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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: June 20, 2005

Subject: Occupational and Residential Exposure/Risk Assessment for the Uses of Amicarbazone on Field Corn (including Corn Grown for Silage).
PC Code: 114004 DP Barcode: D313746

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The enclosed document is an assessment of potential occupational and residential exposures/ risk resulting from the proposed Section 3 registration for a new chemical, amicarbazone, to be used on field corn (including corn grown for silage).

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1.0 Executive Summary

A Section 3 registration is being requested for an end-use product containing the new chemical, amicarbazone, as active ingredient. The proposed uses include the use of Battalion® DF herbicide (amicarbazone 70%, dry flowable) on field corn (including corn grown for silage, 0.45 lb ai/A) by ground equipment.

No data regarding the number of exposure days per year were provided. However, due to the frequency of applications, EPA assumes that handlers involved in applications would be exposed for less than 6 months per year. Thus, handler exposures are expected to be short-/intermediate-term in duration. Long-term exposures (> 6 months) are not expected.

Since no chemical-specific data for assessing human exposures during pesticide handling activities were submitted to the Agency in support of the registration of amicarbazone, HED used surrogate data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. Standard values established by the Health Effects Division (HED) Science Advisory Council for Exposure were used for acres treated per day and body weight.

Toxicological endpoints from the HED toxicological review (see forthcoming risk assessment, D288216) were used to assess risks. No dermal endpoint was selected based on the lack of systemic activity in a dermal rat study. The inhalation NOAEL (for both short- & intermediate-terms) is based on increased thyroid vacuolization and decreased food consumption and glucose in females; increased platelets, phosphate, bile acids, absolute and relative liver weights, and lymphoid hyperplasia of the gall bladder in males; and decreased albumin and increased triglycerides, N-demethylase, and O-demethylase in both sexes from a 90-Day Oral Toxicity in Dogs. Daily inhalation doses were compared to the NOAEL of 6.28 mg/kg/day to determine the level of risks. The level of concern(LOC) is a margin of exposure (MOE) of 100. Amicarbazone was classified as "not likely" to be a carcinogen and no Q_1^* was assigned for quantitative cancer risk assessment.

Occupational handler assessments were based primarily on surrogate unit exposures from the PHED, as presented in the PHED Surrogate Exposure Guide (8/98). All MOEs are above the level of concern at the baseline level (6,300~6,600).

Post-application exposure assessments were not performed because no dermal endpoints were selected and inhalation exposures are expected to be negligible. The 12 hour restricted entry interval (REI) appearing on the label is appropriate for this chemical.

Currently, amicarbazone is not registered for residential uses, therefore, the risk assessments for non-occupational/residential handler and post-application exposures are not required.

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2.0 Hazard Information

The Health Effects Division (HED) toxicologist reviewed the toxicology data for amicarbazone with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for occupational & residential exposure/risk assessments. The potential for increased susceptibility of infants and children from exposures to amicarbazone was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The acute toxicity categories for the technical material are summarized in **Table 1**. The toxicological conclusions, the doses and toxicological endpoints for various exposure scenarios are summarized and presented in **Table 2** (from the toxicological review by K. Kosick in forthcoming HED risk assessment, D288216).

The HED toxicologist also determined that amicarbazone is classified as "not likely" to be a carcinogen and no Q_1^* was assigned for quantitative cancer risk assessment.

Table 1. Acute Toxicity Profile for Amicarbazone (Technical Grade).

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral - Wistar rats	45121504	Males LD_{50} > 2050 mg/kg Females LD_{50} = 1015 mg/kg	III
870.1200	Acute dermal - Wistar rats	45121503	LD_{50} > 5000 mg/kg	IV
870.1300	Acute inhalation - Wistar rats	45121506	LC_{50} > 2.030 mg/L	IV
870.2400	Acute eye irritation - New Zealand white rabbit	45121510	Eye irritation was present (including corneal opacity) at 24 hours, but had cleared by day 7.	III
870.2500	Acute dermal irritation - New Zealand white rabbit	45121509	Primary irritation indexes were 0	IV
870.2600	Skin sensitization - Hartley guinea pig	45121628 45121505	All scores during induction and challenge periods were 0.	Not a dermal sensitizer

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Table 2. Summary of Toxicological Doses and Endpoints for Amicarbazone.			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (females 13-49)	NOAEL = 10 mg/kg/day UF = 100X **Acute RfD = 0.10 mg/kg/day**	Special FQPA SF = 1X **aPAD = 0.10 mg/kg/day**	Acute Neurotoxicity Screening Battery LOAEL = 20 mg/kg/day, based on eyelid ptosis, decreased approach response, red nasal staining in ♂
Acute Dietary (general population)	NOAEL = 10 mg/kg/day UF = 100X **Acute RfD = 0.10 mg/kg/day**	Special FQPA SF = 1X **aPAD = 0.10 mg/kg/day**	Acute Neurotoxicity Screening Battery LOAEL = 20 mg/kg/day, based on eyelid ptosis, decreased approach response, red nasal staining in ♂
Chronic Dietary (all populations)	NOAEL = 2.3 mg/kd/day UF = 100X Chronic RfD = .023mg/kg/day	Special FQPA SF = 1X **cPAD = 0.023 mg/kg/day**	Chronic Rat and Chronic Dog LOAEL = 25.3 and 8.7, respectively, based on RAT - decreased BW and BWG DOG - liver effects, including increased absolute and relative liver weights, and O-demethylase in ♂; increased globulin and cytochrome p450 in ♀; and increased triglycerides and cholesterol in both sexes
Inhalation Short-Term (1 - 30 days)	NOAEL = 6.28 mg/kg/day	LOC for MOE = 100	90-Day Oral Toxicity in Dogs LOAEL = 24.99 mg/kg/day, based on increased thyroid vacuolization and decreased food consumption and glucose in females; increased platelets, phosphate, bile acids, absolute and relative liver weights, and lymphoid hyperplasia of the gall bladder in males; and decreased albumin and increased triglycerides, N-demethylase, and O-demethylase in both sexes
Inhalation Intermediate-Term (1 - 6 months)	NOAEL = 6.28 mg/kg/day	LOC for MOE = 100	90-Day Oral Toxicity in Dogs LOAEL = 24.99 mg/kg/day, based on increased thyroid vacuolization and decreased food consumption and glucose in females; increased platelets, phosphate, bile acids, absolute and relative liver weights, and lymphoid hyperplasia of the gall bladder in males; and decreased albumin and increased triglycerides, N-demethylase, and O-demethylase in both sexes
Cancer (oral, dermal, inhalation)	**Classification:**There was no treatment related increase in tumor incidence when compared to control. Dosing was considered adequate. This chemical is not likely to be a carcinogen.		

3.0 Product Use information

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

Table 3. Proposed Use Patterns

Crop	Product, Formulation	Treatment Type	Applications Per Season [1]	Maximum Application Rate[2] (lb ai/acre)		PHI[3] (days)
				Per Application	Per Season	
Field Corn and Corn grown for silage	Battalion DF[4], dry flowable	ground	1~2	0.45	0.45	Not given

[1] Maximum number of applications allowed on label.

[2] Rate = Maximum application rates specified on proposed labels.

[3] PHI = Pre-harvest Interval

[4] Active Ingredient (ai) = Amicarbazone, 70%

4.0 Non-Occupational/Residential Exposure

Currently, amicarbazone is not registered for residential uses, therefore, the risk assessments for non-occupation/residential handler and post-application exposures are not required.

5.0 Occupational Exposure

5.1 Handlers

Equations/Calculations

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

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

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)

Inhalation MOE = $\frac{\text{NOAEL (6.28 mg/kg/day)}}{\text{Inhalation Daily Dose (mg/kg/day)}}$

Exposure Scenarios

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

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- Mixing/Loading Dry Flowable for Ground Applications (Scenario 1)
- Applying Sprays with Groundboom Equipment (Scenario 2)

Application Rate

The maximum application rate listed on the proposed labels provided by the Registration Division was used for all exposure assessments. The maximum rate is 0.45 lb ai/A.

Area Treated

Based on HED's Exposure Science Advisory Council Policy Number 9.1, 200 acres per day treated was assumed for application on corn using groundboom equipment.

Body Weight

The average body weight for general population (70 kg) was used for all exposure scenarios covered in this risk assessment.

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 6 months per year (i.e. short-/intermediate-term in duration).

Unit Exposures

The unit exposures used in this assessments 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).

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:

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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

All MOEs are above the levels of concern at the baseline level (6,300~ 6,600). Assumptions and calculations of the 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 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 judgement.

5.2 Post-application

Post-application exposure assessments were not performed because no dermal endpoints were selected and inhalation exposures are expected to be negligible.

The technical material has a Category IV for acute dermal toxicity & acute dermal irritation, and a Category III for acute eye irritation. Per the Worker Protection Standard (WPS), a 12-hr restricted entry interval (REI) is required. Therefore, the 12 hour REI appearing on the label is appropriate for this chemical.

Table 4. Non-Cancer Risk for Handlers.

Exposure Scenario (Scenario #)	Mitigation Level[a]	Dermal Unit Exposure[b] (mg/lb ai)	Inhalation Unit Exposure[c] (Ug/lb ai)	Application Rate (lb ai/A)	Amount Treated[d] (A/day)	Daily Inhalation Dose[e] (mg/kg/day)	Short and Intermediate-Term MOE[f]
Mixer/Loader							
Mixing/Loading Dry Flowable for Ground application (1)	Baseline	0.066	0.77	0.45	200	0.00099	6,300
Applicator							
Applying Sprays with Groundboom (2)	Baseline	0.014	0.74	0.45	200	0.00095	6,600

a Baseline consists of long-sleeve shirt, long pants, shoes, and socks and no respirator.

b Baseline Dermal Unit Exposure represents long pants, long sleeved shirt, no gloves, open mixing/loading, and open cab tractors, as appropriate. Eng. Cont. Dermal Unit Exposure represents enclosed cockpit.

c 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.

d Daily acres treated values are from EPA estimates of acreage that could be treated in a single day for each exposure scenario of concern.

e 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.

f Inhalation MOE = NOAEL (6.28 mg/kg/d) / daily inhalation dose (mg/kg/d). UF = 100.

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