



Pesticide Fact Sheet

Name of Chemical: Topramezone
Reason for Issuance: Conditional Registration
Date Issued: August 10, 2005

DESCRIPTION OF CHEMICAL

Generic Name: [3-(4,5-dihydro-isoxazol-3-yl)-4-methylsulfonyl-2-methylphenyl](5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone

Common Name: Topramezone

Trade Names: Topramezone Technical
Topramezone SC

EPA Chemical Code: 123009

Chemical Abstracts
Service (CAS)
Number: 210631-68-8

Year of Initial
Registration: 2005

Pesticide Type: Herbicide

U.S.
Producers: Amvac
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Foreign
Producers: BASF Corporation
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USE PATTERNS AND FORMULATIONS

Topramezone will be applied post-emergence to field corn, sweet corn and popcorn through ground or aerial application equipment. Topramezone has herbicidal activity against broadleaf weeds and grasses. It's efficacy is the result of the inhibition of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD) enzyme in target plants. Following treatment in sensitive plants carotenoid pigment formation, membrane structure and photosynthesis is disrupted.

SCIENCE FINDINGS

Hazard and risk assessments were conducted in relation to this registration application and tolerance petition for topramezone on corn suggest that its use, consistent with the proposed labeling measures, will be protective of the public health and the environment.

The risk assessment is a joint review with the Pesticide Management Regulatory Agency (PMRA) of Health Canada and the Health Effects Division (HED) and the Environmental Fate and Effects Division (EFED) in EPA.

Health Effects Division's Review - Hazard Identification

In estimating risks from this use, HED used conservative Tier 1 exposure assumptions. Tolerance level residues and 100 percent crop treated exposure assumptions were used in the acute and chronic risk analysis. There are no other registrations for this chemical. Aggregate exposures to the general public are based on food plus water calculations derived from this use.

Topramezone has a low acute toxicity via the oral, dermal, or inhalation route. It is a slight eye and dermal irritant, and it is not a skin sensitizer. Following oral administration, topramezone is rapidly absorbed and excreted *via* urine and feces. Topramezone is an inhibitor of 4-HPPD; this results in elevated serum tyrosine levels. However, no data could determine at what level increases of tyrosine levels would result in detrimental (adverse) effects. As a consequence of the elevated tyrosine levels, topramezone has been shown to cause adverse effects in the eye, liver, kidney, pancreas, and thyroid. Histopathological evaluations showed dose-dependent increases of adverse effects in the thyroid (follicular cell hyperplasia) in rats and dogs, pancreas (diffuse degeneration) in rats, liver (hepatocellular hypertrophy and focal necrosis) in rats and mice, and eyes (chronic keratitis) in rats. The reproductive toxicity study in rats did not demonstrate adverse reproductive effects; however, developmental toxicity studies in rats and rabbits showed increased incidences of skeletal variation and alterations in skeletal ossification sites. Animal studies show that skeletal variations are associated with 4-HPPD inhibitor herbicides (mesotrione and isoxaflutole). Mutagenicity studies conducted on technical topramezone and its major metabolites did not demonstrate any mutagenic potential. Increased incidences of thyroid follicular cell adenomas and adenoma and/or adenocarcinomas combined were observed in the carcinogenicity study in rats of both sexes. In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the HED classified topramezone as "Not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis". HED 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.

FQPA Decision

The toxicology database is complete for FQPA purposes and there are no residual uncertainties for pre-/post-natal toxicity. Based on the quality of the exposure data, EPA determined that the 10X SF to protect infants and children should be removed. The FQPA factor is removed based on the following:

- ▶ The dietary food exposure assessment utilizes proposed tolerance level or higher residues and 100% CT information for all commodities. By using these screening-level assessments, acute and chronic exposures/risks will not be underestimated.
- ▶ The dietary drinking water assessment (Tier 2 estimates) utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations.
- ▶ There are no residential uses of topramezone.

Consideration of Risks to Pesticide Applicators and Handlers

Risks to agricultural workers were also considered. HED determined that short- and intermediate-term exposures may occur. Since topramezone may be applied only twice per year, long-term exposures are not expected from the proposed uses. No more than 30 days exposure are expected for most handlers. The worst case occupational risk for short-term exposure from mixer/loader open pour supporting aerial application is a 3 Margin of Exposure (MOE) without gloves and 253 MOE with gloves. It might be possible for commercial applicators to experience intermediate-term exposures (1-6 months). The worst case occupational risk for intermediate-term operations with aerial application is 1,400 MOE. A MOE ≥ 100 is sufficient to protect occupational pesticide handlers. Provided that mixer/loaders use protective gloves as required on the Topramezone SC label registered under the Federal Insecticide, Fungicide and Rodenticide Act, all MOEs are >100 and therefore do not exceed HED's level of concern (LOC).

Acute and Chronic Dietary Exposure

An acute and chronic dietary exposure analysis was conducted using Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™), which incorporates food consumption data as reported by respondents in the USDA 1994-1996 and 1998 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII), and accumulated exposure to the chemical for each commodity. The following assumptions were made for the acute and chronic exposure assessments: tolerance-level residues were assumed for all food commodities with proposed topramezone tolerances, and it was assumed that all of the crops included in the analysis were treated. Percent Crop Treated (PCT) and/or anticipated residues were not used in the acute and chronic risk assessments.

Drinking Water

The Agency lacks sufficient monitoring exposure data to complete a comprehensive dietary exposure analysis and risk assessment for topramezone in drinking water. Because the Agency does not have comprehensive monitoring data, drinking water concentration estimates are made by reliance on simulation or modeling taking into account data on the physical characteristics of

topramezone. Based on the PRZM/EXAMS and SCI-GROW models, the EECs of topramezone for acute exposures are estimated to be 0.77 parts per billion (ppb) for surface water and 0.0671 ppb for ground water. The EECs for chronic exposures are estimated to be 0.14 ppb for surface water and 0.0671 ppb for ground water. The acute dietary exposure from food and drinking water to topramezone will occupy 1.4 % of the aPAD for females 13 years and older. The chronic exposure to topramezone from food and drinking water will utilize 0.6 % of the cPAD for the U.S. population, 0.9 % of the cPAD for all infants (< 1 year old), and 1.2 % of the cPAD for children 3-5 years old. .

Topramezone is not registered for use on any sites that would result in residential exposure. Therefore, the aggregate risk is the sum of the risk from food and water, which do not exceed the Agency's level of concern.

Environmental Fate and Effects Division's Review

The EFED has reviewed this action and the Agency concludes based on EFED's ecological risk assessment that plants, including terrestrial and aquatic vascular plants are directly at risk from the proposed use of topramezone on corn. This includes Federally listed endangered plant species. All other organisms, including aquatic and terrestrial animals, beneficial insects, and non-vascular aquatic plants, are presumed not to be at *direct* risk. This is logical, based on the fact that the primary mode of action (inhibition of the photosynthesis), is specific to plants. Aquatic non-vascular plants are not at risk because the modeled exposures in water are below the thresholds of concern. However, some growth effects were observed in an avian laboratory study that creates uncertainty in potential for chronic effects. Amvac is a member of the Endangered Species and Spray Drift Task Forces and any measures developed by the Task Forces to mitigate risks to non-target plants will be applied to topramezone as well as other registered herbicides.

Topramezone can be persistent in aerobic soils (half-life >125 days). Although formation of metabolites involve microorganisms, dissipation of topramezone in the environment appears to be predominantly controlled by time-dependent sorption. Even though the batch-equilibrium adsorption/ desorption studies indicate that topramezone may be very mobile in some soils/sediments, increasing non-extractable residues with time provides evidence for time-dependent sorption behavior. Intact residues of topramezone may remain associated with the humic material and/or mineral components in soils and pose a potential to accumulate from season to season. Slow desorption may free topramezone residues and extend the phytotoxicity of the soils. Neither abiotic hydrolysis nor direct photolysis in water nor photolysis on soil are significant dissipation routes for topramezone.

Drift and/or runoff were identified as the routes leading to residues of topramezone in aquatic ecosystems. Drift and/or runoff , as well as post-treatment residues in soils, can be associated as potential exposure routes for non-target terrestrial plants. Inadvertent residues of topramezone can also be present in irrigation water and may be phytotoxic to irrigated non-target plants. In addition, soils containing residues of topramezone have the potential to be transported off-site by airborne dust or soil erosion. Recommended rotational crop intervals greater than 18 months suggest that residues of topramezone in soil are still active and may cause injury to sensitive, non-target plants.

As expected for a herbicide, the major effects were on plants. For aquatic plants, toxic effects were higher on vascular than on non-vascular plants. Vascular plants are more sensitive to topramezone (TGAI) than to M670H05 (metabolite) or to Topramezone SC (formulated topramezone). The most pronounced effects on frond counts were observed for topramezone TGAI. No tests were conducted with "M670H01" or "M670H10", which may exhibit herbicidal activity.

All terrestrial plants showed toxic effects in seedling emergence and vegetative vigor studies, but at varying degree depending on the species and exposure concentrations. In seedling emergence and vegetative vigor studies, monocots were observed to be less sensitive than dicots. The most sensitive plants to seedling emergence were ryegrass (monocot) and cabbage (dicot). The most sensitive plants to vegetative vigor were onion (monocots) and soybeans (dicots). Dry weight was selected as the most sensitive endpoint. However, phytotoxic effects and other growth effects such as shoot height were also observed.

Overall, topramezone is practically nontoxic to avian, mammals, honeybees, earthworms, freshwater fish and invertebrates and estuarine/marine fish and moderately toxic to estuarine/marine invertebrates. Chronic effects for bobwhite quail reproduction include reduction in the ratio of number hatched to live embryos (a measure of hatchability) at the highest treatment level, 1012 mg ai/kg dw and the mallard duck reproduction had significant reductions in hatchling body weight and female weight gain at all three treatment levels, resulting in the inability to define a NOAEC. No chronic effects were observed in mammals as high as 4000 ppm, based on a two-generation toxicity study on laboratory rats. Chronic effects were apparent for freshwater fish with reduced growth (length and weight) at 9.01 mg aiL⁻¹. Estimated chronic effects for estuarine/marine fish are uncertain because no chronic data were submitted by the registrant; therefore, the NOAEC value was derived based on the assumption that the freshwater and estuarine/marine fish are of equal sensitivity.

M670H05 is practically nontoxic to freshwater fish and invertebrates. The formulated product Topramezone SC is practically nontoxic to honeybee, terrestrial invertebrates, and freshwater fish and invertebrates.

OUTSTANDING DATA

The following details the data gaps and/or additional information required from the registrant:

Product Chemistry

- ▶ Five batch analysis of technical produced on commercial scale

Environmental Fate and Effects

- ▶ Aerobic Soil Metabolism (162-4)
- ▶ Anaerobic Aquatic Metabolism (162-3)
- ▶ Mobility in Soils (163-1)
- ▶ Frozen Storage Stability

Ecological Effects

- ▶ Avian Subacute Dietary (71-2(a))
- ▶ Avian Reproduction (71-4(a))
- ▶ Avian Reproduction (71-4(b))
- ▶ Aquatic Invertebrate Life-Cycle (72-4(b))
- ▶ Aquatic Plant Growth (Tier 2) (123-2)
- ▶ Seedling Emergence (Tier 2) (123-1(a))
- ▶ Vegetative Vigor (Tier 2) 123-1(b)

PUBLIC INTEREST FINDING:

Topramezone SC will fill a niche for certain sweet corn and white popcorn hybrid growers with a new mode of action to control grasses and broadleaf weeds and who have few herbicide options available. These growers also have concerns with triazine and ALS inhibitor resistance, and crop tolerance that registration of topramezone will mitigate. Topramezone may be useful to field corn growers as a resistance management tool, and would be the only HPPD inhibitor available for post-emergent application that would not have insecticide restrictions on the label.

GOVERNMENT PERFORMANCE AND RESULTS ACT (GPRA)

Registering topramezone will meet the objectives of GPRA title 3.1.1 by assuring new pesticides that enter the market are safe for humans and the environment and title 4.1.2 by reducing environmental exposure to herbicides.

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