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MEMORANDUM

Date: October 22, 2009

Subject: Aminopyralid: Occupational Exposure Assessment for the Registration of Milestone® Herbicide for Use on Corn.

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Decision No.: 401475
Petition No.: N/A
Risk Assessment Type: Single Chemical
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MRID No.: N/A

DP Barcode: D370497
Registration No.: 62719-519
Regulatory Action: Section 3
Case No.: N/A
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BACKGROUND

Dow AgroSciences has submitted a Section 3 application to register a new end-use product formulation, Milestone® Herbicide (EPA Reg. No.: 62719-519) containing aminopyralid as the sole active ingredient (ai) for use on field corn. This document summarizes an occupational risk assessment conducted for evaluating the exposure and risk to handlers and post-application workers who will be using the product.

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1.0 EXECUTIVE SUMMARY

Dow AgroSciences is proposing to register Milestone® Herbicide for post emergent broadleaf weed control in field corn and field corn grown for ensilage. It is formulated as a liquid and contains 40.6% of the active ingredient (a.i.) aminopyralid in the form of its triisopropanolammonium salt or 21.1% aminopyralid acid equivalent (a.e.). Based on the proposed uses specified in the label, occupational exposure is expected to be short- and intermediate-term in duration. No long-term (chronic) exposure is expected.

Aminopyralid is a pyridine carboxylic acid herbicide registered for use in rangeland, permanent grass pastures, non-cropland areas, natural areas, grazed areas in and around these sites, as well as wheat. Aminopyralid provides systemic postemergence broad-spectrum control of a number of key noxious and invasive annual, biennial and perennial weed species, as well as agronomic broadleaf weeds. Aminopyralid can also provide residual weed control activity controlling re-infestations and reducing the need for re-treatment depending on the rate applied and the target weeds. Aminopyralid Technical is a 95.3% manufacturing use product.

Hazard Characterization

Acute toxicity data indicate that aminopyralid (XDE-750 and GF-871) has low toxicity via oral, dermal, and inhalation routes of exposure; however, the free acid form (XDE-750) of the molecule produces severe eye irritation. The stomach, ileum and cecum appear to be targets for this chemical. At mid- and high-level doses, ulcers and erosion of the mucosal lining were noted in the stomach. At high level doses, effects on the mucosal lining of the ileum and cecum were observed. Developmental and reproduction studies show that there is no evidence of increased qualitative or quantitative susceptibility of the fetuses to aminopyralid. Dermal studies indicate that aminopyralid does not have any significant toxicity via the dermal route of exposure. Aminopyralid has been classified as "not likely to be carcinogenic to humans" and there is no evidence that aminopyralid is mutagenic or an endocrine disruptor. Additionally, short-, and intermediate-term durations for inhalation exposures were assessed based on the results (inanition, body weight changes, incoordinated gait) of the developmental toxicity study in rabbits. No systemic toxicity was observed in a 28 day dermal toxicity study in rats up to the limit dose of 1000 mg/kg/day. A dermal point of departure (POD) was not selected since no toxicity was observed in a 28 day dermal toxicity study at the limit dose. Although a developmental toxicity study was used for inhalation risk assessment, the endpoint selected was based on maternal effects (severe inanition (exhaustion due to lack of food) and body weight loss, decreased fecal output, and mild incoordinated gait) and there is no concern for developmental toxicity. The primary toxic effects of concern observed in the developmental toxicity study as well as the toxicity database were adequately addressed in the dermal study. Therefore, a dermal risk assessment is not required for short- and intermediate-term dermal exposure. As part of the new EPA40 CFR Part 158 requirements, an immunotoxicity study in rats and/or mice is now required for aminopyralid.

Residential Exposure

Residential exposures associated with the use of aminopyralid to control weeds on residential and recreational sites were previously assessed (M. Collantes; D305672; May 24, 2005). The results of the residential exposure assessment indicate no risks of concern to the Agency. The registrant has not proposed any new residential and/or non-occupational uses for aminopyralid at this time; therefore, a residential/non-occupational exposure assessment is not required.

Occupational Exposure

The registrant did not submit any chemical-specific exposure data for assessing the occupational risks involved while handling the product in support of this application. In its absence, the Agency used surrogate exposure data from the Pesticide Handlers Exposure Database (PHED) and the Outdoor Residential Exposure Task Force (ORETF) default values established by the HED's Science Advisory Council for Exposure (ExpoSAC) for calculating the exposure to mixers, loaders and applicators.

Margins of Exposure (MOEs) of 100 are required for handlers of agricultural crops in order for risks not to be of concern to HED. All handler short- and intermediate-term MOEs were greater than 100 and therefore risks were not of concern to the Agency (i.e., an MOE $\geq$100).

HED has determined that there are potential dermal exposures to persons entering treated sites (e.g. harvesters) after application of pesticide is complete. However, since no dermal POD was selected, a quantitative postapplication risk assessment for agricultural uses was not possible and there are no concerns with such risks.

Restricted Entry Interval

Milestone® Herbicide contains the triisopropanolammonium salt of aminopyralid. However, after application of the product agricultural workers could be exposed to residues from both the aminopyralid salt and the parent acid. Therefore, the restricted entry interval (REI) for agricultural occupational exposure resulting from treated corn is based on the acute toxicity of both aminopyralid acid technical and the triisopropanolammonium salt. Aminopyralid acid is classified as Category IV for acute dermal and dermal irritation and Category I for eye irritation. Chemicals identified as toxicity Category I require a 48-hour REI. Furthermore, chemicals classified as toxicity Category I for eye irritation require the use of protective eyewear. The supplemental label does not include an REI. **Therefore, HED recommends that the Registration Division ensure that the proper REI of 48 hours is included on the registered master label and all the supplemental labels.**

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED) and the Outdoor Residential Exposure Task Force (ORETF), have been determined to require a review of their ethical conduct, have received that review, and have been determined to be ethical.

Regulatory Recommendations

The following amendments on the proposed label of Milestone® Herbicide are recommended:

1. **A 48 hour REI is required based on the acute toxicity category of the active ingredient in the formulation for eye irritation (Category I).**
2. **HED recommends that the Registration Division ensure that the proper personal protective equipment (PPE) is included on the registered master label and all the supplemental labels. Early entry PPE should be coveralls, not just long pants and shirt.**

3. **The proposed supplemental label states "*Do not aerially apply Milestone unless permitted by EPA approved supplemental labeling.*" HED recommends that the Registration Division ensure that no aerial applications are allowed in the Milestone® Herbicide supplemental label for use on corn.**

2.0 USE PATTERN SUMMARY

The proposed use pattern for the Milestone® Herbicide on field corn is summarized in Table 1.

Table 1. Summary of the Use Pattern of Force® CS Insecticide on Corn

End-use Product	Application Equipment and Timing [1]	No. of Applications/ Season	Max. Application Rate (lb ai/A)		PHI [2] (days)
			Per Single Application	Per Year	
Milestone® Herbicide 40.6% ai 21.1% ae Reg No. 62719-519	ground, handgun, foliar and band, early post emergence	1	0.027 lb ae/A (broadcast & spot)	0.027 lb ae/A (broadcast & spot)	0 days for grain; 8 days for forage or ensilage

1. Apply as a broadcast treatment to actively growing corn before it reaches 20 inches in height or V6 growth stage (whichever occurs first). Do not apply this product to sweet corn or popcorn. Do not apply through any type of chemigation. Tank mixing is permitted.
2. PHI = Proposed Pre-harvest Interval. Note that the 0 and 8 days PHIs are not consistent with the growth stage at which application is to occur. HED will be recommending that the PHIs be revised in the human health risk assessment document (D359088).

3.0 HAZARD CHARACTERIZATION

The toxicology database for aminopyralid includes toxicity studies with the acid as well as the triisopropanolamine salt. The acute toxicity data indicate that acid has low toxicity (Category IV) via oral, dermal, and inhalation routes of exposure. It is not irritating to the skin: however, it is severely irritating to the eye (Category I). Aminopyralid is not a skin sensitizer. The salt also has low toxicity via oral, dermal, and inhalation routes of exposure (Category IV). It is not irritating to the eye or skin and it is not a skin sensitizer.

The toxicology database for aminopyralid indicates that the stomach, ileum and cecum are targets for this chemical. Aminopyralid is classified as "not likely to be carcinogenic to humans." No increase in any tumors was found in carcinogenicity studies in rats and mice. Aminopyralid was negative in all mutagenicity studies, except for an *in vitro* chromosome aberration assay in Sprague Dawley rats. In this assay, the acid induced chromosome aberrations, but only at cytotoxic concentrations. The clastogenic response was induced secondary to toxicity.

For incidental oral exposure (short- and intermediate-term), as well as short- and intermediate-term inhalation exposures, the developmental toxicity study in rabbits was used for endpoint selection, based on inanition, body weight changes, and incoordinated gait seen at the LOAEL of 260 mg ae/kg/day (NOAEL = 104 mg ae/kg/day).

No systemic toxicity was observed in a 28 day dermal toxicity study in rats up to the limit dose of 1000 mg/kg/day. A dermal point of departure (POD) was not selected since no toxicity was observed in a 28 day dermal toxicity study at the limit dose. Although a developmental toxicity study was used for inhalation risk

assessment, the endpoint selected was based on maternal effects (severe inanition (exhaustion due to lack of food) and body weight loss, decreased fecal output, and mild uncoordinated gait) and there is no concern for developmental toxicity. The primary toxic effects of concern observed in the developmental toxicity study as well as the toxicity database were adequately addressed in the dermal study. Therefore, a dermal risk assessment is not required for short- and intermediate-term dermal exposure.

Table 2: Acute Toxicity Profile - Aminopyralid Technical (XDE-750)

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral-rat	46235603	LD_{50} = >5000 mg/kg/bw (both sexes)	IV
870.1200	Acute dermal-rabbit	46235605	LD_{50} = >5000 mg/kg/bw (both sexes)	IV
870.1300	Acute inhalation-rat	46235607	LC_{50} = >5.5 mg/L (both sexes)	IV
870.2400	Acute eye irritation-rabbit	46235609	Corneal opacity in 1/3 unresolved through day 35	I
870.2500	Acute dermal irritation -rabbit	46235611	non-irritant	IV
870.2600	Skin sensitization-guinea pig	46235613	Not a sensitizer	N/A

Table 3: Acute Toxicity Profile - Aminopyralid Triisopropanolamine salt (GF-871)

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral-rat	46235604	LD_{50} = >5000 mg/kg/bw (both sexes)	IV
870.1200	Acute dermal-rabbit	46235606	LD_{50} = >5000 mg/kg/bw (both sexes)	IV
870.1300	Acute inhalation-rat	46235608	LC_{50} = >5.79 mg/L (both sexes)	IV
870.2400	Acute eye irritation-rabbit	46235610	No positive signs of corneal opacity, iritis or conjunctivitis observed	IV
870.2500	Acute dermal irritation -rabbit	46235612	Slight erythema observed at 24 hours and 72 hours, resolving by study day 7	IV
870.2600	Skin sensitization-guinea pig	46235614	Not a sensitizer	N/A

Table 4: Summary of Toxicological Doses and Endpoints for Aminopyralid for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days) Intermediate-Term (1-6 months)	N/A	N/A	N/A	No systemic toxicity seen at the limit dose (1000 mg/kg/day) in the 28-day dermal toxicity study in rats. **This risk assessment is not required.**
Inhalation Short-Term (1-30 days) Intermediate-Term (1-6 months)	NOAEL=104 mg ae/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=1x	Occupational LOC for MOE = 100	Developmental rabbit study (GF-871) LOAEL=260 mg/kg/day based on severe inanition (exhaustion due to lack of food) and body weight loss, decreased fecal output, and mild incoordinated gait.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

4.0 RESIDENTIAL AND NON-OCCUPATIONAL EXPOSURE

Residential exposures associated with the use of aminopyralid to control weeds on residential and recreational sites were previously assessed (M. Collantes; D305672; May 24, 2005). The results of the residential exposure assessment indicated that risks are not of concern (MOE >100). In addition, the registrant has not proposed any new residential and/or non-occupational uses for aminopyralid at this time; therefore, a residential/non-occupational exposure assessment is not required.

5.0 OCCUPATIONAL EXPOSURE

Milestone® is an herbicide for control of broadleaf weeds in wheat. It is formulated as a liquid and contains 40.6% of the active ingredient (a.i.) aminopyralid in the form of its triisopropanolammonium salt or 21.1% aminopyralid acid equivalent (a.e.). Based on the proposed uses specified in the label, occupational exposure is expected to be short- and intermediate-term in duration. No long-term (chronic) exposure is expected.

5. 1 Handler Exposure

The aminopyralid end-use product (Milestone®) will be formulated as a soluble liquid containing 2 pounds acid equivalent per gallon and will be applied by ground and handgun equipment (spot treatment).

The maximum amount of Milestone® used in corn as a single broadcast application is 1.7 fl oz per acre (0.027 lb a.e./A). The total amount of Milestone® applied broadcast cannot exceed 1.7 fl oz per acre per year (0.027 lb a.e./A) . For spot treatments, the maximum single application rate is 1.2 mL per 1,000 ft^2 (0.027 lb a.e./A).

5.1.1 Data and Assumptions for Proposed Handler Exposure Scenarios

Workers may be exposed to aminopyralid during mixing, loading and applying activities associated with agricultural crops. Based on the proposed use patterns short- and intermediate-term dermal and inhalation exposure are expected to occur. However, since no dermal point of departure was selected, this risk assessment will only assess inhalation exposure risks.

The following exposure scenarios will be assessed for aminopyralid:

- Mixing/loading liquid sprays for groundboom
- Applying liquid sprays for groundboom
- Mixing/loading/applying liquid sprays for handgun spray

The registrant did not submit a chemical-specific exposure study for assessing the occupational exposure to handlers. Therefore, the Agency used surrogate exposure data from the Pesticide Handlers Exposure Database (PHED) version 1.1 and default values established by the HED's ExpoSAC for the calculating the extent of exposures to handlers from the proposed use on corn. For assessing the occupational exposure and risk to handlers (mixers/loaders and applicators) when using Milestone® Herbicide on corn, the following assumptions and parameters were considered:

Application Rates

Maximum Single Broadcast Application Rate
(1.7 fl oz/A) (1 gal/128 oz) (2 lbs a.e./gal) = 0.027 lb a.e./A

Maximum Single Spot Application Rate
(1.2 mL/1,000 ft^2) (1oz/29.57 mL) (1 gal/128 oz) (2 lbs a.e./gal) (43,560 ft^2/1 A) = 0.027 lb a.e./A

Unit Exposures

Mixer/Loader Unit Exposure (Baseline Liquid Formulation: Open Mixing)
Inhalation = 1.2 µg/lb ae or 0.0012 mg/lb ae

Applicator Unit Exposure (Groundboom Open Cab)
Inhalation = 0.74 µg/lb ae or 0.00074 mg/lb ae

Mixer/Loader/Applicator Unit Exposure (Handgun)
Inhalation = 1.8 µg/lb ae or 0.0018 mg/lb ae

The default unit exposures values from PHED are surrogate values for the baseline PPE for an emulsifiable concentrate formulation applied using ground equipment.

Area Treated

Based on HED's Exposure Science Advisory Committee Policy Number 9.1, the following amount treated per day was assumed:

- 200 acres/day for mixing/loading and applying liquids for groundboom for field corn;
- 25 acre/day for mixing/loading and applying liquids for handgun for field corn (spot treatment).

Personal Protective Equipment

The personal level of protection for baseline unit exposure represents long pants, long sleeve shirt, no respirator, no gloves, and shoes plus socks.

Body Weight

The average adult body weight of 70 kg was used for non-cancer assessments since the endpoints was based on effects that were not sex-specific.

Handler Equations and Calculations

$PDD = (UE \times AR \times A)/(BW)$

PDD = Potential Daily Dose (mg/kg/day)
UE = Unit Exposure (mg/lb ai)
AR = Maximum Application Rate (lb ai/A)
A = Maximum Area Treated (A/day)
BW = Body Weight (kg)

Inhalation MOE (All Durations) = Inhalation NOAEL (104 mg/kg/day)/Dose (mg/kg/day)

5.1.2 Handler Risk and Exposure

Applying these assumptions and risk parameters, the short- and intermediate term risks to mixers/loaders and applicators were calculated (Table 5). Margins of Exposure (MOEs) of 100 are required for handlers of agricultural crops in order for risks not to be of concern to HED. All handler short- and intermediate-term MOEs were greater than the target MOE of 100 and therefore risks did not exceed HED's level of concern.

Based on the proposed use pattern, long-term exposure is not anticipated for occupational handlers. There is no evidence of carcinogenicity for aminopyralid; therefore, a cancer risk assessment for handlers is not applicable.

5.2 Postapplication Exposure

HED has determined that there are potential exposures to persons entering treated sites (e.g. scouting, harvesting) after application of pesticide is complete. However, since no dermal POD was selected, a postapplication risk assessment for agricultural uses was not possible.

Aminopyralid has a relatively low vapor pressure (7.14×10^{-11} mm Hg at 20° C) and is intended to be used during early season post emergence broadleaf control. Due to outdoor air dilution and the chemical low vapor pressure, postapplication inhalation exposures are expected to be negligible and less than handler's inhalation exposures. Therefore, a quantitative postapplication inhalation exposure assessment was not performed.

Restricted Entry Interval

Milestone® Herbicide contains the triisopropanolammonium salt of aminopyralid. However, after application of the product, agricultural workers could be exposed to residues from both the aminopyralid salt and the parent acid. Therefore, the restricted entry interval (REI) for agricultural occupational exposure resulting from treated corn is based on the acute toxicity of both aminopyralid acid technical and the triisopropanolammonium salt. Aminopyralid acid is classified as Category IV for acute dermal and dermal irritation and Category I for eye irritation. Chemicals identified as toxicity Category I require a 48-hour REI. Furthermore, chemicals classified as toxicity Category I for eye irritation require the use of protective eyewear. The supplemental label does not include an REI. **Therefore, HED recommends that the Registration Division ensure that the proper REI of 48 hours is included on the registered master label and all the supplemental labels.**

6.0 CONCLUSIONS AND REGULATORY RECOMMENDATIONS

1. Mixer, loader, and applicator short- and intermediate-term exposures from the application of Milestone® Herbicide on corn do not exceed HED's LOC. All MOEs exceed the LOC of 100.
2. **The following amendment on the proposed label of Milestone® Herbicide is recommended. A 48 hour REI is required based on the acute toxicity category of the active ingredient in the formulation for eye irritation (Category I).**
3. **HED recommends that the Registration Division ensure that the proper PPE is included on the registered master label and all the supplemental labels.** The personal protective equipment (PPE) on the label is incorrect. Early entry PPE should be coveralls, not just long pants and shirt.
4. The proposed supplemental label states "*Do not aerially apply Milestone unless permitted by EPA approved supplemental labeling.*" **HED recommends that the Registration Division ensure that no aerial applications are allowed in the Milestone® Herbicide supplemental label for use on corn.**

7.0 REFERENCES

M. Collantes. Occupational and Residential Exposure Risk Assessment for Proposed Uses of Aminopyralid. 05/24/2005. D305672.

D. Dotson. Aminopyralid. Human Health Risk Assessment for the Proposed Use on Field Corn (PP#8F7455). D359088.

Table 6. Short- and Intermediate-Term Handler Exposure for Aminopyralid

Exposure Scenario (Scenario #)	Mitigation Level	Inhalation Unit Exposure (mg/lb ai)	Crop	Application Rate (lb ae/A)	Amount Treated	Inhalation Dose (mg/kg/day)	Total MOE
Mixer/Loader							
Mixing/Loading liquid sprays for groundboom (PHED data)	Baseline	0.0012	Corn	0.027	200 acres/day (broadcast)	0.0000926	1,100,000
Applicator							
Applying liquid sprays for groundboom (PHED data)	Baseline	0.00074	Corn	0.027	200 acres/day (broadcast)	0.000057	1,800,000
Mixer/Loader/Applicator							
Mixing/Loading Applying sprays for handgun (ORETF data)	Baseline	0.0018	Corn	0.027	25 acres/day (spot treatment)	0.0000174	6,000,000

Note:
Short- and Intermediate-term Inhalation Dose (mg/kg/day) = [Rate (lb ai/A) x UE (mg /lb ai) x IAF (1.0) x Amount Treated (acres or gal/day)] / BW (70 kg)
Total MOE = NOAEL (104 mg/kg/day) / Total Dose (mg/kg/day)