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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: March 21, 2000

Subject: Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration (New Inert) of Cloquintocet-Mexyl on Wheat

DP Barcode:	PC Code:	Trade Name:	EPA Reg#	MRID#	PRAT Case	Class	Caswell#	40 CFR
D264565	N/A	Discover™	N/A	44399232 44399233 44399234 44399235 44399236	N/A	Herbicide	N/A	N/A

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Introduction

The registrant, Novartis, requests the establishment of tolerances for residues of the herbicide, clodinafop-propargyl, on wheat. Clodinafop-propargyl is the active ingredient (ai) in Discover™, an emulsifiable concentrate formulated for use in post-emergent control of annual grass weeds in wheat. Discover™ also contains the safener, cloquintocet-mexyl, at 5.6%. This memorandum addresses risk from occupational and residential exposure to cloquintocet-mexyl only. Clodinafop-propargyl risks are presented in a separate assessment. Also, an aggregate human risk assessment will be included as a separate HED memorandum.

1.0 Executive Summary

Cloquintocet-mexyl is being considered as a safener for the new active ingredient (ai), clodinafop-proargyl in a product to control grass weeds in wheat. The formulated end use product will be labeled under the trade name Discover™. In this memorandum, the name cloquintocet-mexyl will be used for the ingredient being assessed, and will be referred to as the "ai", even though serving as an inert in the product. It should be noted that the Canadian government has reviewed this same product for registration in Canada under the tradename, Horizon™.

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 (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 Horizon™.

Handlers of cloquintocet-mexyl (Discover™) 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 250 to 4,500,000 for handlers. **These MOEs are greater than the target (100) and do not exceed HED's level of concern.**

The proposed label for Discover™ 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, hoe, irrigate and harvest. It should be noted that wheat is assumed to be mechanically harvested, with exposure being limited to ancillary activities associated with operating the harvesting equipment in the field. The MOE resulting from postapplication exposure is 49,000. **This MOE is greater than the target (100) and does not exceed HED's level of concern.**

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) Intermediate-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
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 of Applications	Max. Annual Rate (lb ai/A)	PHI (days)
Discover™	Spring/Winter Wheat (for the post- emergent control of grass weeds)	0.016 *	1 per crop, per season (Early application recommended: when weeds are in active growth phase and wheat is between 2-leaf stage and 4th tiller)	Not Specified	60

* Conversion to lb ai/acre assumed that cloquintocet-mexyl has same density as clodinafop-propargyl (i.e., 8.97 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; 5) mixing, loading and applying by groundboom; and, (6) flagging for aerial application. Flaggers for aerial application are assessed for 350 acres per day application, because a larger number of acres treated would likely require pilot-activated mechanical flagging or Global Positioning Systems, and not human flaggers.

Chemical-specific handler exposure data were submitted in support of this Section 3 registration. Specifically, the following submissions were made:

* MRID# 443992-32: Detailed Study Assessments Covering Worker Exposure (i.e., summary of the following four submissions)
* MRID# 443992-33: Assessment of Potential Exposure to Mixer-Loaders and Groundboom Applicators from the Use of Clodinafop 2E on Wheat
* MRID# 443992-34: Assessment of Potential Exposure and Margins of Safety Resulting from the Aerial Application of Horizon to Spring Wheat
* MRID# 443992-35: Field Operator Exposure Study with CGA-184927 as Horizon™ 240 EC
* MRID# 443992-36: Operator Exposure Study Verification of Sample Stability- CGA-184927 as Horizon™ 240 EC

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

The Field Operator Exposure study (MRID# 443992-35) was previously submitted to, and reviewed by, Health Canada's Pesticide Management Regulatory Agency (Memorandum from Ron Bell of the Exposure Assessment Section to John Worgan of the Exposure Assessment Section, Sub #93-0518, dated October 24, 1994). HED concurs with the general methods and conclusions of Health Canada's review, and therefore, has utilized the unit exposure values determined therein,

rather than conducting its own formal evaluation (A copy of this memorandum is provided as an attachment). Data from the submission was used in a modified form to assess exposure to workers who mix, load and apply cloquintocet-mexyl using groundboom equipment. The modification was based on poor recovery of spiked field samples and poor storage stability results. In this study, fifteen volunteer farmers mixed, loaded and applied cloquintocet-mexyl (5.6% in a clodinafop propargyl herbicide formulation), at a rate of approximately 0.015 lb ai per acre to fallow land in the Saskatchewan Province of Canada in June of 1993. The application was made to approximately 100 acres using groundboom equipment. Passive dosimetry was used to monitor dermal exposure to workers. Analysis of long underwear, inner cotton gloves and hand washes were used to estimate exposure to protected areas of the body. Analysis of hat patch, coveralls and nitrile glove washes were used to estimate exposure to the unprotected body. Exposure received by the head area was estimated using residue results from the hat patch and the collar of the coveralls. Inhalation exposure was monitored with a Gillian air pump and polyethylene foam cartridges, sampling in the workers breathing zone at 2 L/minute. Average field recoveries for clodinafop propargyl from spiked dosimeter materials and handwash solution were all in the range of approximately 100 to 135%. Whereas, average field recoveries for cloquintocet-mexyl were all in the range of approximately 20 to 30%. Recovery from storage stability studies, likewise, showed good recovery for clodinafop propargyl, but poor recovery for cloquintocet-mexyl.

Because recoveries for cloquintocet-mexyl were too poor to rely on for correcting measured residue values from the field study, it was decided to use the residue levels of clodinafop propargyl as a surrogate. The unit exposure value (ug ai/lb ai handled) for clodinafop propargyl should also serve as an indicator of the exposure potential from handling cloquintocet-mexyl in this same formulation, with the percent of individual components accounting for differences in the amount of ai handled in the calculation. This approach is believed to be reasonable because the conditions of application are the same for both chemicals. The approach is ~~also~~ consistent with the one used by Health Canada in its evaluation and use of this study to assess the risks of the product Horizon™.

As mentioned above, no chemical-specific handler exposure data were submitted for aerial mixers, loaders or applicators. In accordance with HED's Exposure Science Advisory Council (SAC) policy, 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 32,000 to 3,000,000 for handlers. **These MOEs are greater than the target (100) and 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 ai)	Maximum Application Rate	Area/Amount Treated	Daily Dose[2] (mg/kg/day) [70 kg BW]	Short/Intermediate Term Dermal Risk (MOE)[3]	Short-term Inhalation Risk (MOE)[4]	Intermediate-term Inhalation Risk (MOE)[5]
(1) Mix/load : liquid to support aerial (open)	Dermal: 2.9	0.016 lb ai/A	1200	0.80	250	260,000	13,000
	Inhalation: 0.0012			0.00033			
(2) Apply: aerial (closed cab)	Dermal: 0.0050	0.016 lb ai/A	1200	0.0014	140,000	4,500,000	230,000
	Inhalation: 0.000068			0.000019			
(3) Mix/load : liquid to support groundboom (open)	Dermal: 2.9	0.016 lb ai/A	200	0.13	1500	1,600,000	78,000
	Inhalation: 0.0012			0.000055			
(4) Apply: groundboom (open cab)	Dermal: 0.014	0.016 lb ai/A	200	0.00064	310,000	2,500,000	130,000
	Inhalation: 0.00074			0.000034			
(5) Mix/Load/Apply: groundboom (closed cab)[6]	Dermal: 0.099[6]	0.016 lb ai/A	200	0.0045	44,000	540,000	27,000
	Inhalation: 0.0034[6]			0.00016			
(6) Flaggers for aerial application	Dermal: 0.011	0.016 lb ai/A	350	0.00088	220,000	3,000,000	170,000
	Inhalation: 0.00035			0.000028			

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

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

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

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

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

[6] Unit Exposure values based on data provided by registrant field study.

4.2 Post-Application Exposure and Risk

Postapplication occupational risks from working in wheat fields treated with cloquitocet-mexyl were assessed for scouting, hoeing, irrigation and activities ancillary to harvesting equipment operation (although harvesting is not recommended for 60 days following treatment).

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.

Inputs and calculated postapplication risk can be seen in Table 5. Risk calculations for postapplication workers result in an MOE = 49,000 on the day of application. Because this MOE well exceeds the target MOE of 100, this risk does not trigger HED concern for postapplication workers in wheat fields treated with cloquintocet-mexyl in the product Discover™.

The proposed label for Discover™ 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.

Table 5. Exposure and Risk Assessment for Occupational Postapplication Activities

Crop Group	Application Rate (lb ai/A)	Dermal Transfer Coefficient (cm^2/hr)	Dislodgeable Foliar Residue (ug/cm^2)	Postapplication Day (t)	Daily Dose[2] (mg/kg/day)	Short-/Intermed. Term Dermal MOE[3]
Wheat	0.016	1000[1]	0.036	0	0.0041	49,000

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

5.0 Non-Occupational/Residential Exposure

There are no existing or proposed residential uses for this product. Therefore a non-occupational/residential risk assessment has not been performed.

This assessment for cloquintocet mexyl reflects the Agency's current approaches for completing residential exposure assessments based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines, the Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment*, and the *Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP)*. The Agency is, however, currently in the process of revising its guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available. This will include expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from other sources already not addressed such as from spray drift; residential residue track-in; exposures to farmworker children; and exposures to children in schools.

CC: RAB3 RF, Anna Lowit (HED), and Jack Arthur (HED)

SignOff Date:	3/ /00
DP Barcode:	D261582
HED DOC Number:	

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Chemical:	**Inert ingredient undetermined**
PC Code:	**999999**
HED File Code	**12000 Exposure Reviews**
Memo Date:	**03/21/2000**
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