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OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

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MEMORANDUM

Date: 20-FEB-2009

SUBJECT: Topramezone: Human-Health Risk Assessment for Uses Proposed on Non-crop Ornamentals, Rights-of-Way, Tree Plantations, and Other Non-Crop Areas.

PC Code: 123009
Decision No.: 392747
Petition No.: N/A
Risk Assessment Type: Single Chemical/Aggregate
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DP Barcode: 352696
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Case No.: NA
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40 CFR: §180.612

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Under Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act, as amended, BASF Corporation has submitted a petition proposing application of topramezone [3-(4,5-dihydro-isoxazol-3-yl)-4-methylsulfonyl-2-methylphenyl](5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone to trees and other ornamentals, rights of way, and non-crop areas. Topramezone 2.8 soluble concentrate (SC) Specialty Products Herbicide® contains 29.7% active ingredient (ai). Topramezone is also known as BAS-670H.

A very broad list of non-crop, non-food use sites is stated on the Topramezone 2.8 SC label. Tree plantations, rights-of-way, utility substations, tank farms, fence rows, and ditch banks are some of the use sites. None of the proposed uses are expected to result in food residues, nor are there any existing or proposed residential use sites.

Human exposure is possible from the proposed uses. A human-health risk assessment was performed for occupational and non-occupational exposure pathways. Food-based dietary

Rec'd in RIC 2/25/2009

exposure is not expected (only water-source dietary exposure is expected).

A summary of findings and an assessment of human risk resulting from the proposed uses is provided in this document. The risk assessment was provided by Mary Clock-Rust (RAB1), the dietary exposure assessment was performed by Jennifer R. Tyler (RAB1), the hazard assessment was performed by Robert Mitkus (RAB1), and the drinking water assessment was provided by Silvia Termes and James Wolf of the Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Background
Topramezone is a broad-spectrum, post-emergent herbicide used to control grassy and broadleaf weeds. A topramezone product (BAS-670 336 SC) is registered on corn (HED assessment: memo, M. Clock-Rust, *et al.*, D319704, 7/14/05).

BASF Corporation has submitted a petition proposing application of topramezone [3-(4,5-dihydro-isoxazol-3-yl)-4-methylsulfonyl-2-methylphenyl](5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone to trees and other ornamentals, rights of way, and non-crop areas. Topramezone 2.8 SC Specialty Products Herbicide® contains 29.7% active ingredient (ai). Topramezone is also known as BAS-670H.

Proposed Use
A very broad list of non-crop, non-food use sites is stated on the Topramezone 2.8 SC label. Tree plantations, rights-of-way, utility substations, tank farms, fence rows and ditch banks are some of the use sites (see Section 2.1 for a complete list of proposed use sites). There are no existing or proposed residential use sites. None of the proposed uses are expected to result in food residues.

The maximum single application rate is 0.089 lb ai/acre (4 oz formulation/acre). Treatments are proposed to be made with aerial sprayers, groundboom sprayers, rights-of-way sprayers as well as backpack sprayers and low-pressure handwands for spot treatments. There are no proposed residential uses.

The proposed label requires applicators and other handlers to wear a long-sleeved shirt and long pants, chemical-resistant gloves (Category A) and shoes plus socks. There is a 12-hour restricted-entry interval (REI).

The most recent human-health risk assessment for topramezone was completed in 2005 (Memo, M. Clock-Rust, *et al.*, D319704, 7/14/2005). Please refer to the 2005 risk assessment for details on the active ingredient profile, hazard assessment, dose-response assessment, drinking water and residue chemistry assessment. These aspects of the topramezone human-health risk assessment are not affected by the current action and a summary is provided in this document. For the current action, no food uses are proposed. Therefore, for the current action, HED has assessed dietary risk from drinking water sources and occupational exposure and risk.

Hazard Characterization
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. The critical effect for the overall risk assessment is based on the toxic effects on the most sensitive target organs in the eyes, liver, kidney, thyroid, and pancreas. The rat is the most sensitive species.

Following oral administration, topramezone is rapidly absorbed and excreted via urine and feces. Topramezone is an inhibitor of 4-hydroxyphenylpyruvate dioxygenase (4-HPPD); this results in elevated serum tyrosine levels. 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 Cancer Assessment Review Committee (CARC) classified topramezone 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 no-observed adverse effect level (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.

Dose-Response Assessment and Food Quality Protection Act (FQPA) Decision
The critical effect for the overall risk assessment is based on the toxic effects on the most sensitive target organs in the eyes, liver, kidney, thyroid, and pancreas. The rat is the most sensitive species.

For oral exposure, a developmental toxicity study in rabbits was selected for the acute dietary reference dose (aRfD) for females 13-50 years of age group, based on alterations in skeletal development (delayed ossification and supernumerary ribs). For the general population including infants and children, an endpoint of concern for a single day (24 hours) dietary exposure was not identified. For the short- and intermediate-term incidental oral exposure scenarios and the chronic reference dose (cRfD), a carcinogenicity study in rats was selected based on an increased incidence of corneal opacity, decreased body weight and body-weight gains in males, and histopathological evaluations in the thyroid, pancreas, and eyes of both sexes. 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.

An adjusted dermal-absorption factor of 13% based on a rat dermal-absorption study was used for all dermal exposure assessments. A carcinogenicity study in rats was selected for all dermal exposure scenarios 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. 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. A 28-day dermal toxicity study was not selected because the study did not measure developmental toxic endpoints of concern (skeletal development); further, the NOAEL in the dermal toxicity study would not provide adequate protection for females ages 13 to 50

years old. An oral study was selected because the effects of concern (in liver, thyroid, pancreas and eyes) occurred at a lower dose than the thyroid effects seen in the 28-day dermal toxicity study.

The same dose and endpoint were selected for dermal and inhalation exposure scenarios (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). Since no repeated- dose inhalation toxicity studies are available, an oral study was selected for inhalation risk assessment. HED assumes 100% inhalation absorption for inhalation exposures.

A 100x uncertainty factor was used in determining the RfD (10x for intraspecies variation and 10x for interspecies extrapolation). The level of concern (LOC) for all non-dietary exposure durations (short-, intermediate- and long-term) is a margin of exposure (MOE) of at least 100.

Based on toxicological considerations, and the assumptions used in the exposure assessments, the topramezone risk assessment team determined that a 1x FQPA safety factor was appropriate.

HED notes that 40 CFR Part 158 was revised in 2007 to require an immunotoxicity test for registration of a pesticide (food and non-food uses). The immunotoxicity test guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. These data have not been submitted and are required for topramezone.

Drinking Water
Topramezone is persistent and mobile in terrestrial and aquatic environments. Major routes of dissipation are expected to be anaerobic microbial-mediated degradation, leaching, surface water runoff, and spray drift. These data suggest a high potential for off-site movement of topramezone into surface and ground water. Degradation products of topramezone include M670H05 (15% of applied parent at 365 days), and M670H01 (>15% of applied), M670H 10 (>16% of applied). M670H05 is also persistent and mobile. The degradation products are not considered in the drinking water assessment because they are not considered to be residues of concern.

EFED performed a drinking water assessment based on topramezone use in nurseries (one of the proposed non-crop use sites). EDWCs were modeled using the Pesticide Root Zone Model (PRZM-Exposure Analysis Modeling System (EXAMS) (PRZM-EXAMS) Tier II simulation models for surface water and the Screening Concentration In Ground Water (SCI-GROW) model for ground water. HED used the surface water value in the dietary exposure assessment for topramezone.

Dietary-Exposure Assessment
An assessment of dietary risk was performed based on dietary exposure from the currently registered corn use as well as drinking water residues resulting from the proposed uses on non-crop areas. No food residues are expected to result from the proposed new uses.

Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model DEEM-FCID™ (DEEM), Version 2.03 which use food consumption data from the U.S. Department of Agriculture's (USDA's)

Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. No new tolerances have been proposed or recommended to support the proposed uses. However, updated EDWCs have been provided by EFED and were used in the dietary analyses.

The results of the dietary assessment indicate that risks are not of concern (<100% population-adjusted dose (PAD)).

Aggregate Risk
There are no proposed or registered residential uses of topramezone. Therefore, aggregate risk consists of dietary exposure only. Since no food uses are proposed in the current action, dietary exposure is comprised of exposure from drinking water sources only. Dietary risk from drinking water was assessed and indicated no concerns (<100% PAD). In conclusion, acute and chronic aggregate risks do not exceed HED's LOC.

Occupational Handler Risk
Based on the proposed uses on non-crop areas, a variety of application methods may be used to apply topramezone, including aerial, groundboom, and rights-of-way sprayer application and backpack and low-pressure handwand for spot treatment. Assessments of handler exposure and risk were performed using HED's standard assumptions and are considered to be conservative. All short- or intermediate-term handler exposures resulted in MOEs that do not exceed HED's LOC assuming handlers wear gloves (as required on the label).

Occupational Post-Application Risk
The proposed use on non-crop areas is not expected to result in dermal post-application exposure because workers are not expected to enter treated areas as would be the case with agricultural crops. However, HED assessed post-application dermal exposure for workers who prune and harvest containerized ornamental plants. MOEs for the post-application forestry uses are not of concern.

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), were previously determined to require a review of their ethical conduct, and have received that review. The studies in PHED were considered appropriate (or ethically conducted) for use in risk assessments.

HED Recommendations
Provided the label is amended to prohibit use on areas that may be grazed or cut for hay, HED concludes that there are no residue chemistry, toxicology or occupational/residential exposure data requirements that would preclude the registration of topramezone on the proposed non-crop use sites.

2.0 Ingredient Profile

Topramezone belongs to the phenylpyrazolyl ketone class of chemicals. It inhibits 4-HPPD and thereby impairs carotenoid biosynthesis in the chlorophyll synthesis pathway, ultimately leading to the breakdown of chloroplasts.

2.1 Summary of Registered/Proposed Uses

Registered Uses of Topramezone
Tolerances have been established under 40 CFR §180.612 for residues of the herbicide topramezone, [3-(4,5-dihydro-3-isoxazolyl)-2-methyl-4-(methylsulfonyl)phenyl](5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone, in or on the commodities listed below.

Commodity	Tolerance (ppm)
Corn, field, forage	0.05
Corn, field, stover	0.05
Corn, field, grain	0.01
Corn, pop, grain	0.01
Corn, pop, stover	0.05
Corn, sweet, kernel plus cob with husks removed	0.01
Corn, sweet, forage	0.05
Corn, sweet, stover	0.05
Cattle, kidney	0.05
Cattle, liver	0.15
Goat, kidney	0.05
Goat, liver	0.15
Horse, kidney	0.05
Horse, liver	0.15
Sheep, kidney	0.05
Sheep, liver	0.15

Proposed Uses
A very broad list of use sites is stated on the Topramezone 2.8 SC label. The label states, "For preemergence and postemergence weed control in Christmas tree, conifer, and hardwood plantations; field-grown ornamental production; and non-cropland areas such as railroad, utility, highway, and pipeline rights-of-way; highway guardrails, delineators, and sign posts; utility substations, petroleum tank farms, pumping installations, farmyards and around farm buildings,; fence rows, storage areas, airports, nonirrigation ditch banks, and for the establishment and maintenance of wildlife openings, (label should say "not" here) including areas within these sites that may be grazed or cut for hay."

The maximum single application rate is 4 oz formulation or 0.089 lb ai per acre. Treatment is expected to be made by aerial (fixed and rotary wing aircraft), groundboom, and rights-of-way sprayers, as well as by backpack and low-pressure handwand sprayers for spot treatments. There are no proposed residential uses.

Table 2.1. Summary of Proposed Non-Crop Uses for Topramezone.					
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	Use Directions and Limitations
Tree Plantations, Ornamentals, Rights-of-Way, Airports and Other Non-Crop Areas					
Pre and Post-emergence; Aerial, Ground and Backpack Sprayers	Topramezone 2.8 SC Specialty Products Herbicide® [7969-XXX]	0.089 lb ai/Acre (4 fl. Oz product per acre)	Not Stated on Label	0.089 lb ai/A/ Season	Personal Protective Equipment for Applicators and other Handlers includes long pants, long sleeved shirt, chemical-resistant gloves (Category A) and shoes plus socks. REI =12 hours Broadcast applications should be made in at least 10 gallons/acre.

3.0 Hazard Characterization and Dose-Response Assessment

Topramezone has a low acute toxicity via the oral, dermal, or inhalation route (see Appendix for acute toxicity table). It is a slight eye and dermal irritant but is not a skin sensitizer. Absorption following oral administration of topramezone is rapid but limited (20%). The majority of the radioactivity was excreted via urine and feces in 48 hours. Topramezone is an inhibitor of 4-HPPD; this results in elevated serum tyrosine levels. 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 two-generation reproductive toxicity study in rats did not demonstrate adverse reproductive effects; however, developmental toxicity studies in rats and rabbits showed increased incidences of skeletal variations 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. In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified topramezone 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. Therefore, a cancer assessment was not necessary.

There is a concern about the elevated tyrosine levels observed in treated rats and mice with the rat as the most-sensitive species. However, none of the data in the submitted studies permit a determination of the percentage of increased tyrosine levels that result in detrimental or adverse effects. Therefore, the endpoints selected for the various exposure scenarios are based on critical tyrosine-mediated toxic effects, rather than on increased tyrosine levels alone. The developmental toxicity study in rabbits was selected as the critical study for the acute dietary risk assessment for females 13-50 years of age, based on alterations in skeletal development (delayed ossification and supernumerary ribs). For the general population, including infants and children,

an oral endpoint of concern for a single exposure was not identified. For the short- and intermediate-term incidental oral exposure scenarios and the chronic RfD, a carcinogenicity study in rats was selected based on increased incidences of corneal opacity, decreased body weight and body-weight gains in males, and histopathological findings in the thyroid, pancreas, and eyes of both sexes.

An adjusted dermal-absorption factor of 13% based on a rat dermal-absorption study was used for all dermal exposure assessments. A carcinogenicity study in rats was selected for all dermal-exposure scenarios based on increased incidences of corneal opacity, decreased body weight and body-weight gains in males, and histopathological findings. 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 rat 28-day dermal toxicity study was not selected because developmental toxic effects (i.e., skeletal variations, delayed ossification and increased numbers of ribs) were not measured in this study. In addition, the NOAEL (100 mg/kg/day) in the 28-day dermal toxicity study would not be protective of developmental effects for which the oral NOAEL was 0.5 mg/kg/day using a dermal-absorption factor of 13% (dermal equivalent NOAEL = 4 mg/kg bw/day). The rat carcinogenicity study with a longer duration and a NOAEL of 0.4 mg/kg/day based on observed effects in the eye, pancreas, and thyroid will be protective and is appropriate for short-, intermediate-, and long-term dermal risk assessment. Since an oral NOAEL was selected, a 13% dermal-absorption factor was used for route-to-route extrapolation.

The inhalation endpoints selected paralleled the determinations made for the dermal exposure assessments above and assumed a 100% default assumption in the absence of a repeated-exposure inhalation toxicity study.

The uncertainty factors used in determining the acute and chronic RfDs (aRfD and cRfD) were 100 (10x for intraspecies variation and 10x for interspecies extrapolation).

There are no/low concerns or residual uncertainties for pre- and post-natal toxicity. Based on toxicological considerations, and the assumptions used in the exposure assessments, the topramezone risk assessment team determined that a 1x FQPA safety factor was appropriate.

Table 3.0. Summary of Toxicology Endpoint Selection for Topramezone.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and LOC 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	FQPA SF= 1X aRfD = aPAD = 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.
Chronic Dietary (All populations)	NOAEL= 0.4 mg/kg/day UF=100	FQPA SF= 1X cRfD = cPAD = 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

Table 3.0. Summary of Toxicology Endpoint Selection for Topramezone.			
Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and LOC for Risk Assessment	Study and Toxicological Effects
			histopathological evaluations in the thyroid, pancreas, and eyes of both sexes.
Short- and Intermediate-Term Incidental Oral	NOAEL= 0.4 mg/kg/day	Residential LOC for MOE = 100	Carcinogenicity Study in Rats See above.
Short-, Intermediate-, and Long-Term Dermal	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.
Short-, Intermediate-, and Long-Term Inhalation	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.
Cancer (Oral, dermal, inhalation)	In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified topramezone 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.		

3.1 FQPA Safety Factor

The topramezone risk assessment team evaluated the quality of the hazard and exposure data and determined that based on the hazard and exposure data, the FQPA SF should be reduced to 1x.

In terms of hazard, there are no/low concerns and no residual uncertainties with regard to pre- and/or post-natal toxicity. The recommendation is also based on the following:

- The dietary food exposure assessment utilizes proposed tolerance-level or higher residues and 100% crop treated (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 was based on values generated by model with associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations.

- There are no proposed or existing residential uses of topramezone.

- There is no evidence of immunotoxicity in the topramezone database. In addition, topramezone does not belong to a class of chemicals (e.g., the organotins, heavy metals, or halogenated aromatic hydrocarbons) that would be expected to be immunotoxic. Based on the above considerations, HED does not believe that conducting a special series 870.7800 immunotoxicity study will result in a point of departure less than the NOAEL of 0.4 mg/kg/day already set for topramezone; therefore, an additional uncertainty factor (UFDB) for database uncertainties does not need to be applied.

3.2 Endocrine Disruption

EPA is required under the Federal Food, Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally-occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, topramezone may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health Data

Topramezone is a relatively new active ingredient (2005). A search conducted February 17, 2009 did not result in any human health poisoning incidences.

5.0 Exposure Characterization/Assessment

While there are no food uses proposed in this action, dietary exposure was assessed based on drinking water and existing tolerances on corn, meat and milk. Also, occupational risk was assessed for the proposed non-crop uses.

Topramezone acute and chronic dietary exposure assessments were conducted using DEEM-FCID™, Version 2.03 which incorporates consumption data from USDA's CSFII, 1994-1996 and 1998.

5.1 Drinking Water

Topramezone is persistent and mobile in terrestrial and aquatic environments. Major routes of dissipation are expected to be anaerobic microbial-mediated degradation, leaching, surface water runoff, and spray drift. These data suggest a high potential for off-site movement of topramezone into surface and ground water. Degradation products of topramezone include M670H05 (15% of applied parent at 365 days), and M670H01 (> 15% of applied), M670H 10 (>16% of applied). M670H05 is also persistent and mobile. The degradation products are not considered in the drinking water assessment because they are not considered to be residues of concern.

Topramezone *per se* is the residue of concern in drinking water for purposes of risk assessment.

EDWCs for topramezone in drinking water were estimated using the PRZM-EXAMS Tier II simulation models for surface water and SCI-GROW for ground water. Table 5.1 summarizes the EDWCs for topramezone in surface and ground water.

Table 5.1. Tier 1 and Tier II EDWCs for Topramezone Use in Non-Crop Use Patterns.

Assessment	Concentration (µgL-1)		
	Peak	Annual Mean	30-year Mean
Tier II Surface Water	5.281[a]	1.998[b]	1.016[b]
Ground Water	0.0671[c]		

From: EFED memo: J. Hetrick, D356497, 9/29/08.
a - 1-in-10 year concentration in TN nursery scenario using aerial application.
b - 1-in-10 year concentration in CA nursery scenario using aerial application.
c - SCI-GROW number from previous drinking water assessment for corn (DP 314642).

These drinking water values were incorporated directly into this dietary assessment. For acute dietary risk, the 1-in-10 year peak surface water concentration was used (5.281 ug/L) and for chronic dietary risk assessment, the 1-in-10 year annual mean (1.998 ug/L) was used. Water residues were incorporated in the DEEM-FCID™ into the food categories "water, direct, all sources" and "water, indirect, all sources."

Topramezone acute and chronic dietary exposure assessments were conducted using DEEM-FCID™, Version 2.03 which incorporates consumption data from USDA's CSFII, 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g., apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/Agriculture Research Service and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

For acute and chronic assessments, HED is concerned when dietary risk exceeds 100% of the PAD.

5.2 Acute Dietary Exposure and Risk

The acute analysis assumed 100 %CT, DEEM™ 7.81 default processing factors and tolerance-level residues for all commodities. Drinking water was incorporated directly into the dietary assessment using the 1-in-10 year annual peak concentration for surface water generated by the PRZM-EXAMS Tier II model.

As an appropriate endpoint attributable to a single dose was not identified for the general U.S.

population (including infants and children), the acute dietary exposure and risk analysis was performed for females 13-49 years old only.

The resulting acute dietary exposure and risk estimate using the DEEM-FCID™ model at the 95th percentile was 0.000278 mg/kg/day (5.6% of the acute population adjusted dose (aPAD) and are thus below HED's level of concern (<100% aPAD). Results are reported in Table 5.3 below.

5.3 Chronic Dietary Exposure and Risk

The Tier 1 chronic analysis assumed 100% CT, DEEM™ 7.81 default processing factors and tolerance-level residues. Drinking water was incorporated directly into the dietary assessment using the 1-in-10 year annual mean concentration for surface water generated by the PRZM-EXAMS model as a high-end estimate.

The resulting chronic dietary exposure estimates using the DEEM-FCID™ model were less than 4.1% of the cPAD for the U.S. population and all population subgroups.

The chronic dietary exposure and risk estimates (food + water) were estimated at 0.000062 mg/kg/day for the general U.S. population (1.5% of the cPAD) and 0.000166 mg/kg/day (4.1% of the cPAD) for the most highly exposed population subgroup (all infants <1 year old) and are thus below HED's level of concern (<100 %cPAD). Results are reported in Table 5.3 below.

Table 5.3. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Topramezone.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	N/A		0.000062	1.5
All Infants (< 1 year old)			0.000166	4.1
Children 1-2 years old			0.000101	2.5
Children 3-5 years old			0.000104	2.6
Children 6-12 years old			0.000075	1.9
Youth 13-19 years old			0.000058	1.4
Adults 20-49 years old			0.000055	1.4
Adults 50+ years old			0.000051	1.3
Females 13-49 years old	0.000278	5.6	0.000055	1.4

These acute and chronic dietary exposure and risk estimates are conservative since they assumed 100% CT, DEEM™ 7.81 default processing factors and tolerance-level residues and were based on screening level estimates of drinking water concentrations generated by the PRZM-EXAMS models. They could be further refined through the use of anticipated residues, empirical processing factors and % CT data, as well as refined drinking water estimates.

6.0 Residential (Non-Occupational) Exposure/Risk Pathway

There are no proposed or existing residential uses of topramezone. Therefore, a residential risk assessment is not necessary.

6.1 Spray Drift

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 topramezone. HED 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. On a chemical by chemical basis, HED is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. HED 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, HED may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

For topramezone, no residential uses are proposed. Also, no food residues are expected from the proposed use. Therefore, aggregate risk is comprised of dietary exposure from the existing food use on corn and drinking water sources only. Acute (females 13-49 years old only) and chronic aggregate risks were calculated.

7.1 Acute Aggregate Risk (females 13-49 years old only)

To assess acute aggregate risk, HED incorporated drinking water estimates directly into the dietary analysis. Results are reported in Table 5.3.

7.2 Short-Term Aggregate Risk

Since there are no existing or proposed residential uses for topramezone, short-term aggregate risk was not calculated. There are no concerns for short-term aggregate risk.

7.3 Intermediate-Term Aggregate Risk

Since there are no existing or proposed residential uses for topramezone, intermediate-term aggregate risk was not calculated. There are no concerns for intermediate-term aggregate risk.

7.4 Long-Term (Chronic) Aggregate Risk

To assess chronic aggregate risk, HED incorporated drinking water estimates directly into the

dietary analysis. Results are reported in Table 5.3.

Since drinking water was included directly into the chronic dietary analysis, the risk estimate represents chronic aggregate risk from topramezone.

8.0 Cumulative Risk Characterization/Assessment

There are marked differences among species in the ocular toxicity associated with inhibition of HPPD. Ocular effects following treatment with HPPD inhibitor herbicides are seen in the rat but not in the mouse. Monkeys also seem to be recalcitrant to the ocular toxicity induced by HPPD inhibition. One explanation for this species-specific response in ocular opacity may be related to species differences in the clearance of tyrosine. A metabolic pathway exists to remove tyrosine from the blood that involves the liver enzyme tyrosine aminotransferase (TAT). In contrast to rats where ocular toxicity is observed following exposure to HPPD-inhibiting herbicides, mice and humans are unlikely to achieve the levels of plasma tyrosine necessary to produce ocular opacities because the activity of TAT in these species is much greater compared to rats.

HPPD inhibitors (*e.g.*, nitisinone) are used as an effective therapeutic agent to treat patients suffering from rare genetic diseases of tyrosine catabolism. Treatment starts in childhood but is often sustained throughout patient's lifetime. The human experience indicates that a therapeutic dose (1 mg/kg/day dose) of nitisinone has an excellent safety record in infants, children, and adults and that serious adverse health outcomes have not been observed in a population followed for approximately a decade. Rarely, ocular effects are seen in patients with high plasma tyrosine levels; however, these effects are transient and can be readily reversed upon adherence to a restricted protein diet. This observation indicates that an HPPD-inhibitor in and of itself cannot easily overwhelm the tyrosine-clearance mechanism in humans.

Therefore, exposures to environmental residues of HPPD-inhibiting herbicides are unlikely to result in the high blood levels of tyrosine and ocular toxicity in humans due to an efficient metabolic process to handle excess tyrosine. The Agency continues to study the complex relationships between elevated tyrosine levels and biological effects in various species. In the future, assessments of HPPD-inhibiting herbicides will consider more appropriate models and cross species extrapolation methods. Therefore, EPA has not conducted cumulative risk assessment with other HPPD-inhibitors.

For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure and Risk

Based on the proposed uses of topramezone on numerous non-crop areas, worker exposure is possible.

9.1 Occupational Handler Exposure and Risk

Occupational handlers may experience short- and intermediate-term exposure to topramezone while mixing/loading and applying sprays to the proposed non-crop areas. Exposure scenarios for different uses have been created to reflect conservative risk estimates.

Use Information
Topramezone 2.8 SC Herbicide® contains 29.7% topramezone in a SC formulation. The maximum single application rate is 0.089 lb/ai/acre (4 oz. product per acre). Treatment will be made with aerial sprayers (fixed and rotary-wing aircraft), groundboom and rights-of-way sprayers, as well as backpack and low-pressure handwand sprayers for spot treatments. There are no proposed residential uses. Although the number of applications per season is not specified on the label, handler exposures are expected to be of short- or intermediate-term duration (1 to 30 days and 1 to 6 months, respectively). Long-term exposure (more than 6 months) is not expected. According to the label, handlers (mixer/loaders and applicators) of this product must wear long-sleeved shirt and long pants, socks, shoes and chemical-resistant gloves. See Table 2.1 for more information.

A very broad list of non-crop use sites is stated on the Topramezone 2.8 SC label (see Section 2.1 for entire list). Tree plantations, rights-of-way, utility substations, tank farms, fence rows, and ditch banks are some of the use sites.

In this assessment, HED has addressed the following occupational handler exposure scenarios:

- Mixing/loading SC formulations for aerial application;
- Mixing/loading SC formulations for groundboom application;
- Applying sprays aerially (fixed-wing aircraft);
- Applying sprays by groundboom equipment;
- Applying sprays using rights-of-way sprayer;
- Mixing/Loading/Applying sprays using backpack sprayer (spot treatment);
- Mixing/Loading/Applying sprays using low-pressure handwand (spot treatment).

9.1.1 Data and Assumptions for Handler Exposure Scenarios

Unit Exposures
No chemical-specific data for assessing exposure during pesticide handling activities were submitted to the Agency in support of this action. When chemical-specific data are not available, it is HED policy to use data from PHED Version 1.1 to assess handler exposures. Exposure data for all scenarios in this assessment were obtained from PHED.

An occupational handler exposure assessment was completed by HED for workers wearing "baseline" attire, which represents long pants, a long-sleeved shirt, shoes, socks, no gloves, and no respirator. Exposure and risk estimates for handlers wearing gloves in addition to baseline personal-protective equipment (PPE) (without gloves) were also provided. The label requires applicators and other handlers to wear a long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks. However, HED assessed exposure to pilots assuming they do not wear gloves while applying topramezone with aircraft.

The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the data available for monitoring of these two activities separately. These exposure scenarios are outlined in the PHED Surrogate Exposure Guide (HED Science Advisory Council for Exposure (ExpoSAC), 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. For example, 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 PPE for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader.

Short- and intermediate-term dermal and inhalation handler risks were estimated. HED assumes 100% inhalation absorption and 13% dermal absorption for topramezone. Dermal and inhalation exposures were summed and compared to the short- and intermediate-term NOAEL of 0.4 mg/kg/day from the carcinogenicity study in rats (LOAEL = 3.6 mg/kg/day). Since doses and endpoints are the same for inhalation and dermal risk assessment, it is appropriate to sum exposure across these exposure routes.

Area Treated
Based on professional judgment and HED's ExpoSAC Policy Number 9.1 (rev. 7/5/2000), the following assumptions for acres per day treated (or amount handled) were made:

- 350 acres/day for application with aerial equipment;
- 80 acres/day for application with groundboom equipment;
- 350 acres/day for flaggers supporting aerial application;
- 1000 gallons/day for applicator using rights-of-way sprayer (50 acres/day or 20 gallons per acre for topramezone);
- 5 acres/day for mixer/loader/applicator using low-pressure handwand; and
- 5 acres/day for mixer/loader/applicator using backpack sprayer.

Body Weight
A body weight of 70 kg was used for short- and intermediate-term risk calculations.

Equations/Calculations
The following equation was used to calculate handler exposure and risk:

Dermal or Inhalation Dose (mg/kg/day) =

$$\frac{\textbf{\textit{Rate (lb ai/A)}} \times \textbf{\textit{UE (mg /lb ai)}} \times \textbf{\textit{Area Treated (A/day)}} \times \textbf{\textit{AF}}}{\textbf{\textit{BW (kg)}}}$$

Where:

Rate (Application Rate) = Maximum application rate on product label (lb ai/A)
UE (Unit Exposure) = Exposure value derived from August 1998 PHED Surrogate Exposure Table
Area Treated = Maximum number of acres treated per day (A/day) or Amount Handled

AF = Absorption Factor (dermal absorption is 13%; inhalation absorption is 100%)
BW = Body weight (70 kg)

Short-term or Intermediate-term MOE = NOAEL (0.4 mg/kg/day)/ Dose (mg/kg/day)

9.1.2 Handler Exposure and Risk

All short- or intermediate-term handler exposures resulted in MOEs that do not exceed HED's LOC assuming handlers wear gloves (as required on the label). A summary of dermal and inhalation exposure and risks (MOEs) for handlers are presented in Table 9.1.2.

Table 9.1.2. Estimated Occupational Handler Exposure and Risk to Topramezone.

Unit Exposure[1] mg/lb handled	Application Rate[2] lb ai/A	Units Treated[3] Per Day	Daily Dose[4] mg/kg/day	Short- or Intermediate-term MOE[5]
Mixer/Loader -Liquids – Open - Supporting Aerial Applications				
Dermal: No Gloves 2.9 HC With Gloves 0.023 HC Inhalation 0.0012 HC	0.089	350 Acres	No Gloves: 0.17 W/Gloves: 0.0013 Inhal: 0.00053	No Gloves: 2 W/Gloves: 220
Mixer/Loader – Liquids – Open – Supporting Groundboom Applications				
Dermal: No Gloves 2.9 HC With Gloves 0.023 MC Inhalation 0.0012 HC	0.089	80 Acres	No Gloves: 0.038 W/Gloves: 0.0003 Inhal: 0.00012	No Gloves: 10 W/Gloves: 940
Applicator – Fixed-wing Aircraft-Applicators Wear No Gloves				
Dermal: No Gloves 0. 0050 MC Inhalation 0.000068 MC	0.089	350 Acres	No Gloves:0.00029 Inhal: 0.00003	No Gloves: 1300
Applicator – Groundboom Sprayer-Open Cab				
Dermal: No Gloves 0.014 HC With Gloves 0.014 MC Inhalation 0.00074 MC	0.089	80 Acres	No Glove or W/Gloves: 0.00019 Inhal: 0.00008	No Gloves or W/Gloves: 1500
Applicator-Rights-of-way Sprayer				
Dermal: No Gloves 1.3 LC Gloves 0.39 LC Inhalation 0.0039 HC	0.089	50 Acres (1000 Gallons)	No Gloves: 0.011 W/Gloves: 0.0032 Inhal: 0.00025	No Gloves: 35 W/Gloves: 120
Mixer/Loader/Applicator-Backpack-Liquids-Spot Treatment				
Dermal: No Gloves No Data Gloves 2.5 LC Inhalation 0.030 LC	0.089	5 Acres	W/Gloves: 0.0021 Inhal: 0.00019	W/Gloves: 180
Mixer/Loader/Applicator- Low Pressure Handwand				

Table 9.1.2. Estimated Occupational Handler Exposure and Risk to Topramezone.					
Dermal: No Gloves Gloves Inhalation	 100 LC 0.43 LC 0.03 LC	0.089	5 Acres	No Gloves: 0.082 W/Gloves: 0.00036 Inhal: 0.00019	No Gloves: 5 W/Gloves: 730

1. Unit Exposures are taken from "PHED Surrogate Exposure Guide," PHED Version 1.1, August, 1998. Dermal = Single Layer Work Clothing, No Gloves; Single Layer Work Clothing with Gloves; Units = mg ai/lb ai handled. Data Confidence: MC = Medium Confidence, HC = High Confidence.
2. Application Rate = Taken from proposed Topramezone 2.8 SC label.
3. Units Treated are taken from ExpoSAC SOP No. 9.1 "Standard Values for Daily Acres Treated in Agriculture" Revised 9/25/2001.
4. Average Daily Dose = Unit Exposure * Application Rate * Units Treated * Absorption Rate (13% dermal absorption, 100% inhalation absorption) ÷ Body Weight (70 kg).
5. MOE = Margin of Exposure = NOAEL ÷ ADD (dermal + inhalation). Short- and Intermediate-term NOAEL = 0.4 mg/kg/day.

9.2 Occupational Post-Application Risk

The proposed use on non-crop areas is not expected to result in dermal post-application exposure because workers are not expected to enter treated non-crop areas as would be the case with agricultural crops. However, post-application dermal exposure is possible for workers who tend to containerized ornamentals (nurseries). Therefore, an assessment of this use was performed and is summarized below. Post-application inhalation exposure is expected to be negligible and was not assessed.

The proposed uses include forestry uses, which may involve containerized plants. Workers may handle these plants after application of topramezone by hand pruning as well as harvesting the plants for transplant (ball/burlap). HED has developed transfer coefficients (TCs) to quantify pesticide residues and match residue levels to activity patterns, which take place after application, to estimate potential human exposure. The TCs used in this assessment are from an interim TC guidance document developed by HED's ExpoSAC using proprietary data from the Agricultural Re-entry Task Force (ARTF) database ("ARTF Ornamental Plant Transfer Coefficients," Presented to Exposure SAC in April 2002).

Assumptions:

- Application Rate = 0.089 lb ai/A
- Exposure Duration = 8 hours per day
- Body Weight = 70 kg
- Dermal Absorption = 13%
- Fraction of ai retained on foliage is assumed to be 20% (0.2) on day zero (= % dislodgeable foliar residue, DFR, after initial treatment). This fraction is assumed to further dissipate at the rate of 10% (0.1) per day on following days. These are default values established by HED's ExpoSAC.

TCs for Nursery Stock*	
Activity	TC (cm^2/hr)
Hand pruning containerized ornamentals	110
Harvesting, ball/burlap containerized ornamentals	400

* TCs and associated activities are taken from ExpoSAC's "ARTF Ornamental Plant Transfer Coefficients," Presented to Exposure SAC in April 2002.

Daily dermal exposures were calculated for the day of application using the following equation:

$$DE_{(t)}\ (mg/day) = (TR_{(t)}\ (\mu g/cm^2) \times TC\ (cm^2/hr) \times Hr/Day)/1000\ (\mu g/mg)$$

Where:

DE(t)	=	Daily exposure or amount deposited on the surface of the skin at time (t) attributable for activity in a previously treated area, also referred to as potential dose (mg ai/day);
TR(t)	=	Transferable residues that can be dislodgeable foliar residue (DFR) at time "t" ($\mu g/cm^2$);
TC	=	Transfer Coefficient (cm^2/hour); and
Hr/day	=	Exposure duration meant to represent a typical workday (8 hours).

Note that the ($TR_{(t)}$) input represents levels on the day of application. Once daily exposures are calculated, the calculation of daily absorbed dose and the resulting Margin of Exposures use the same algorithms that are described above for the handler exposures.

Since chemical-specific data were not submitted for the proposed use, HED calculated surrogate DFR levels using the following equation:

Surrogate DFR = application rate * 20% available as dislodgeable residue * $(1\text{-}D)^t$ * 4.54×10^8 µg/lb * 2.47×10^{-8} A/cm^2.

DFR = 0.089 lb ai/A * 0.20 * $(1\text{-}0)^0$ * 4.54×10^8 µg/lb * 2.47×10^{-8} A/cm^2

DFR = 0.20 $\mu g/cm^2$

Postapplication MOEs were estimated for "Day 0" exposure (i.e., the day of application). The post-application risk assessment should be considered a conservative estimate due to the use of several high-end assumptions. As shown below, the short-/intermediate-term MOEs for nursery stock ornamentals are greater than 100 on the day of application and are not of concern.

Table 9.2. Post-Application Exposure and Risk for Nursery Workers.

Containerized Ornamentals			
Exposure Scenario	Application Rate (lb ai/Acre)	Dermal Exposure (mg/kg/day)*	Short- and Intermediate-term MOE
Hand-pruning	0.089	0.00033	1200
Harvesting, Ball/Burlap	0.089	0.0012	340

* Body weight of 70 kg; dermal absorption rate of 13%.

9.3 Restricted-Entry Interval (REI)

The proposed label for Topramezone 2.8 SC Herbicide® indicates a REI of 12 hours. While most of the proposed uses are out of the scope of the Worker Protection Standard, the forestry uses are within the scope and justify having an REI state on topramezone labels. Based on the toxicity of topramezone (acute dermal Toxicity Category 3), the REI is appropriate. HED

recommends that RD ensure that the proper REI for ornamental plants grown in containers in greenhouses, nurseries, and shadehouses be included on the topramezone labels.

10.0 Data Needs and Label Requirements

10.1 Toxicology

HED notes that 40 CFR Part 158 was revised in 2007 to require an immunotoxicity test for registration of a pesticide (food and non-food uses). The immunotoxicity test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. These data have not been submitted and are required for topramezone.

10.2 Residue Chemistry

Amended label to prohibit use on areas that may be grazed or cut for hay.

Appendix 1. Toxicological Data

Table A.1. Acute Toxicity Profile on Topramezone

OPPTS Guideline	Study Type	Results	Toxicity Category
870.1100	Acute oral toxicity / rat	LD50 ≥2000 mg/kg (males and females)	III
870.1200	Acute dermal toxicity / rat	LD50 ≥2000 mg/kg (males and females)	III
870.1300	Acute inhalation toxicity / rat	LC50 ≥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	--

Table A.2. Subchronic, Chronic and Other Toxicity Profile for Topramezone

Guideline No/ Study Type/	MRID Nos. Doses/Classification	Results
870.3100 Subchronic Oral - Rat	45902203, 45902204 (2001, 2003) (0, 15, 30 ppm) M:0, 1.1, 2.1 mg/kg/day F:0, 1.3, 2.5 mg/kg/day Acceptable/guideline	Males: NOAEL=1.1 mg/kg/day, LOAEL= 2.1 mg/kg/day based on diffuse degeneration in the pancreas. Females: NOAEL= 2.1 mg/kg/day, the LOAEL was not established.
870.3100 Subchronic Oral - Mouse	45902202 (2000) (0, 125, 1000, 8000 ppm) M: 0, 3 7, 288, 2289 mg/kg/day F: 0, 51, 406, 3010 mg/kg/day Acceptable/guideline	NOAEL= 2289/3010 mg/kg/day (M/F). LOAEL= Not established.
870.3150 Subchronic Oral - Dog	45902205 (2002) (0, 3000, 9000, 25000 ppm) 0, 182, 535, 1511 mg/kg/day (M) 0, 205, 624, 1712 mg/kg/day(F) Acceptable/guideline	Males: NOAEL= 535 mg/kg/day, and the LOAEL = 1511 mg/kg/day based on decreased body-weight gain, impaired food efficiency, and inflammation of the urinary bladder. Females: NOAEL = 1712 mg/kg/day, the LOAEL for females is not established.
870.3200 28-Day dermal toxicity - Rat	45902206 (2002) 0, 100, 300, 1000 mg/kg/day Acceptable/Guideline	Males: NOAEL= 100 mg/kg/day, the LOAEL= 300 mg/kg/day based on thyroid follicular cell hypertrophy. Females: NOAEL=300 mg/kg/day, the LOAEL= 1000 mg/kg/day based on thyroid follicular cell hypertrophy.
870.3700a Prenatal developmental - Rat	45902207 (2003) 0, 100, 300, 1000 mg/kg/day Acceptable/Guideline	Maternal: NOAEL= not established, the LOAEL= 100 mg/kg/day based on decreased body-weight gains. Developmental: NOAEL= not established, the LOAEL= 100 mg/kg/day based on decreased fetal body weight and increased incidences of skeletal variation.
870.3700b Prenatal developmental - NZW Rabbit	45902210 (2003) 0, 0.5, 5, 50, 450 mg/kg/day Acceptable/Guideline	Maternal: NOAEL= not established, the LOAEL= 0.5 mg/kg/day based on increased serum tyrosine level. Developmental: NOAEL= 0.5 mg/kg/day, the LOAEL= 5 mg/kg/day based on alterations in skeletal ossification sites and increased number of pairs of ribs.
870.3700b Prenatal developmental - NZW Rabbit	45902211 (2003) 0, 5, 50, 500 mg/kg/day Unacceptable/Guideline	Maternal: NOAEL= not established. LOAEL= 5 mg/kg/day based on increased tyrosine level. Developmental: Unable to established because fetal skeletons were not evaluated.
870.3700b Prenatal developmental - NZW Rabbit	45902212 (2003) 0, 1.5, 5.0 mg/kg/day Acceptable/Non-guideline	Maternal: NOAEL= not established. LOAEL= 1.5 mg/kg/day based on increased serum tyrosine level. Developmental: NOAEL= not established, the LOAEL= 1.5 mg/kg/day based on an increased incidence of absent kidney and ureter and increased incidences of supernumerary thoracic vertebrae and supernumerary 13th rib.
870.3700b	45902213 (2003)	Maternal: NOAEL= 5.0 mg/kg/day. LOAEL was not established.

Table A.2. Subchronic, Chronic and Other Toxicity Profile for Topramezone

Guideline No/ Study Type/	MRID Nos. Doses/Classification	Results
Prenatal developmental - NZW Rabbit	0, 1.5, 5.0 mg/kg/day Acceptable/Non-guideline	Developmental: NOAEL= not established, the LOAEL for N33 and N17/CFR 1-2 was 1.5 mg/kg/day based on increased presence of supernumerary thoracic vertebrae and supernumerary 13th rib. No effect was observed for N17/CFR 3 at 0.5 mg/kg/day (the only dose tested).
870.3700b Prenatal developmental - NZW Rabbit	46020301 (2003) 0, 5, 50, 450 mg/kg/day Acceptable/Guideline	Maternal: NOAEL= 450 mg/kg/day. LOAEL not established. Developmental: NOAEL= not established, the LOAEL = 5 mg/kg/day based on visceral findings (fluid-filled abdomen, pale liver, and dark content of the stomach and intestines) and alterations in skeletal development (i.e., incomplete ossification of the vertebrae and talus, and supernumerary thoracic vertebrae and 13th rib).
870.3700b Prenatal developmental - Himalayan Rabbit	46020302 (2003) 0, 50, 150, 450 mg/kg/day Acceptable/Guideline	Maternal: NOAEL= 150 mg/kg/day. LOAEL= 450 mg/kg/day based on decreased body weight body-weight gains, food consumption and increased incidences of abortion and lack of defecation. No serum tyrosine level was measured. Developmental: NOAEL= not established. LOAEL= 50 mg/kg/day based on decreased fetal weight and increased an incidence of visceral malformations, and skeletal malformations, variations, and unclassified abnormalities.
870.3700b Prenatal developmental - NZW Rabbit	46020303 (2003) 0, 0.5, 5, 50, 450 mg/kg/day Acceptable/Guideline	Maternal: NOAEL=450 mg/kg/day. LOAEL= not established. Developmental: NOAEL= 0.5 mg/kg/day. LOAEL = 5 mg/kg/day based on increased presence of 27 pre-sacral vertebrae and increased an incidence of full supernumerary 13th rib.
870.3700b Prenatal developmental - Himalayan Rabbit	46020304 (2003) 0, 50, 150, 450 mg/kg/day Acceptable/Guideline	Maternal: NOAEL=450 mg/kg/day. LOAEL= not established. Developmental: NOAEL= not established. LOAEL= 50 mg/kg/day based on an increased incidence of extra sternebral ossification sites and supernumerary 13th rib.
870.3700a Prenatal developmental - Mouse	45902208, 45902209 (2003) 0, 30, 200, 1000 mg/kg/day Acceptable/guideline	Maternal: NOAEL= not established. LOAEL= 30 mg/kg/day based on increased serum tyrosine level. Developmental: NOAEL= 1000 mg/kg/day. LOAEL= Not established.
870.3800 Reproduction and fertility effects - Rat	45902214 (2003) (0, 4, 40, 400, 4000 ppm) M: 0, 0.4, 4.2, 42.2, 426.8 mg/kg/day F: 0, 0.5, 4.6, 46.9, 471.9 mg/kg/day Acceptable/guideline	Parental/system: NOAEL= 0.4/0.5 mg/kg/day (M/F), LOAEL =4.2/4.6 mg/kg/day (M/F) based on decreased body weight, body-weight gain in males, increased thyroid and kidney weights of both sexes, and microscopic findings in eyes, kidney and thyroid of both sexes. Reproductive: NOAEL= 426.8/471.9 mg/kg/day (M/F), LOAEL= Not established Offspring: NOAEL= 0.4/0.5 mg/kg/day (M/F), LOAEL= 4.2/4.6 mg/kg/day (M/F) based on decreased pup weight and weight gain in F2 male and female pups and increased time to preputial separation in the F1 males.
870.4300 Chronic toxicity -Rat	45902217 (2002) (0, 6, 60, 600, 6000 ppm) M: 0, 0.4, 3.9, 42.0, 422.6 mg/kg/day F: 0, 0.5, 5.3, 53.2, 535.0 mg/kg/day Acceptable/guideline	NOAEL= 0.4/0.5 mg/kg/day (M/F), LOAEL= 3.9/5.3 mg/kg/day (M/F) based on corneal opacity and pannus and chronic keratitis in both sexes, and thyroid hypertrophy in males.
870.4200a Carcinogenicity -Rat	45902222 (2003) (0, 6, 60, 600, or 6000 ppm) M: 0, 0.4, 3.6, 36.4, 381.5 mg/kg/day F: 0, 0.5, 4.7, 50.8, 524.1 mg/kg/day Acceptable/Guideline	NOAEL= 0.4/0/5 mg/kg/day (M/F), LOAEL= 3.6/4.7 mg/kg/day (9M/F) based on increased incidences of corneal opacity, decreased body weight and body-weight gains (males only) and histopathological evaluations in the thyroids, pancreas, and eyes of both sexes. Neoplastic pathology showed increased incidences of follicular cell adenomas in the thyroid glands of both sexes.
870.4100b Chronic toxicity - Dog	45902215, 45902216 (2002) (0, 100, 500, 3000/2600, 9000/7800, 25000/22000 ppm). M: 0, 2.9, 15.3, 81, 248, 688 mg/kg/day F: 0, 3.1, 15.4, 92, 287, 780 mg/kg/day Acceptable/guideline	For males, NOAEL= 2.9 mg/kg, LOAEL= 15.3 mg/kg/day based on increased incidence of thyroid C-cell hyperplasia. For females, NOAEL= 15.4 mg/kg/day, LOAEL= 92 mg/kg/day based on decreased body weight, body-weight gain and food efficiency.
870.4200b Carcinogenicity - Mouse	45902221 (2002) (0, 80, 800, 8000 ppm) M: 0, 19, 194, 1903 mg/kg/day	NOAEL= not established, LOAEL= 19/26 mg/kg/day (M/F) based on decreased body weight and body-weight gains in males. No serum tyrosine level was measured. No treatment-related tumors were

Table A.2. Subchronic, Chronic and Other Toxicity Profile for Topramezone		
Guideline No/ Study Type/	MRID Nos. Doses/Classification	Results
	F: 0, 26, 256, 2467 mg/kg/day Acceptable/guideline	demonstrated.
870.5100 Gene mutation Salmonella typhimurium	45902225 (1999) Acceptable/guideline	No indication of a mutagenic response in any strain at any level up to cytotoxic concentrations either with or without S9 activation.
870.5100 Gene mutation Salmonella typhimurium	45902226 (2002) Acceptable/Guideline	No indication of a mutagenic response in any strain at any level up to cytotoxic concentrations either with or without S9 activation.
870.5100 Gene mutation Salmonella typhimurium	45902227 (2002) Acceptable/Guideline	No indication of a mutagenic response in any strain at any level up to cytotoxic concentrations either with or without S9 activation.
870.5100 Gene mutation Salmonella typhimurium	45902228 (2003) Acceptable/Guideline	Based on these considerations, it was concluded that there was confirmed evidence of a mutagenic response in S. typhimurium TA98 in the nonactivated portion of both the plate incorporation and preincubation assays. The effect was, however, observed at high concentrations (≥3000 µg/plate–plate incorporation and ≥2500 µg/plate–preincubation). It was further concluded that the mutagenic effect was likely due to impurities in the test article because: 1) the response was seen at high concentrations including and exceeding the limit dose, 2) bacterial gene mutation assays conducted with other lots of the test material were negative up to the limit dose (see MRID Nos. 45902225 through 45902227, and 3) the active ingredient (a.i.) used in the current study has the lowest percentage of purity (95.8% versus 97.7 to 99.3% a.i. for the other lots).
870.5100 Gene mutation Salmonella typhimurium	45902229 (2001) Acceptable/Guideline	No indication of a mutagenic response in any strain up to cytotoxic levels either with or without S9 activation.
870.5300 In vitro Mammalian Cell Gene Mutation	45902230 Acceptable/guideline	No indication that topramezone induced a mutagenic response, either in the presence of absence of S9 activation.
870.5375 In vitro Mammalian Chromosome Aberration	45902233 (2002) Acceptable/guideline	Topramezone-induced a clastogenic response in the presence of S9 activation with significant effects recorded only at an insoluble limit concentration.
870.5375 In vitro Mammalian Chromosome Aberration	45902232 (1999) Acceptable/guideline	Topramezone-induced a clastogenic response in the presence of S9 activation with significant effects recorded only at an insoluble limit concentration.
870.5395 In vivo Mouse Bone Morrow Micronucleus	45902234 (1999) Acceptable/guideline	No evidence that topramezone was clastogenic or aneugenic.
870.5550 UDS	45902302 (1999) Acceptable/Guideline	No evidence that topramezone-induced UDS, as determined by radioactive tracer procedures [nuclear silver grain counts] at any concentration tested.
870.6200 Acute Neurotoxicity - Rat	45902303 (2002) 0, 125, 500, 2000 mg/kg Acceptable/guideline	NOAEL= 2000 mg/kg/day, no neurotoxicity observed.
870.6200 Subchronic neurotoxicity - Rat	45902201 (2002) (0,60,600,6000 ppm) M: 0, 4.2, 43.8, 432.9 mg/kg/day F: 0, 5.0, 50.9, 510.1 mg/kg/day Acceptable/guideline	No neurotoxicity observed. Systemic NOAEL= not established, LOAEL= 4.2/5/0 mg/kg/day (M/F) based on elevated levels of granular casts and transitional epithelial cells in the urinary sediment of the males, increased incidences of corneal clouding in females, minimal diffuse degeneration of the pancreas (both sexes), and slight to moderate flaky colloid in the thyroid of the males.
870.6300 Developmental Neurotoxicity -Rat	45902304 (2003) 0, 8, 80, 800 mg/kg/day Acceptable/Non-guideline	Maternal: NOAEL= not established. LOAEL= 8 mg/kg/day based on corneal opacities. Offspring: NOAEL= not established. LOAEL= 8 mg/kg/day based on decreased auditory startle reflex response.
870.7485 Metabolism	45902305, 45902306 (2002) 1, 100, 200, 400, 500 mg/kg Acceptable/Guideline	Absorption of [14C]-topramezone following a single oral dose was rapid but limited, with the highest plasma concentrations observed at 1 hour (first time point measured). Oral absorption is estimated to be approximately 20% of the administered dose. The majority of the dose

Table A.2. Subchronic, Chronic and Other Toxicity Profile for Topramezone		
Guideline No/ Study Type/	MRID Nos. Doses/Classification	Results
		was recovered within 48 hours in the feces (73-91% dose) and urine (8-29% dose).
870.7600 Rodent In Vivo Dermal Penetration Study - Rat	45902307 (2002) Doses 0, 0.004, 0.068, or 3.36 mg ai/cm2.	The majority of the applied dose for each group was not absorbed (91.0-98.3% dose), with the greatest amount of the non-absorbed material being recovered from the skin wash (90.8-96.0% dose). Absorbed radioactivity was low and accounted for 0.16-2.60% of the dose for all groups for all exposures.

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

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