UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

**MEMORANDUM**

**Date:** December 19, 2007

**Subject:** **Pyroxsulam:** Occupational and Residential Exposure/Risk Assessment for New Chemical Use on Wheat
PC Code: 108702 DP Barcode: D335503

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The enclosed document is an assessment of potential occupational and residential exposures/ risks to support the proposed Section 3 registration for pyroxsulam, a new chemical use on wheat.

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## 1.0 Executive Summary

A Section 3 registration is being requested for the end-use products containing the active ingredient, pyroxsulam. The proposed end-use products are: GF-1674™ herbicide (pyroxsulam 2.87%, liquid) and GF-1274™ herbicide (pyroxsulam 7.5%, water dispersible granule) for use on wheat. The proposed products, GF-1674 ™ and GF-1274 ™ are applied at respective application rates of 0.013 lb ai/A and 0.016 lb ai/A by ground or aerial equipment. The number of exposure days per year was not provided. However, based on the frequency/interval of applications on the plants, EPA assumes that all exposures would be less than 30 days per year (short-term exposures).

Acute toxicity of pyroxsulam is low via the oral, dermal (Toxicity Category III) and inhalation (Toxicity Category IV) routes of exposure. Pyroxsulam is not an eye or dermal irritant (Category IV); however, it is a skin sensitizer.

A NOAEL (100 mg/kg/day) was used to assess short-term inhalation risks. The NOAEL is based on increased absolute and relative liver weights and increased incidence of hepatocellular clear cell foci of alteration in males as observed in a carcinogenicity study in mice. The inhalation absorption rate used was 100%. No dermal endpoints were selected; therefore, a dermal risk assessment was not required. The level of concern for the margin of exposure (MOE) is 100. Pyroxsulam is classified as "not likely to be carcinogenic to humans", and, therefore, the quantification of human cancer risk is not required.

A non-occupational and residential exposure/risk assessment was not performed since there are currently no registered or newly proposed non-occupational or residential uses.

Since no chemical-specific data for assessing human exposures during pesticide handling activities were submitted to the Agency in support of the registration of pyroxsulam , HED used surrogate data from the PHED Version 1.1 (PHED Surrogate Exposure Guide, 8/98) to assess exposures. Defaults established by the HED Science Advisory Council for Exposure were used for acres treated per day and body weight.

No MOEs for handlers exceed the level of concern at the baseline level (370,000 ~ 6,700,000). Aerial applicators in the enclosed cockpit are technically evaluated at engineering control level; however, it has been considered practically as baseline level in the HED. The HED level of concern is an MOE of <100. Post-application exposures/risks were not evaluated since no dermal endpoints were selected and inhalation exposure is expected to be negligible.

The technical material has a Toxicity Category IV for eye irritation/skin irritation, and a Category III for acute dermal Toxicity. Per the Worker Protection Standard (WPS), a 12-hr restricted entry interval (REI) is required. HED recommends that the Registration Division (RD) ensure that the appropriate REI (a minimum of 12-hours) be stated on the proposed product labels.

## 2.0 Hazard Information

Acute toxicity of pyroxsulam is low via the oral, dermal (Toxicity Category III) and inhalation (Toxicity Category IV) routes of exposure. Pyroxsulam is not an eye or dermal irritant (Toxcity Category IV); however, it is a skin sensitizer.

On October 24, 2007, the Health Effects Division (HED) Risk Assessment Review Committee 1 (RARC 1) selected an endpoint for short-term inhalation exposures to pyroxsulam The inhalation endpoint was based on increased absolute and relative liver weights and increased incidence of hepatocellular clear cell foci of alteration in males as observed in a carcinogenicity study in mice. The NOAEL was 100 mg/kg/day. The inhalation absorption rate was assumed to be 100%. No dermal endpoints were selected.

The potential for increased susceptibility of infants and children from exposure to pyroxsulam was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The FQPA safety factor was reduced to 1X. Pyroxsulam is classified as, "not likely to be carcinogenic to humans", and, therefore, the quantification of human cancer risk is not required.

The acute toxicity categories for the technical material are summarized in **Table 1**. The doses and toxicological endpoints for various exposure scenarios are summarized and presented in **Table 2**.

**Table 1. Acute Toxicity Profile - Pyroxsulam Technical**

| Guideline No. | Study Type | MRID(s) | Results | Toxicity Category |
|---|---|---|---|---|
| 870.1100 | Acute oral – rat | 46908337<br>46908538 | LD50 > 5000 mg/kg bw | III |
| 870.1200 | Acute dermal – rabbit | 46908399<br>46908540 | LD50 > 5000 mg/kg bw | III |
| 870.1300 | Acute inhalation – rat | 47236401<br>47236402 | LC 50 > 5.12 mg/L | IV |
| 870.2400 | Acute eye irritation – rabbit | 46908343<br>46908542 | Slight conjuctival redness and chemosis clearing within 72 hours | IV |
| 870.2500 | Acute dermal irritation – rabbit | 46908345<br>46908544 | Slight erythema up to one hour after patch removal; no lasting erythema or edema | IV |
| 870.2600 | Skin sensitization – guinea pig | 46908347<br>46908546 | After the challenge dose, intense erythema, swelling, scaling, and severe scaling were observed in all test groups | Positive |

**Table 2. Summary of Toxicological Dose and Endpoints for Pyroxsulam**

| Exposure/ Scenario | Point of Departure | Uncertainty Factors | Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|---|
| Dermal short - (1-30 days) and Intermediate-term (1-6 months) | N/A | N/A | N/A | **The risk assessment is not required** |
| Inhalation Short-Term (1-30 days) | NOAEL = 100 mg/kg/day<br><br>IAF=100% | $UF_A$ = 10X<br>$UF_H$ = 10X<br>FQPA SF = 1X | Residential and occupational LOC for MOE = 100 | Carcinogenicity study in mice<br><br>LOAEL = 1000 based on increased absolute and relative liver weights and increased incidence of hepatocellular clear cell foci of alteration in males |
| Cancer (oral, dermal, inhalation) | No treatment-related tumors observed in carcinogenicity studies in rats and mice. Classified as "not likely to be carcinogenic to humans." | | | |

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). MOE = margin of exposure. LOC = level of concern. N/A = not applicable. IAF=inhalation absorption factor.

## 3.0 Product Use information

Proposed use patterns for pyroxsulam are summarized in **Table 3**.

**Table 3. Proposed Use Patterns for Pyroxsulam**

| Crop | Product, Formulation | Treatment Type | Applications Per Season [1] | Maximum Application Rate[2] (lb ai/acre) or (lb ai/100 lb seed) | | PHI[3] (days) |
|---|---|---|---|---|---|---|
| | | | | Per Application | Per Season | |
| Wheat | GF-1674, liquid; and GF-1274, water-dispersable granule | Ground, or Aerial Equipment | 1 | GF-1674 ™ =0.013 lb ai/A and GF-1274 ™ =0.016 lb ai/A | GF-1674 ™ =0.013 lb ai/A and GF-1274 ™ =0.016 lb ai/A | 60 |

[1] Maximum number of applications allowed on label.
[2] Rate = Maximum application rates specified on proposed labels.
[3] PHI = Pre-harvest Interval

## 4.0 Non-Occupational/Residential Exposure

A non-occupational and residential exposure/risk assessment was not performed since there are currently no registered or newly proposed non-occupational or residential uses.

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 ground application method employed for pyroxsulam. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State

Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

## 5.0 Occupational Exposure

A Section 3 registration is being requested for the end-use products containing the active ingredient, pyroxsulam. The proposed end-use products are: GF-1674™ herbicide (pyroxsulam 2.87%, liquid) and GF-1274™ herbicide (pyroxsulam 7.5%, water dispersible granule) for use on wheat. The proposed products, GF-1674 ™and GF-1274 ™ are applied at respective application rates of 0.013 lb ai/A and 0.016 lb ai/A by ground or aerial equipment. Based on the frequency/interval of applications on the plants, EPA assumes that all exposures would be less than 30 days per year (short-term exposures).

### 5.1 Handlers

Equations/Calculations

The following equations were used to calculate handler exposure and risk:

**Inhalation Dose** (mg/kg/day) = $\frac{\text{Rate (lb ai/acre) } \mathbf{x} \text{ UE (mg/lb ai) } \mathbf{x} \text{ Acres Treated (A/day)}}{\text{BW (kg)}}$

Where:

| | | |
|---|---|---|
| Rate (Application Rate) | = | Maximum application rate on product label (lb ai/acre) |
| UE (Unit Exposure) | = | Exposure value derived from August 1998 PHED Surrogate Exposure Table (mg/lb ai handled) |
| Acres Treated | = | Maximum number of acres treated per day (acres/day) |
| BW | = | Body weight (kg) |

**MOE** = $\frac{\text{Inhalation NOAEL (100 mg/kg/day)}}{\text{Inhalation Daily Dose (mg/kg/day)}}$

Exposure Scenarios

There are 7 handler scenarios that are expected to result in the highest exposure for the proposed uses:

- Mixing/Loading Liquid for Ground-boom Applications (Scenario 1)
- Mixing/Loading Dry Flowable for Ground-boom Applications (Scenario 2)
- Mixing/Loading Liquid for Aerial Applications (Scenario 3)
- Mixing/Loading Dry Flowable for Aerial Applications (Scenario 4)

- Applying Sprays with Ground-boom Equipment (Scenario 5)
- Applying Sprays with Aerial Equipment (Scenario 6)
- Flagging during Aerial Application (Scenario 7)

Application Rate

The maximum application rates listed on the proposed labels provided by the Registration Division were used for all exposure assessments. The maximum rates were 0.013 lb ai/A for GF-1674 and 0.016 lb ai/A for GF-1274.

Area or the Amount Treated

Based on HED's Exposure Science Advisory Council Policy Number 9.1, 200 acres/day for applications using ground-boom equipment, and 1200 acres/day for applications using fix-wing aerial equipment, were assumed.

Body Weight

The average body weight for general population (70 kg) was used for all assessments.

Exposure Frequency

No data on the number of exposure days per year was provided For this risk assessment, it was assumed that handlers would be exposed for less than 30 days per year (short-term exposures).

Unit Exposures

The unit exposures are based on the PHED Version 1.1 as presented in the August 1998 PHED Surrogate Exposure Guide. PHED was designed by a task force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a software system consisting of two parts–a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates).

Users select criteria to subset the PHED database to reflect the exposure scenario being evaluated. The subsetting algorithms in PHED are based on the central assumption that the magnitude of handler exposures to pesticides is primarily a function of activity (e.g., mixing/loading, applying), formulation type (e.g., wettable powders, granulars), application method (e.g., aerial, groundboom), and clothing scenarios (e.g., gloves, double layer clothing).

Once the data for a given exposure scenario have been selected, the data are normalized (i.e., divided by) by the amount of pesticide handled resulting in standard unit exposures (milligrams of exposure per pound of active ingredient handled). Following normalization, the data are statistically summarized. The distribution of exposure values for each body part (e.g., chest, upper arm) is categorized as normal, lognormal, or "other" (i.e., neither normal nor lognormal). A central tendency value is then selected from the distribution of the exposure values for each

body part. These values are the arithmetic mean for normal distributions, the geometric mean for lognormal distributions, and the median for all "other" distributions. Once selected, the central tendency values for each body part are composited into a "best fit" exposure" value representing the entire body.

There are three basic risk mitigation approaches considered appropriate for controlling occupational exposures. These include administrative controls, the use of personal protective equipment or PPE, and the use of engineering controls. Occupational handler exposure assessments were completed by HED using baseline, PPE, and engineering controls. [Note: Administrative controls available generally involve altering application rates for handler exposure scenarios. These are typically not utilized for completing handler exposure assessments.] The baseline clothing level scenario for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, no chemical resistant gloves, and no respirator. The first level of mitigation generally applied is PPE. As reflected in the calculations included herein, PPE may involve the use of an additional layer of clothing, chemical-resistant gloves, and a respirator. The next level of mitigation considered in the risk assessment process is the use of appropriate engineering controls which, by design, attempt to eliminate the possibility of human exposure. Examples of commonly used engineering controls include enclosed tractor cabs and cockpits, closed mixing/loading/transfer systems, and water-soluble packets.

Handlers' Exposure and Risk

No MOEs for handlers exceed the level of concern at the baseline level (370,000 ~ 6,700,000). Aerial applicators in the enclosed cockpit are technically evaluated at engineering control level; however, it has been considered practically as baseline level in the HED. The HED level of concern is an MOE of <100. Summaries of the exposures/risks for handlers are presented in **Table 4**.

The handler exposure estimates in this assessment are based on a central tendency estimate of unit exposure and an upper-percentile assumption for the application rate, and they are assumed to be representative of high-end exposures. The uncertainties associated with this assessment stem from the use of surrogate exposure data (e.g., differences in use scenario and data confidence), and assumptions regarding that amount of chemical handled. The estimated exposures are believed to be reasonable high-end estimates based on observations from field studies and professional judgment.

### 5.2 Post-application

The post-application exposures/risks were not evaluated because no dermal endpoints were selected and inhalation exposure is expected to be negligible.

The technical material has a Toxicity Category IV for eye irritation/skin irritation, and a Category III for acute dermal Toxicity. Per the Worker Protection Standard (WPS), a 12-hr restricted entry interval (REI) is required. HED recommends that the Registration Division (RD) ensure that the appropriate REI (a minimum of 12-hours) be stated on the proposed product labels.

| Table 4: Pyroxsulam Handler Exposure and Risk | | | | | | |
|---|---|---|---|---|---|---|
| **Exposure Scenario (Scenario #)** | **Mitigation Level[a]** | **Inhalation Unit Exposure[b] (Ug/lb ai)** | **Application Rate (lb ai/A)** | **Amount Treated[c] (A/day)** | **Daily Inhalation Dose[d] (mg/kg/day)** | **Inhalation MOE[e]** |
| Mixer/Loader | | | | | | |
| Liquids for Ground application (1) | Baseline | 1.2 | 0.013 | 200 | 0.000045 | 2,200,000 |
| Dry Flowables for Ground application (2) | Baseline | 0.77 | 0.016 | 200 | 0.000035 | 2,900,000 |
| Liquids for Aerial application (3) | Baseline | 1.2 | 0.013 | 1200 | 0.00027 | 370,000 |
| Dry Flowables for Aerial application (4) | Baseline | 0.77 | 0.016 | 1200 | 0.00021 | 480,000 |
| Applicator | | | | | | |
| Sprays with Groundboom (5) | Baseline | 0.74 | 0.013<br>0.016 | 200<br>200 | 0.000027<br>0.000034 | 3,700,000<br>2,900,000 |
| Sprays with Fix-Wing aircraft (6) | Eng. Cont | 0.068 | 0.013<br>0.016 | 1200<br>1200 | 0.000015<br>0.0000186 | 6,70,000<br>5,400,000 |
| Flagger | | | | | | |
| Flagging during Aerial applications (7) | Baseline | 0.35 | 0.013<br>0.016 | 350<br>350 | 0.000023<br>0.000028 | 4,300,000<br>3,600,000 |

a Baseline consists of long-sleeve shirt, long pants, shoes, and socks and no respirator. Eng. Cont. consists of enclosed cockpit.
b Baseline Inhalation Unit Exposure represents no respiratory protection, open mixing/loading, and open cab tractors, as appropriate. Eng. Cont. Inhalation Unit Exposure represents enclosed cockpit.
c Daily acres treated values are from EPA estimates of acreage that could be treated in a single day for each exposure scenario of concern. Exposure SAC Policy 9, 7/5/2000.
d Daily inhalation dose (mg/kg/d) = (unit exposure (µg/lb ai) * (1mg/1000 µg) conversion * appl. rate (lb ai/acre) * daily acres treated / body weight (70kg).
e Inhalation MOE = NOAEL (100 mg/kg/d) / daily inhalation dose. UF = 100.

CC: RAB2 RF, D. Dotson, S. Wang