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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: November 10, 2005

Subject: Occupational and Residential Risk Assessment to Support Request for a Section 3 New Use Registration of Safener, Cloquintocet-Mexyl, on Wheat and Barley.

DP Barcode:	PC Code:	Trade Name:	EPA Reg#	MRID#	PRAT Case	Class	Caswell#	40 CFR
D322950	700099	N/A	N/A	NA	N/A	Herbicide	N/A	N/A

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Introduction

The registrant, Syngenta Crop Protection, Inc., has requested an increase in the tolerances for residues of the safener, cloquintocet-mexyl, on wheat and barley. Cloquintocet-mexyl is currently present as a safener in products registered for these uses: one containing the active ingredient, clodinafop-propargyl, and another containing the active ingredient, pinoxaden; both used in post-emergent control of annual grass weeds. This memorandum addresses risk from occupational and residential exposure to cloquintocet-mexyl only, and specifically regarding its use in the pinoxaden herbicide product.

1.0 Executive Summary

Cloquintocet-mexyl is being used as a safener for the active ingredient (ai), clodinafop-propargyl in a product to control grass weeds in wheat, and for the ai pinoxadem to control grass weeds in wheat and barley. An occupational and residential exposure (ORE) assessment has been completed for a clodinafop-propargyl product used on wheat (ref: D264699, K. O'Rourke, 05/04/00), and a separate ORE assessment for cloquintocet-mexyl used as a safener in this product (ref: D264565, J. Arthur, 05/08/00). Further, an ORE assessment has been completed for a pinoxaden product used on wheat and barley (ref: D315788, M. Dow, 04/13/05), but was not accompanied by a separate ORE assessment on the cloquintocet-mexyl safener in this product. This document presents the ORE assessment for cloquintocet-mexyl use as a safener in the aforementioned pinoxaden product. In this memorandum, the name cloquintocet-mexyl will be used for the ingredient being assessed, and will be referred to as the "safener."

Occupational Handler Exposure

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, in which a higher incidence of skeletal variants and a decrease in fetal body weights were observed. 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, in which thyroid hyperplasia was observed. These calculations result in Margins of Exposure (MOE) which are compared to the level of concern (LOC) of 100 to determine any risk concerns.

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

Occupational Postapplication Exposure

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

The acute toxicity of technical cloquintocet-mexyl (as seen in Table 2 below) would require an interim restricted entry interval (REI) of 12 hours under the requirements of the Worker Protection Standard (WPS). However, the label for the pinoxaden product in which cloquintocet-mexyl serves as a safener lists a 48-hour interim restricted entry interval (REI) under requirements of the Worker Protection Standard, and therefore, this requirement will restrict the cloquintocet-mexyl component as well.

Residential Exposure

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

2.0 Hazard Profile

On June 17, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database on cloquintocet-mexyl, and selected the doses and toxicological endpoints for occupational exposure/risk assessments. These endpoints and results from acute studies with the technical grade substance are seen in Tables 1 and 2 below.

Table 1. Summary of Toxicology Endpoint Selection.

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
	Acute RfD (females 13+) = 1 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 Toxicity -Rat
		Chronic RfD = 0.04 mg/kg/day	
Short-term (Dermal)	Dermal NOAEL=200	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
Intermediate-Term (Dermal)			
Long-term (Dermal)	Not Applicable	Based on the current use pattern, no long-term dermal exposure is expected to occur.	
Short-term (Inhalation)	Oral NOAEL= 100[a]	See acute dietary	Developmental Toxicity- Rats
Intermediate-Term (Inhalation)	Oral NOAEL=4.3 [a]	See chronic dietary	Chronic Toxicity- Rats
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

Table 2. Summary of Acute Toxicity for Technical Cloquintocet-mexyl

GDLN	Study Type	MRID	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

3.0 Use Profile

The use profile proposed for this Section 3 registration is summarized in Table 3.

Table 3. Summary of Proposed New Uses for the Safener, Cloquintocet-mexyl

Product	Use Sites (Pests Controlled)	Max. Application Rate (lb ai/acre)	Number/Timing of Applications	Max. Annual Rate (lb ai/A)	PHI (days)
Cloquintocet-mexyl (in liquid formulation with pinoxaden)	Wheat (including durum), and Barley (for the post- emergent control of grass weeds)	0.016 *	1 per crop, per season (from 2-leaf stage to pre-boot stage of wheat and barley, or from 1 - 6 leaf stage on main stem of weed species)	Not Specified	60

* Conversion to lb ai/acre assumed that cloquintocet-mexyl has density of 8.6 lb/gal

4.0 Occupational Exposure

4.1 Handler Exposure and Risk

There is a potential for exposure to cloquintocet-mexyl during mixing, loading, and application activities. An exposure/risk assessment using applicable endpoints selected by the HIARC was performed. Handler's exposure and risk were estimated for the following scenarios: 1) mixing/loading liquid to support aerial application; 2) aerial application 3) mixing/loading liquid to support groundboom application; 4) groundboom application; and, 5) flagging for aerial application. Flaggers for aerial application are assessed for 350 acres per day application, because a larger number of acres treated would likely require pilot-activated mechanical flagging or Global Positioning Systems, and not human flaggers.

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

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

Exposure assumptions and estimates for occupational handlers are summarized in Table 4. The MOEs range from 250 to 4,600,000 for handlers. **These MOEs are greater than 100, and therefore, do not exceed HED's level of concern.**

Table 4. Exposure and Risk Assessment for Occupational Handlers

PHED Scenarios for Cloquintocet-mexyl Uses	PHED Unit Exposure[1] (mg/lb safener)	Maximum Application Rate	Area/Amount Treated	Daily Dose[2] (mg/kg/day) [70 kg BW]	Short/Interm.-term Dermal Risk (MOE)[3]	Interm.-term Inhalation Daily Dose (60 kg BW)	Short-term Inhalation Risk (MOE)[4]	Intermediate-term Inhalation Risk (MOE)[5]
(1) Mix/load : liquid to support aerial (open)	Dermal: 2.9	0.016 lb ai/A	1200	0.80	250	0.000384	260,000	13,000
	Inhalation: 0.0012			0.00033				
(2) Apply: aerial (closed cab)	Dermal: 0.0050	0.016 lb ai/A	1200	0.0014	150,000	0.00002176	4,600,000	230,000
	Inhalation: 0.000068			0.000019				
(3) Mix/load : liquid to support groundboom (open)	Dermal: 2.9	0.016 lb ai/A	200	0.13	1500	0.000064	1,600,000	78,000
	Inhalation: 0.0012			0.000055				
(4) Apply: groundboom (open cab)	Dermal: 0.014	0.016 lb ai/A	200	0.00064	310,000	0.00003947	2,500,000	130,000
	Inhalation: 0.00074			0.000034				
(5) Flaggers for aerial application	Dermal: 0.011	0.016 lb ai/A	350	0.00088	230,000	0.0000327	3,100,000	150,000
	Inhalation: 0.00035			0.000028				

[1] PHED Unit Exposure values are for baseline protection (long-sleeved shirt, long pants, shoes plus socks) unless otherwise indicted.

[2] Daily Dose =(Unit Exposure x Application Rate x Area Treated)/Body Weight [Body weight of 60 kg used for short-term inhalation; 70 kg used for other endpoints]

[3] MOE = NOAEL/ Daily Dose. Short- and Intermediate-term dermal NOAEL= 200 mg/kg/day.

[4] MOE = NOAEL/ Daily Dose. Short-term inhalation NOAEL=100 mg/kg/day.

[5] MOE = NOAEL/ Daily Dose. Intermediate-term inhalation NOAEL= 4.3 mg/kg/day.

4.2 Post-Application Exposure and Risk

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

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

Inputs and calculated postapplication risk can be seen in Table 5. Risk calculations for postapplication workers result in an MOE = 490,000 on the day of application. Because this MOE well exceeds 100, this risk does not trigger HED concern for postapplication workers in wheat or barley fields treated with cloquintocet-mexyl (in formulation with pinoxaden).

Table 5. Exposure and Risk Assessment for Occupational Postapplication Activities

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

[1] Transfer Coefficient for scouting and irrigating.

[2] Daily Dose = [Dislodgeable Foliar Residue x Dermal Transfer Coefficient x Exposure Time (8hrs)] / [(CF: 1000 ug/mg) x Body weight (70 kg)]

[3] MOE = NOAEL/Daily Dose. Short-/Intermediate-Term Dermal NOAEL = 200 mg/kg/day

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

5.0 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.

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Chemical:	**Acetic acid, {(5-chloro-8-quinolinyl)oxy}-, 1-methylhexyl ester**
	PC Code: 700099
HED File Code:	**14000 Risk Reviews**
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