CLOQUINTOCET-MEXYL* - Report of the FQPA Safety Factor Committee (3/20/99, B. Tarplee).

Attachment 4: Acute and Chronic Dietary Exposure Analyses for Proposed Tolerances for Cloquintocet-mexyl in/on Wheat Commodities. (3/27/2000, M. Xue).

Attachment 5: PP#7E04920. Cloquintocet-mexyl (Safener) in/on Wheat. Review of Analytical Methods and Residue Data. First Food Use Review. (4/7/2000, N. Dodd).

Attachment 6: Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration (New Inert) of Cloquintocet-Mexyl on Wheat. (5/8/2000, J. Arthur).

Attachment 7: Tier I Estimated Environmental Concentrations of Cloquintocet mexyl (Chemical: 700099) (11/7/1999, H. Nelson).

Attachment 8: Cloquintocet-mexyl. Metabolism Assessment Review Committee (MARC) Decision Document for Meeting Held on 2/15/00. Chemical # 999999. DP Barcodes: D263289 and D263319.

Attachment 9: Names and Structures of Cloquintocet-mexyl and its Metabolite; Proposed Wheat, Goat, and Hen Metabolism Pathway of Cloquintocet-mexyl

8.0 DISTRIBUTION

cc **WITH** Attachments: RAB3 Reading File, PP#7E04920

cc without Attachments: A. Lowit, N. Dodd, J. Arthur, S. Gross, M. Xue

9.0 CONFIDENTIAL APPENDIX

13544

003400

Chemical:	**Inert ingredient undetermined**
PC Code:	**999999**
HED File Code	**14000 Risk Reviews**
Memo Date:	**05/08/2000**
File ID:	***TX014171***
Accession Number:	**412-01-0121**

HED Records Reference Center
02/12/2001