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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 9 MAY 2005

SUBJECT: **TOPRAMEZONE (BAS 670 H)** - Exposure/Risk Assessment for the Proposed Use of Topramezone On Corn (Field, Pop, Seed and Sweet)

PC Code: 123009 DP Code: 317065

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INTRODUCTION

Under Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act, as amended, the BASF Corporation has requested registration of the herbicide topramezone (formerly identified as BAS 670 H). Topramezone is chemically known as [3-(4,5-dihydro-isoxazol)-4-methansulfonyl-2-methyl-phenyl]-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)methanone. The proposed uses are for field corn (including conventional and herbicide resistant/tolerant varieties), pop corn, sweet corn and seed corn. This memorandum serves as HED estimates of exposure and risk to occupational pesticide handlers and to agricultural workers from post-application exposures.

USE PATTERN SUMMARY

The proposed product is identified as BAS 670 336 SC which contains 2.8 lb of active ingredient per gallon and is formulated as a soluble concentrate. Topramezone is a postemergence herbicide intended for control of broadleaf weed species and some annual grasses that infest corn fields. Applications should be made prior to the 6" inch growth stage of most weed species.

Giant ragweed, volunteer and wild sunflower may be 8" tall at treatment time. Topramezone is to be applied as a foliar spray using either ground equipment or aircraft. If applied by ground equipment it should be applied in 10 or more gallons of water per acre. If applied aerially, it should be applied in 2 or more gallons of water per acre. Topramezone is to be applied broadcast at a rate of 0.5 - 1.0 fl. oz/A (0.011 - 0.022 lb a.i./A). Split applications may be made, however a maximum of 0.022 lb a.i./A/season may be applied. If applications are split, there is a 7 day retreatment interval. There is a 45 day preharvest interval. For use of corn as an animal feed, there is a 45 day pregrazing or prefeeding interval.

The proposed product label involved in this assessment directs applicators and other handlers to wear long-sleeved shirt, long pants, shoes plus socks and chemical resistant gloves made of any waterproof material such as nitrile, butyl, neoprene and/or barrier laminate.

See Table 1.0 for a summary of the proposed use pattern.

Table 1.0 Summary of Proposed New Uses of BAS670 on Corn

Formulation	BAS 670; 2.8 lb a.i./gallon soluble concentrate.
Method of Application	ground boom and aerial
Use Site	Corn, field (including conventional and herbicide resistant/tolerant varieties), popcorn, sweet corn, seed corn.
Pest	broad leaf weeds species and certain species of grass weeds
Rate of Application lb. a.i./A	0.011 - 0.022 lb a.i./A
Maximum Rate/Yr	0.022 lb a.i./A
Frequency of Applic.	2 applications per season if applied at 0.011 lb a.i./A
Application Interval	7 days
PreHarvest Interval	45 days
Restricted Entry Interval	12 hours
Manufacturer	BASF Corporation

OCCUPATIONAL PESTICIDE HANDLERS

Based upon the proposed use pattern, HED believes the most highly exposed occupational pesticide handlers (i.e., mixers, loaders, applicators) are:

1) mixer/loader using open pour loading of liquids in support of aerial operations
2) applicator using open-cab ground-boom equipment
3) pilot (aerial applicator).

Applicators using open-cab ground equipment typically experience greater exposures than aerial applicators however the estimated exposure for an aerial applicator is presented. HED expects most occupational handler exposures will be short-term (1 - 30 days) in duration. The Science Advisory Council for Exposure (ExpoSac) maintains that it is possible for a commercial applicator to be exposed to intermediate-term exposures (1 - 6 months) by virtue of treating farm after farm for the same pest complex. RAB1 believes that the probability for intermediate-term exposures is very low. However, estimates of intermediate-term risk are also presented.

It is expected that some private (i.e., grower) applicators may perform all tasks, that is, mix, load and apply the material. However, HED ExpoSac draft Standard Operating Procedure (SOP) (29 March 2000) directs that although the same individual may perform all tasks, in some cases they shall be assessed separately.

The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of personal protective equipment (PPE) for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the Pesticide Handler's Exposure Database (PHED) (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline", that is, for workers wearing a single layer of work clothing consisting of a long sleeved shirt, long pants, shoes plus socks and no protective gloves as well as with a single layer of work clothing **and the use of protective gloves** or other Personal Protective Equipment (PPE) as might be necessary.

The topramezone risk assessment team in conjunction with the HED Risk Assessment Review Committee 1 (RARC1) reviewed the status of the toxicological database regarding topramezone and identified toxicological endpoints for use in risk assessment. Relative to the exposure assessment herein, short-term (1-30 days), intermediate-term (1-6 months) and long-term (> 6 months) dermal toxicological endpoints were identified. The endpoints were identified from a

carcinogenicity/chronic toxicity study in rats where the effects seen were increased incidences of corneal opacity, decreased body weight and body-weight gains in males and histopathological evaluations in the thyroid, pancreas, and eyes of both sexes. The No Observable Adverse Effects Level (NOAEL) is 0.4 mg a.i./kg bw/day.

A dermal absorption factor of 13 % was identified by the Risk Assessment Review Committee (RARC) (during a meeting on 28 April 2005) for use in exposure assessment. A Margin of Exposure (MOE) of 100 is adequate to protect occupational pesticide handlers, agricultural workers and persons from "residential" uses and exposures.

Short-, intermediate-, and long-term duration exposures inhalation endpoints were also identified. The inhalation endpoints are identified from the same rat carcinogenicity/chronic toxicity study. The toxic effects seen are the same and the NOAELs are also the same was noted for the dermal toxicological endpoints. Inhalation Margins of Exposure are also the same. HED assumes 100 % absorption via the inhalation route of exposure.

The Cancer Assessment Review Committee (CARC) met on 27 April 2005 to consider the mode of action for topramezone and determine its cancer classification. CARC concluded that the data are sufficient to determine a mode of action for thyroid tumors seen in rats. Based on the acceptance of a mode of action, and in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), CARC classified topramezone as "not likely to be carcinogenic to humans at doses that do not alter thyroid hormone homeostatis." In the non-guideline thyroid hormone dietary study in rats, the LOAEL was based on increases in thyroid hormone levels in rats is 60 ppm (3.6 mg a.i./kg bw/day) and the NOAEL is 6 ppm (0.4 mg a.i./kg bw/day). The CARC determined that quantification of human cancer risk is not required since the NOAEL (0.4 mg/kg/day) for non-cancer risk assessment is not expected to alter thyroid hormone homeostasis nor result in thyroid tumor formation.

See Table 2.0 for a summary of estimated exposures and risks to occupational pesticide handlers.

Table 2.0 Estimated Handler Exposure and Risk from the Use of Topramezone				
Unit Exposure[1] mg a.i./lb handled	**Applic. Rate[2]** lb a.i./A	**Units Treated[3]** Per Day	**Average Daily Dose[4] mg a.i./kg bw/day**	**MOE[5]**
Mixer/Loader -Liquid - Open Pour - Supporting Aerial Operation				
Dermal: No Glove 2.9 HC With Glove 0.023 HC Inhal 0.0012 HC	0.022	1,200 A	Dermal: No Glove 0.142 With Glove 0.00113 Inhal 0.000453	No Glove 3 With Glove 253
Applicator - Ground-boom - Open Cab				
Dermal: No Glove 0.014 HC With Glove 0.014 MC Inhal 0.00074 HC	0.022	200 A	Dermal: No Glove 0.000114 With Glove 0.000114 Inhal 0.0000465	No Glove 2,500 With Glove 2,500
Applicator - Aerial				
Dermal: No Glove 0.0050 MC Inhal 0.000068 MC	0.022	1,200	Dermal: No Glove 0.000245 Inhal 0.0000256	No Glove 1,480

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. Dermal = Single Layer Work Clothing **No Gloves**; Single Layer Work Clothing **With Gloves**; Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Applic. Rate. = Taken from proposed BAS 670 336SC Herbicide label (active ingredient topramezone).
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; SOP No. 9.1. Science Advisory Council for Exposure; Revised 5 July 2000;
4. Average Daily Dose = Unit Exposure * Applic. Rate * Units Treated * absorption factor (13.0 % dermal; 100 % inhalation) ÷ 70 kg Body Weight
5. MOE (Margin of Exposure) = No Observable Adverse Effect Level (NOAEL) ÷ ADD. In this case, since the dermal and inhalation toxicological endpoints are the same and are identified from the same study, the dermal and inhalation doses are summed then divided into the NOAEL to derive a Margin of Exposure. Dermal and inhalation NOAEL = 0.4 mg a.i./kg bw/day.

For occupational pesticide handlers, a MOE of 100 is adequate to protect them from exposures to topramezone under these application conditions. Provided that mixer/loaders use protective gloves as specified on the proposed label, all MOEs are > 100 and therefore the proposed use pattern does not exceed HED's level of concern.

POST-APPLICATION EXPOSURE TO AGRICULTURAL WORKERS

There is a potential for agricultural workers to have post-application exposure to pesticides during the course of typical agricultural activities. HED in conjunction with the Agricultural Re-entry Task Force (ARTF) has identified a number of post-application agricultural activities that may

occur. HED has also identified Transfer Coefficients (TC) (cm^2/hr) relative to the various activities which expresses the amount of foliar contact over time, during each of the activities. For the proposed use sites, the post-application activities with the highest TCs are summarized in Table 3.0. In this case, the highest TC is associated with detasseling activities. However since topramezone is applied early postemergence (when weeds are approximately 6" tall) and since there is 45 day preharvest interval, HED uses the TC of 400 cm^2/hr for scouting or irrigation activities.

Table 3.0 Summary of Highest Transfer Coefficients (cm^2/hr) For Post-application Activities in Corn

Post-application Activity	Transfer Coefficient cm^2/hr
Detasseling	17,000
Scouting or irrigation activities during high crop height and full corn foliage development	1,000
Scouting or irrigation activities during low crop height and minimum corn foliage development.	400

The transfer coefficients used in this assessment are from an interim transfer coefficient Standard Operating Procedure (SOP) developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-Entry Task Force (ARTF) database (SOP # 3.1). It is the intention of HED's Science Advisory Council for Exposure that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

Lacking compound specific dislodgeable foliar residue (DFR) data, HED assumes 20 % of the application rate is available as dislodgeable foliar residue on day zero after application. This is adapted from the Science Advisory Council For Exposure SOP No. 003 (7 May 1998 - Revised 7 August 2000).

The following convention may be used to estimate post-application exposure.

Average Daily Dose (ADD) (mg a.i./kg bw/day) = DFR $\mu g/cm^2$ * TC cm^2/hr * hr/day * 0.001 mg/µg * 1/70 kg bw

and where:

Surrogate Dislodgeable Foliar Residue (DFR) = application rate * 20% available as dislodgeable

residue * (1-D)[i] * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2.

TC =400 cm^2/hr

0.022 lb a.i./A * 0.20 * $(1-0)^0$ * 4.54 x 10^8 µg/lb * 2.47 x10^{-8} A/cm^2 = 0.0493µg/cm^2, therefore,

0.0493 µg/cm^2 * 400 cm^2/hr * 8 hr/day * 0.001 mg/µg * 0.13 (13 % dermal absorption) * 1/70 kg bw = 0. 00029 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 0.4 mg/kg bw/day ÷ 0.00029 mg/kg bw/day = **1,400.**

A Margin of Exposure of 100 is adequate to protect agricultural workers from post-application exposures to topramezone. The estimated MOE is > 100 and therefore the proposed use pattern does not exceed HED's level of concern.

RESTRICTED ENTRY INTERVAL (REI)

Topramezone is classified in Acute Toxicity Category III for acute dermal toxicity and for primary eye irritation. It is classified in Toxicity Category IV for acute inhalation and dermal irritation. It is not a dermal sensitizer. The interim worker protection standard (WPS) restricted entry interval (as listed on the proposed label) of 12 hours is adequate to protect occupational handlers and agricultural workers from post-application exposures to topramezone.

RESIDENTIAL

Topramezone is a new chemistry. There are no registered or proposed residential uses of the compound.

ATTACHMENT

Acute Toxicity Profile on Topramezone (BAS 670H)

OPPTS Guideline	Study Type	Results	Toxicity Category
870.1100	Acute oral toxicity / rat	LD_{50} => 2000 mg/kg (males and females)	III
870.1200	Acute dermal toxicity / rat	LD_{50} => 2000 mg/kg (males and females)	III
870.1300	Acute inhalation toxicity / rat	LC_{50} => 5.05 mg/L (males and females)	IV
870.2400	Primary eye irritation / rabbit	Slight irritant	III
870.2500	Primary dermal irritation / rabbit	Slight irritant	IV
870.2600	Dermal sensitization / guinea pig	Non-Sensitizer	–

Summary of Toxicology Endpoint Selection for Topramezone

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population including infants and children)	An endpoint of concern for the general population attributable to a single dose was not identified in the hazard database.		
Acute Dietary (females 13-50 years of age)	NOAEL= 0.5 mg/kg/day UF=100 **Acute RfD** = 0.005 mg/kg/day	FQPA SF= 1X **aPAD**= Acute RfD FQPA SF = 0.005 mg/kg/day	**Developmental Toxicity Study in Rabbits** LOAEL = 5 mg/kg/day based on alterations in skeletal ossification sites and increased number of pairs of ribs.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (All populations)	NOAEL= 0.4 mg/kg/day UF=100 **Chronic RfD**= 0.004 mg/kg/day	FQPA SF = 1X **cPAD** = Chronic RfD / FQPA SF = 0.004 mg/kg/day	**Carcinogenicity Study in Rats** LOAEL = 3.6 mg/kg/day based on increased incidences of corneal opacity, decreased body weight and body-weight gains in males and histopathological evaluations in the thyroid, pancreas, and eyes of both sexes.
Short-Term Incidental Oral (1 - 30 Days)	NOAEL= 0.4 mg/kg/day	**Residential** LOC for MOE = 100	**Carcinogenicity Study in Rats** See above section.
Intermediate-Term Incidental Oral (1 - 6 Months)	NOAEL= 0.4 mg/kg/day	**Residential** LOC for MOE = 100	**Carcinogenicity Study in Rats** See above section.
Short-Term Dermal (1 - 30 days)	Oral NOAEL= 0.4 mg/kg/day (dermal-absorption rate = 13%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Carcinogenicity Study in Rats** See above section.
Intermediate-Term Dermal (1 - 6 Months)	Oral NOAEL= 0.4 mg/kg/day (dermal absorption rate = 13%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Carcinogenicity Study in Rats** See above section.
Long-Term Dermal (> 6 Months)	Oral NOAEL= 0.4 mg/kg/day (dermal-absorption rate = 13%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Carcinogenicity Study in Rats** See above section.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Inhalation (1 - 30 days)	Oral NOAEL= 0.4 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Carcinogenicity Study in Rats** See above section.
Intermediate-Term Inhalation (1 - 6 Months)	Oral NOAEL= 0.4 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Carcinogenicity Study in Rats** See above section.
Long-Term Inhalation (>6 Months)	Oral NOAEL= 0.4 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Carcinogenicity Study in Rats** See above section.
Cancer (Oral, dermal, inhalation)	In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified BAS 670H as **"Not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis"**. The CARC determined that quantification of human cancer risk is not required since the NOAEL (0.4 mg/kg/day) for non-cancer risk assessment is not expected to alter thyroid hormone homeostasis nor result in thyroid tumor formation.		

NOTE:* The Special FQPA Safety Factor recommended by the HIARC **assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

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R118336

Chemical:	**Methanone, [3-(4,5-dihydro-3-isoxazolyl)-2-methyl-4-(methylsulfonyl)phenyl](5-hydroxy-1-methyl-1H-pyrazol-4-yl)-**
	PC Code: 123009
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