UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 14-JULY-2005

SUBJECT: **Topramezone/BAS670H**: Amendment to the Human Health Risk Assessment for New Active Ingredient Dated May 11 For Uses Proposed on Field, Pop, Seed and Sweet Corn (DP290075). PC Code: 123009, DP319704. Petition No. 3F6568.

Regulatory Action: Section 3/New Active Ingredient
Risk Assessment Type: Single Chemical Aggregate

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The following risk assessment supercedes the risk assessment dated May 11 (D290075). The following assessment includes revisions to the FQPA and Cumulative sections.

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; BAS 670 336 (soluble concentrate (SC) Herbicide] to field, seed, sweet and pop corn.

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed uses of topramezone on corn (field, seed, sweet and pop).

A summary of the findings and an assessment of human risk resulting from the proposed uses of topramezone is provided in this document. The risk assessment was provided by Mary Clock-Rust (RAB1), the residue chemistry review and dietary exposure assessment were provided by George Kramer (RAB1), the hazard characterization was provided by Yung Yang (Toxicology Branch), the occupational/residential exposure assessment was provided by Mark Dow (RAB1), and the drinking water assessment was provided by Silvia Termes and James Wolf of the Environmental Fate and Effects Division (EFED).

1.0 Executive Summary

Background

Topramezone, also known as BAS670H, is a broad-spectrum, post-emergence herbicide used to control grassy and broadleaf weeds in corn. The herbicide is absorbed by the leaves, roots and shoots, then translocated to the growing points of the sensitive weeds. Topramezone belongs to the phenylpyrazolyl ketone class of chemicals. It inhibits the 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) enzyme and thereby impairs carotenoid biosynthesis in the chlorophyll synthesis pathway, ultimately leading to the breakdown of chloroplasts. The maximum seasonal use rate is 0.022 lb/ai/acre. There is a maximum of two applications at the lowest application rate (at least one week apart) per season. The application rate ranges from 0.011 to 0.022 lb ai/acre. The product controls both broadleaf and grass weeds in all corn types (field, pop, seed and sweet) with a 45-day pre-harvest interval (PHI). There are no proposed residential uses.

This risk assessment is a joint review with the Pesticide Management Regulatory Agency (PMRA) of Health Canada and HED.

There are no existing tolerances, registered uses (including agricultural or residential uses) or exemptions for topramezone.

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. 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 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.

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 no-observed adverse effect level (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.

The uncertainty factors used in determining the RfD were 100 (10x for intraspecies variation and 10x for interspecies extrapolation). The level of concern for all non-dietary exposure durations (short-, intermediate- and long-term) is 100. Based on toxicological considerations, and the assumptions used in the exposure assessments, the topramezone risk assessment team determined that a 1x special FQPA safety factor was appropriate.

Dietary-Exposure Assessment
The Tier 1 acute dietary analysis assumed 100% crop treated (CT), Dietary Exposure Evaluation Model (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 peak concentration for surface water generated by the PRZM (Pesticide Root Zone Model)-EXAMS (Exposure Analysis Modeling System) model as a high-end estimate. As an endpoint of concern attributable to a single dose was not identified in the hazard database for the general population (including infants and children), the acute risk analysis was performed only for the population females 13-49 years of age. The resulting acute dietary exposure and risk estimates (food + water) using the DEEM-FCID™ model at the 95th percentile were 0.000068 mg/kg/day (1.4% of the aPAD) and are thus below HED's level of concern (<100% aPAD).

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 risk estimates were less than 1.2% of the cPAD for the U.S. population and all population subgroups. The chronic dietary exposure and risk estimates (food + water) using the DEEM-FCID™ model were 0.000023 mg/kg/day for the U.S. population (0.6% of the cPAD) and 0.000050 mg/kg/day (1.2% of the cPAD) for the most highly exposed population subgroup (children 3-5 years old) and are thus below HED's level of concern (<100% cPAD).

Aggregate Risk
No residential uses are proposed for topramezone at this time. Therefore, aggregate risk consists of exposure from food and drinking water sources only. Acute (for females 13-49 years old only) and chronic aggregate risks were assessed by incorporating the drinking water directly into the dietary exposure assessment. Risk estimates are reported above under *Dietary Exposure Assessment.* Acute and chronic aggregate risks do not exceed HED's level of concern.

Occupational Risk
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) Aerial applicator (pilot).

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 Pesticide Handlers 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.

Short- and intermediate-term risks were estimated for handlers and postapplication workers. An adjusted dermal-absorption factor of 13% was used to calculate occupational risks. HED assumed 100% inhalation absorption.

Provided that mixer/loaders use protective gloves as specified on the proposed label, all margins

of exposure (MOEs) are ≥100 and therefore do not exceed HED's level of concern.

There is a potential for agricultural workers to have post-application exposure to pesticides during the course of typical agricultural activities. Based upon the proposed use pattern (early post-emergence) for topramezone, HED used the transfer coefficient (TC) of 400 cm^2/hr for scouting or irrigation activities for postapplication risk assessment.

Lacking compound-specific dislodgeable foliar residue (DFR) data, HED assumes 20% of the application rate is available as DFR on day zero after application, adapted from the Science Advisory Council for Exposure (ExpoSAC) SOP No. 003 (7 May 1998 - Revised 7 August 2000). The estimated MOE for postapplication workers is 1,400 and does not exceed HED's level of concern.

HED Recommendations

Provided a revised Section F is submitted and HED validations of the proposed plant and livestock analytical enforcement methods are successful, HED concludes there are no residue chemistry, toxicology or occupational/residential exposure data requirements that would preclude the establishment of an unconditional registration and permanent tolerances for residues of topramezone *per se* in/on the following RACs:

Corn, field, forage	0.05 ppm	Corn, sweet, forage	0.05 ppm
Corn, field, grain	0.01 ppm	Corn, sweet, kernel plus cob with husks removed	0.01 ppm
Corn, field, stover	0.05 ppm	Corn, sweet, stover	0.05 ppm
Corn, pop, grain	0.01 ppm	Cattle, kidney*	0.05 ppm
Corn, pop, stover	0.05 ppm	Cattle, liver*	0.15 ppm

* includes: goat, horse, and sheep

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

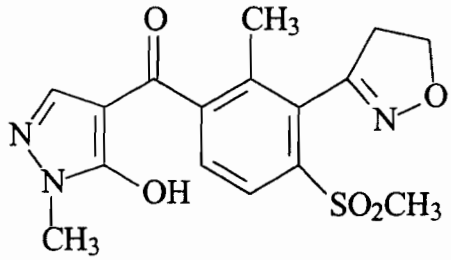
Table 2.1 Summary of Directions for Use of Topramezone.

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)	PHI (days)	Use Directions and Limitations
Field Corn, Popcorn, Seed Corn, Sweet Corn						
Post-emergent, Ground (ground equipment; flat nozzles) Aerial	BAS 670 336SC Post-emergent Corn Herbicide [7969-pending]	0.011 - 0.022 (12.35 - 24.7 g/ha)	2	0.022 (24.7 g/ha)	45 (forage, silage, fodder, grain)	Split applications (2) are allowed, but not to exceed 0.022 lb ai/A per growing season and allowing 7 days between sequential applications. An adjuvant AND a nitrogen fertilizer source are required to achieve optimum weed control. Plantback Restrictions: **Anytime**: All field corn types, field corn grown for seed, sweet corn, popcorn. **3 Months**: Cereal crops (wheat, barley, oats and rye, winter canola). **9 Months**: Alfalfa, cotton, canola, peanuts, sorghum, soybeans, sunflower, edible beans and peas, potato. **18 Months**: All crops not listed above.

PHI = preharvest interval

2.2 Structure and Nomenclature

Table 2.2 Topramezone Nomenclature

Compound	
Common name	Topramezone
Company experimental name	BAS 670 H
IUPAC name	[3-(4,5-dihydro-1,2-oxazol-3-yl)-4-mesyl-*o*-tolyl](5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone
CAS name	[3-(4,5-dihydro-3-isoxazolyl)-2-methyl-4-(methylsulfonyl)phenyl](5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone
CAS #	210631-68-8
End-use product/EP	Soluble Concentrate
Known Impurities of Concern	none

2.3 Physical and Chemical Properties

Table 2.3 Physicochemical Properties of Topramezone

Parameter	Value
Melting point/range	220.9°C - 222.2°C
pH	2.9 (1% deionized water)
Density (20°C)	1.425 g/cm^3
Water solubility (20°C)	pH: 3, 5, 7, 9 g/L: 0.06, 0.98, 15, 23.4
Solvent solubility (g/100 mL at 20°C)	Acetone <1.0 Acetonitrile <1.0 Dichloromethane 2.5 - 2.9 Ethyl acetate <1.0 Methanol <1.0 N-heptane <1.0 N,N-dimethylformamide 11.4-13.3 1-octanol <1.0 Olive oil <1.0 2-propanol <1.0 Toluene <1.0
Vapor pressure at 20°C and 25°C	< 1.0 x 10^{-12} hPa
Dissociation constant (pK_a)	4.06
Octanol/water partition coefficient Log(K_{OW}) at 20°C	Buffer pH: 4, 7, 9 Log K_{ow}: - 0.81, - 1.52, - 2.34
UV/visible absorption spectrum	λ, nm: 207, 272, 300, 410 ξ, mol^{-1}cm^{-1}: 27 077, 8601, 5800, 410

All data came from PMRA Lab Services.

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

The results of the topramezone metabolism studies in corn, rat, ruminants and poultry were similar in that the parent compound was not extensively metabolized. However, significant differences were observed in the metabolic pathways (see figure A-3.1.0 of Appendix 3.0). **In corn**, topramezone underwent hydrolytic cleavage to form the acid metabolite M670H05 and M670H08, while desmethylation formed M670H03. After cleavage, the pyrazole ring appeared to undergo complete catabolism and reincorporation within the carbon backbone of natural products such as starch, soluble polysaccharides and fatty acids. The phenyl ring portion of the molecule also underwent degradation, resulting in the incorporation of radioactivity into natural products. **In ruminants**, the proposed metabolic pathway involved hydroxylation of the parent compound topramezone at the 4-position of the isoxazole ring to form M670H02. The isoxazole

ring was then cleaved to form the cyano metabolite (M670H01). The linkage between the phenyl and pyrazole rings remained intact in all of the metabolites identified. **In poultry**, the proposed metabolic pathway also involved hydroxylation of the parent compound topramezone at the 4-position of the isoxazole ring to form M670H02. Further N-demethylation of M670H02 occurred and formed the desmethyl hydroxy metabolite M670H04. M670H04 was only detected in the phenyl-labeled liver. The pyrazole ring of topramezone could also be cleaved to form the acid metabolite M670H05. **In rats**, the proposed metabolic pathway involved hydroxylation of the parent compound topramezone at the 4-position of the isoxazole ring to form M670H02. The isoxazole ring was then cleaved to form the cyano metabolite (M670H01). The pyrazole ring of topramezone could also be cleaved to form the acid metabolite M670H05. Similar metabolic pathways were also observed in **rotational crops**, with M670H05 and M670H02 being the only metabolites identified. The isoxazole ring of topramezone was not radiolabeled in any study; however, these data are not required as the isoxazole ring was not cleaved from the phenyl ring in any of the proposed metabolic pathways.

3.2 Nature of the Residue in Foods

3.2.1 Description of Primary Crop Metabolism

The metabolism of topramezone in corn involved the hydrolytic cleavage of the parent to form the acid metabolite M670H05. Further hydrolysis and cleavage resulted in the formation of M670H08, while desmethylation resulted in M670H03. After cleavage, the pyrazole ring appeared to undergo complete catabolism and reincorporation within the carbon backbone of natural products such as starch, soluble polysaccharides and fatty acids. The phenyl ring portion of the molecule also underwent degradation, resulting in the incorporation of radioactivity into natural products.

3.2.2 Description of Livestock Metabolism

The metabolic profiles of topramezone in goats were similar between the pyrazole and phenyl treatment groups. The proposed metabolic pathway proceeded from the hydroxylation of the parent compound topramezone at the 4-position of the isoxazole ring to form M670H02. The isoxazole ring was then cleaved to form the cyano metabolite (M670H01). The linkage between the phenyl and pyrazole rings remained intact in all of the metabolites identified.

The metabolic pathway of topramezone in hens proceeded from the hydroxylation at the 4-position of the isoxazole ring to form the hydroxy metabolite M670H02. Further N-demethylation of M670H02 occurred and formed the desmethyl hydroxy metabolite M670H04. M670H04 was only detected in the phenyl labeled liver. The pyrazole ring of topramezone could also be cleaved to form the acid metabolite M670H05.

3.2.3 Description of Rotational Crop Metabolism, including identification of major metabolites and specific routes of biotransformation

The proposed metabolism of topramezone involved the hydrolysis of the parent to form the free acid M670H05. The pyrazole moiety was catabolized after cleavage, then reincorporated into

natural products (as seen in the corn metabolism study). Parent-related adducts were formed from the des-methylation of the pyrazole ring. Hydroxylation of the isoxazole ring formed M670H02 (as seen in the goat metabolism study), then reincorporation into natural products occurred after further ring degradation.

3.3 Environmental Degradation

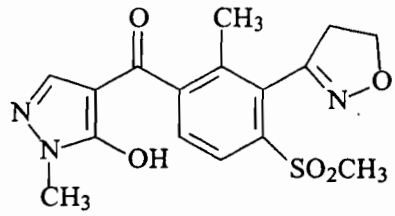
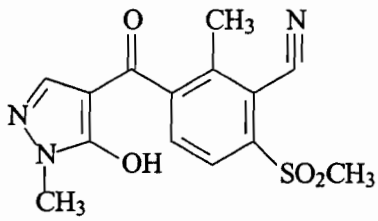
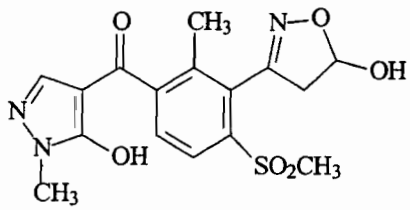
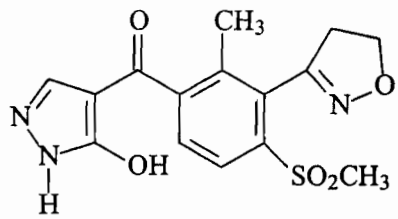
Abiotic hydrolysis and direct photolysis in water are not important transformation pathways for topramezone in the environment, but biotransformation is. However, extensive variability in persistence of topramezone, as well as type and relative ratio of biotransformation products, were found in six aerobically-incubated soils. The half-lives of topramezone in all of these soils were higher than 125 days. The major soil metabolite in some soils was M670H0 (BAS 670 Acid), but at less than 15% maximum of the applied radioactivity at the conclusion of a 1-year study. Some mineralization of topramezone (as evidenced by $^{14}CO_2$ formation) was observed in some of the aerobic soils. In other soils, M670H05 was only a minor metabolite. Only in one soil (Idaho loam), the metabolite M670H01 was observed above 15%, but at less than 10% in most soils. Like topramezone, M670H05 is a weak acid and persistent (> 350 days). The amount of non-extractable residues in soils (and sediments) increased with time, suggesting that time-dependant sorption competes with biotransformation and might be an important dissipation route for topramezone.

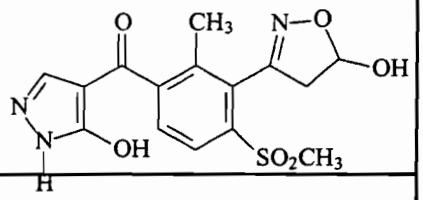
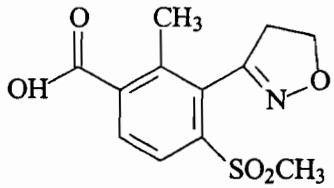
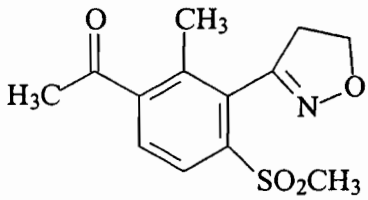
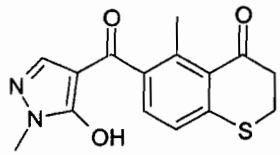
Like in aerobic soils, the persistence of topramezone in two aerobic aquatic systems was variable, as suggested by the half-life. In one system (pond water), the half-life in the aqueous column was 11 days and 44-77 days in the sediment, but persisted for >120 days in a river water-sediment system. The major metabolite was M670H01 (10.2%). This metabolite was predominantly associated with the sediment. In another system (pond water), the half-life was >120 days in water and sediment and no major metabolites were observed. However, there were major differences in physical and chemical composition of the river water-sediment and the pond water-sediment, but it is not clear which property might be responsible for the observed differences in topramezone persistence.

In water-sediments incubated under anaerobic conditions, topramezone degraded slightly faster than under aerobic conditions (11 days in water, 7-15 days in sediment, and 13 days in total system). The major degradate was M670H10, at 16% in water, 26-34% in sediment. This degradate was only found water-sediment under anaerobic conditions. Reduction of the sulfonyl group, S(VI) to a sulfide (thioether; oxidation state S(-II)) is consistent with the type of reactions that can take place in anoxic media.

3.4 Tabular Summary of Metabolites and Degradates

Table 3.4 Tabular Summary of Metabolites and Degradates

Chemical Name (other names in parentheses)	Commodity	Percent TRR (PPM) [1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
Parent Topramezone	Corn	41	-	
	Rotational Crops	64	-	
	Ruminant	83	-	
	Poultry	64	-	
	Rat	83	-	
	Water	persistent		
M670H01	Corn	Not Reported (NR)		
	Rotational Crops	NR		
	Ruminant	-	2.6	
	Poultry	NR		
	Rat	14	-	
	Water	15	-	
M670H02	Corn	NR		
	Rotational Crops	-	4.3	
	Ruminant	30	-	
	Poultry	30	-	
	Rat	35	-	
	Water	NR		
M670H03	Corn	-	4.2	
	Rotational Crops	NR		
	Ruminant	NR		
	Poultry	NR		
	Rat	NR		
	Water	NR		

Chemical Name (other names in parentheses)	Commodity	Percent TRR (PPM)[1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
M670H04	Corn	NR		
	Rotational Crops	NR		
	Ruminant	NR		
	Poultry	-	2.4	
	Rat	NR		
	Water	NR		
M670H05	Corn	10		
	Rotational Crops	45		
	Ruminant	NR		
	Poultry	-	6.3	
	Rat	-	<10	
	Water	34	-	
M670H08	Corn	-	4.6	
	Rotational Crops	NR		
	Ruminant	NR		
	Poultry	NR		
	Rat	NR		
	Water	NR		
M670H10	Corn	NR		
	Rotational Crops	NR		
	Ruminant	NR		
	Poultry	NR		
	Rat	NR		
	Water	16	-	

[1] The maximum % TRR (total radioactive residue) found in any fraction is reported for each commodity.
Corn, 45902401; 0.132 lb a.i./A; 6X rate; 3-5 leaf growth stage; 59-70 day PHI.
Hens, 45902403, 12.3 - 13.4 mg/kg; 1500 - 1700X; 10 days; 21-23 hour PSI.
Goats; 45902402; 9.9 - 11.2 mg/kg; 130 - 150X MTDB; 5 days; 21-23 hour PSI.
Rotational Crops; 45902413; 3.3-3.7X, applied to bare soil;34-99 day PBI
Rat Metabolism; 10, 100, 200, 400, or 500 mg/kg gavage dose; Wistar.

3.5 Toxicity Profile of Major Metabolites and Degradates

Toxicity data on the major metabolites are not available. The metabolites M670H01, M670H02, M670H03, M670H04 and M670H10 have molecular-structural features for chemicals that behave as 4-HPPD inhibitors: at least 2-keto groups and one as a stable enolate and attachment to a substitute benzoyl group (Silvia Termes, Personal Communication). For M670H01, the cyano group also has the potential to bind to the Fe(II) site of the enzyme, but in competition with the diketonato ligand. HED thus assumed that the toxicity of the M670H01, M670H02, M670H03, M670H04 and M670H10 metabolites is equivalent to that of the parent. M670HO5, a cleavage product, does not have all of these features and is not expected to behave as an 4-HPPD inhibitor.

3.6 Summary of Residues for Tolerance Expression and Risk Assessment

3.6.1 Tabular Summary

Table 3.6.1 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Corn	Topramezone	Topramezone
	Rotational Crops	Topramezone	not required
Livestock	Ruminant	Topramezone	Topramezone
	Poultry	tbd*	tbd
Drinking Water		Topramezone	Not Applicable

*To be determined. Note: if future proposed uses significantly increase the dietary exposure to poultry, then the poultry feeding study should include analysis for metabolite M670H02.

3.6.2 Rationale for Inclusion of Metabolites and Degradates

Corn: Topramezone is the predominant residue in corn. M670H05 is a major metabolite in corn stover. The toxicity of M670H05 is expected to be less than the parent compound (see section 3.5). Also, this metabolite can be excluded as a residue of concern as it was not found (<limit of quantitation (LOQ)) in any sample from the field residue trials.

Rotational Crops: Topramezone and M670H05 are the predominant residues in rotational crops. As a result of the proposed plantback restrictions, residues in rotational crops are not expected to result from the proposed uses.

Livestock: Topramezone is the predominant residue in livestock RACs. M670H02 is a major metabolite in cattle liver and poultry liver and eggs. The toxicity of M670H02 is expected to be comparable to the parent compound. However, this metabolite can be excluded as a residue of concern in ruminants as it was not found (<LOQ) in all samples from the cow feeding study. The

petitioner did not submit a poultry feeding study with this petition. As there is no reasonable expectation of finite residues (180.6(a)(3)) in poultry RACs, the residues of concern in poultry tissues and eggs have not been determined. However, if future proposed uses significantly increase the dietary exposure to poultry, then the poultry feeding study should include analysis for metabolite M670H02.

Drinking Water: Topramezone and M670H05 are the predominant residues in water. The toxicity of M670H05 is expected to be less than the parent compound (see Section 3.5). Metabolite M670H02 can be excluded as a residue of concern as it was less than 10% in most soils and its inclusion would not significantly effect the estimated water concentrations due to the long half-life of the parent compound. Metabolite M670H10 can be excluded as a residue of concern as it was found only in anaerobic water-sediment systems. Therefore, the residue of concern in drinking water is topramezone.

4.0 Hazard Characterization/Assessment

4.1 Hazard and Dose-Response Characterization

4.1.1 Database Summary

4.1.1.1 Studies Available and Considered

Acute: Acute neurotoxicity study in rats.
Subchronic: 28-day dermal study in rats, subchronic oral toxicity in rats, mice and dogs, and subchronic neurotoxicity studies in rats.
Chronic: One-year chronic toxicity in dogs, two-year chronic toxicity in rats, two-year carcinogenicity in rats, and 18-month carcinogenicity in mice.
Reproductive/Developmental: Two-generation reproductive toxicity in rats, developmental studies in mice, rats, and rabbits, and developmental neurotoxicity in rats.
Other: General rat metabolism, mutagenicity screens and a dermal-absorption study in rats.

4.1.1.2 Mode of Action, Metabolism, Toxicokinetic Data

Topramezone (BAS 670H), belongs to a family of phenylpyrazolyl ketone herbicides, is a broad-spectrum, post-emergence herbicide used to control grassy and broadleaf weeds in corn. Its mechanism of action is described as an inhibitor of the 4-HPPD enzyme and thereby impairing carotenoid biosynthesis in the chlorophyll synthesis pathway, ultimately leading to the breakdown of chloroplasts. In mammals, the inhibition of the 4-HPPD enzyme resulted in elevated tyrosine levels (tyrosinemia) which was observed in treated rats, rabbits and mice with rats as the most sensitive species. There is a concern about the elevated tyrosine levels on the developing nervous system in children with tyrosinemia type three (an inherited disease of an autosomal recessive disorder in which a deficiency of the 4-HPPD enzyme resulted in high

plasma tyrosine level (Ruetschi *et al.*, 2000)[1]. However, there are no data to determine what increase in levels of serum tyrosine causes adverse effects. It has been shown that the enzyme activities involved in tyrosine metabolism in humans are very similar to those in mice; whereas, the rat is significantly different (Mechanism of Toxicity Science Assessment Review Committee Report, TXR No. 0051908, March 27, 2001). Primary target organs of elevated tyrosine levels have been observed to be the eyes (corneal opacity, keratitis), livers (↑ liver weight, liver cell hypertrophy), kidneys (↑ kidney weight), pancreas (diffuse degeneration), and thyroids (follicular cell hypertrophy and hyperplasia). Metabolism studies in rats showed that following oral administration the absorption of topramezone is rapid but limited. Oral absorption is estimated to be approximately 20% of the administered dose. The majority of the absorbed dose was excreted within 48 hours in the feces and urine. Parent was the predominant component identified in both feces and urine, four other major metabolites also were identified.

4.1.1.3 Sufficiency of Studies/Data

Data are sufficient for each exposure scenario, FQPA evaluation, dose-response evaluation and for important endpoint selection.

4.1.2 Toxicological Effects

Topramezone has a low acute toxicity *via* the oral, dermal, or inhalation route. It is a slight eye and dermal irritant but is not a skin sensitizer. Following oral administration of topramezone is rapid but limited. 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 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.

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[1]Ruetschi, U. *et al* (2000). Mutations in the 4-hydroxyphenylpyruvate dioxygenase gene (HPPD) in patients with tyrosinemia type III. Hum. Genet. 106(6): 654-662.

4.1.3 Dose-Response

There is a concern about the elevated tyrosine levels observed in treated rats and mice with the rat as the most-sensitive species. However, no data could determine at what level increases of tyrosine levels would result in detrimental (adverse) effects. Therefore, the endpoints selected for the various exposure scenarios are based on critical tyrosine-mediated effects. 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 evaluations 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 evaluations. 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 NOAEL was 0.5 mg/kg/day using a dermal-absorption factor of 13%. 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).

4.1.4 FQPA

The hazard database is adequate to characterize the potential for prenatal or post-natal exposure and risk for infants and children. Increased incidences of skeletal variations, supernumerary ribs and alterations in skeletal ossifications sites were observed in rat and rabbit developmental toxicity studies. It has been shown that skeletal variations are associated with 4-HPPD inhibitor herbicides (mesotrione and isoxaflutole). There is a potential of increased quantitative susceptibility following *in utero* and/or pre-/post-natal exposure in the developmental toxicity

and developmental neurotoxicity studies in rats because a NOAEL for parental or offspring systemic toxicity was not established. However, the current NOAEL of 0.5 mg/kg/day for an acute RfD would provide a 200-fold lower dose based on the most sensitive endpoint. In a developmental neurotoxicity (DNT) study in rats, decreased auditory startle reflex was seen at the LOAEL of 8 mg/kg/day in the presence of maternal toxicity manifested as corneal opacity. Therefore, the susceptibility in this study could not be assessed. However, the NOAEL for the chronic RfD is 0.4 mg/kg/day based on the most critical tyrosine-mediated effects which is 20-fold lower than the LOAEL for the DNT study. There is no evidence of increased susceptibility following pre-/post-natal exposure to rats in the two-generation reproduction study. The degree of concern is low for the quantitative susceptibility because the risk assessment was based on the most sensitive endpoint. There are no concerns or residual uncertainties for pre- and post-natal toxicity. Based on the hazard data, the risk assessment team recommended that the special FQPA Safety Factor for pre- and/or post-natal toxicity be reduced to 1x (see details below under Section 4.2.6.1).

Table 4.1.4.1 Acute Toxicity Profile on Topramezone

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	--

Table 4.1.4.2 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 o 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/d 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/da 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 bas 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.

Guideline No./ Study Type/	MRID Nos. Doses/Classification	Results
870.3700b Prenatal developmental - NZW Rabbit	45902213 (2003) 0, 1.5, 5.0 mg/kg/day Acceptable/Non-guideline	Maternal: NOAEL= 5.0 mg/kg/day. LOAEL was not establishe Developmental: NOAEL= not established, the LOAEL for N33 and N17/CFR 1-2 was 1.5 mg/kg/day based on increased presen of supernumerary thoracic vertebrae and supernumerary 13th rib. No effect was observed for N17/CFR 3 at 0.5 mg/kg/day (the on 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 the vertebrae and talus, and supernumerary thoracic vertebrae an 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/d 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 F_2 male and female pups and increased time to preputial separation in the F_1 males.

Guideline No./ Study Type/	MRID Nos. Doses/Classification	Results
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 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 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 F: 0, 26, 256, 2467 mg/kg/day Acceptable/guideline	NOAEL= not established, LOAEL= 19/26 mg/kg/day (M/F) bas on decreased body weight and body-weight gains in males. No serum tyrosine level was measured. No treatment-related tumors were demonstrated.
870.5100 Gene mutation *Salmonella typhimurium*	45902225 (1999) Acceptable/guideline	No indication of a mutagenic response in any strain at any level 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 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 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 th 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 mutatio assays conducted with other lots of the test material were negativ up to the limit dose (see MRID Nos. 45902225 through 4590222 and 3) the active ingredient (a.i.) used in the current study has th lowest percentage of purity (95.8% versus 97.7 to 99.3% a.i. for the other lots).

Guideline No./ Study Type/	MRID Nos. Doses/Classification	Results
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 insolub 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 insolub 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 bas 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 [^{14}C]-BAS 670H following a single oral dose was rapid but limited, with the highest plasma concentrations observe at 1 hour (first time point measured). Oral absorption is estimate to be approximately 20% of the administered dose. The majorit of the dose was recovered within 48 hours in the feces (73-91% dose) and urine (8-29% dose).

Guideline No./ Study Type/	MRID Nos. Doses/Classification	Results
870.7600 Rodent *In Vivo* Dermal Penetration Study - Rat	45902307 (2002) Doses 0, 0.004, 0.068, or 3.36 mg ai/cm^2.	The majority of the applied dose for each group was not absorbe (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% o the dose for all groups for all exposures.

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

A toxicology database for topramezone is available for FQPA consideration. The following studies are available:

- Developmental toxicity studies in mice, rats and rabbits (acceptable).
- Two-generation reproduction study in rats (acceptable).
- Acute and subchronic neurotoxicity studies in rats (acceptable).
- Developmental neurotoxicity study in rats (acceptable).

4.2.2 Evidence of Neurotoxicity

There is no evidence of neurotoxicity resulting from exposure to topramezone.

4.2.2.1 Acute Neurotoxicity

In an acute oral neurotoxicity study (MRID 45902303), topramezone (95.8% a.i., Batch/Lot # N26) in 0.5% carboxymethylcellulose was administered in a single dose by gavage (10 mL/kg) to non-fasted Wistar rats (10/sex/dose) at doses of 0, 125, 500, or 2000 mg/kg (limit dose). All animals were observed for up to 14 days post-dosing. FOB and motor activity were evaluated pretreatment and on Days 0 (at approximately one hour post-dosing), 7, and 14. At termination, five rats/sex/group were perfused *in situ* for neurohistological examination. Positive control data were provided.

No compound-related effects on mortality, clinical signs, body weight, body-weight gain, FOB, motor activity, or gross and histopathology were observed at any dose in either sex.

No evidence of neurotoxicity was observed. The NOAEL was 2000 mg/kg (limit dose). The lowest-observed adverse effect level (LOAEL) was not observed.

The submitted study is classified as **acceptable/guideline** and satisfies the Guideline requirements for an acute neurotoxicity screening battery in rats.

4.2.2.2 Subchronic Neurotoxicity

In a subchronic neurotoxicity study (MRID 45902201), topramezone was administered in the diet

to Wistar rats (15/sex/group) at doses of 0, 60, 600, or 6000 ppm (equivalent to 0/0, 4.2/5.0, 43.8/50.9, or 432.9/510.1 mg/kg/day [M/F]) for 13 weeks. FOB and motor activity were evaluated on Days -7 (prior to dosing), 22, 50, and 85. At termination, five rats/sex/group were perfused *in situ,* and tissues from the control and 6000 ppm (M/F) groups were examined microscopically. Positive control data were provided.

No treatment-related effects on mortality, body weight, body-weight gain, food consumption, FOB, locomotor activity, hematology, clinical chemistry, and neuropathology parameters were observed.

The neurotoxicity LOAEL was not observed. The neurotoxicity NOAEL is 6000 ppm (equivalent to 432.9/510.1 mg/kg/day [M/F]). There was no evidence of neurotoxicity at any dose tested.

For systemic toxicity, the target organ was the eye. During clinical observations, corneal opacity was observed in males at 600 ppm and in females at 6000 ppm beginning on Day 86. Ophthalmoscopic examinations revealed following treatment-related ocular lesions (# affected/10 vs. 0 controls, unless otherwise stated): (i) striation of lenses in the 6000 ppm males (four treated vs. 1 control); (ii) corneal clouding in the ≥600 ppm males (two each dose) and in the ≥60 ppm females (three each dose); (iii) vascularization of the cornea in the 600 ppm males (2) and the ≥600 ppm females (1-2); and (iv) fundus not visible in the 600 ppm males (2) and the ≥600 ppm females (one each dose). Necropsy findings (# affected vs. 0 controls) were limited to cloudiness in the cornea noted at 600 ppm in the perfused males and females (1/5 treated each), and in the non-perfused males (2/10 treated). In the perfused animals, neuro- and histopathological effects (# affected/5 vs. 0 controls) were limited to chronic keratitis in one 600 ppm male and in the ≥600 ppm females (2-3). Similarly in the non-perfused animals, histopathological effects (# affected/10 vs. 0 controls) were limited to minimal to severe chronic keratitis in the ≥600 ppm males (two each) and females (3-4). It was stated that the mode of action of the test material is inhibition of the enzyme p-hydroxyphenylpyruvate-dioxygenase, an enzyme involved in tyrosine catabolism in animals, and furthermore, the effects in the eyes were likely correlated to the increased tyrosine levels in the blood, a feature that is inherent to the type of chemicals to which the test material belongs.

Urinalyses showed an increased incidence (# affected/10) of elevated levels of granular casts (three each dose), and transitional epithelial cells (4-5 treated vs. 1 control) in the urinary sediment of ≥60 ppm males. Additional kidney effects were observed in the 6000 ppm males which included increased absolute (20%) and relative (to body, 23%) kidney weight, and one male showed severe chronic nephropathy. These findings are indicative of renal dysfunction and kidney damage.

Increased relative (to body) liver weights were observed ($p \leq 0.01$) in the ≥60 ppm males (↑11-21%) and in the ≥60 ppm females (↑6-9%). However, there was no dose-response at these doses. Additionally, minimal diffuse degeneration of the pancreas in the males (5-6 treated vs. 1 control) and females (3-4), and slight to moderate flaky colloid in the thyroid of the males (9-10) were also observed.

The systemic LOAEL is 60 ppm (equivalent to 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. The systemic NOAEL was not established.

The study is classified as **acceptable/guideline** and satisfies the guideline requirements (870.6200b) for a subchronic neurotoxicity study in the rat.

4.2.2.3 Developmental Neurotoxicity Study in Rats

In a developmental neurotoxicity study (MRID 45902304), topramezone was administered in the diet to pregnant Wistar rats (38-39/dose) from gestation day (GD) six to post-natal day (PND) 21 at nominal doses of 0, 8, 80, or 800 mg/kg/day (actual doses were 0/0, 8.2/6.7, 83.7/69.6, and 848.6/739.1 mg/kg/day [gestation/lactation]). Dams were allowed to deliver naturally and were killed on lactation day (LD) 21. On PND 4, at least twenty-two litters of appropriate size (≥eight pups/litter) were available. These litters were standardized to eight pups/litter; the remaining offspring and dams were sacrificed and discarded without further examinations. Subsequently, 10 pups/sex/group were allocated to subsets 1-6 for neurobehavioral testing and neuropathological examination.

For maternal toxicity, clinical observations such as opacities of the cornea indicating general toxicity were noted in parental females of all dose groups. Food consumption and body weights/ body-weight gain were temporarily lowered in the mid (80 mg/kg body weight/day) and high-dose (800 mg/kg body weight/day) dams during gestation and/or lactation. There are no indications from the clinical examinations, that the administration of the test substance had adverse effects on reproductive performance of the parental females. Conception, gestation, parturition, lactation and weaning were comparable between the test substance treated rats and the corresponding control.

The maternal LOAEL is 8 mg/kg/day based on corneal opacities. The maternal NOAEL was not established.

For offspring, no significant treatment-related differences in live litter size, post-natal survival, or sex ratios were observed in any treated group through PND 21. Clinical signs were limited to corneal opacity in both sexes at 80 mg/kg (1/sex) and 800 mg/kg (3/sex). Throughout pre-weaning (Days 4-21), body weights were decreased in both sexes at ≥80 mg/kg (↓8-15%). Likewise, overall (Days 4-21) pre-weaning body-weight gain was decreased in both sexes at ≥80 mg/kg (↓15-17%). Throughout post-weaning, body weights were decreased in the ≥80 mg/kg males (↓7-19%) and females (↓6-20%); however, the differences became less over time. Body-weight gains were decreased in the ≥80 mg/kg males during weeks 0-2 (↓12-15) and weeks 3-4 (↓9-12), and in the ≥80 mg/kg females during weeks 0-1 (↓10-13%). Overall (weeks 0-5) body-weight gains were slightly decreased in the ≥80 mg/kg males (↓9% each); however, overall gains were similar between treated females and controls. Food consumption was not reported for the F_1 animals.

A slight delay ($p \leq 0.01$) in time to preputial separation was noted at 80 (45.6 days) and 800 mg/kg (46.3 days) compared to controls (43.6 days). No treatment-related effect on time to vaginal patency was observed.

For behavioral assessments, no treatment-related effects were observed in FOB. Motor activity did not show significant differences from controls in overall session of cumulative distance or number of rears in either sex at any dose. Habituation was unaffected by treatment.

For auditory startle reflex response, the average maximum amplitude (over all five blocks) was decreased on PND 24 compared to controls in the 8 mg/kg/day (↓30%, ↓22%), 80 mg/kg (↓27%, ↓34%), and 800 mg/kg (↓38%, ↓54%) for males and females, respectively. No significant differences from control were noted in startle response maximum amplitude at any dose in either sex on PND 60. On PND 24, latency was increased ($p \leq 0.05$) in the 800 mg/kg females during Blocks 3 & 4 (↑31-34%); however, no significant increase was observed in the average latency (over all five blocks). Additionally, latency was increased by 26-27% in the 8 mg/kg females during blocks 3 and 4. No significant differences in latency (individual blocks or overall) were observed in the males on PNDs 24 or 60, or in the females on PND 60. No treatment-related differences in learning or memory were noted in any treated group relative to concurrent controls in the water maze test. The decrease ($p \leq 0.01$) in relearning noted in the 80 mg/kg females of Subset 6 was considered unrelated to treatment because it was not dose-dependent.

For postmortem examination, absolute brain weights on PND 22 were decreased ($p \leq 0.01$) at ≥80 mg/kg in the males (↓7% each) and in the females (↓12-13%). Relative (to body) brain weights were increased ($p \leq 0.01$) at ≥80 mg/kg in the males (↑8-9%) and in the females (↑9-14%). On PND 62, absolute brain weights were decreased ($p \leq 0.01$) at ≥80 mg/kg in the males (↓5-6%) and in the females (↓6% each); however, these findings were considered unrelated to treatment because they were minor and not dose-dependent. Similarly the findings noted in the 8 mg/kg groups on both PND 22 and 62 were considered unrelated to treatment. Relative (to body) brain weights were similar between treated and control groups in both sexes on PND 62.

Microscopic examination revealed increased incidences (# affect/10 vs. 0/10 controls) of minimal to moderate, bi- or unilateral keratitis of the cornea in both sexes on PND 22 at 8 (one male), 80 (3/sex) and 800 mg/kg (10/sex). No adverse histopathological evaluations were noted in any group at PND 62. Numerous minor decreases ($p \leq 0.05$) in thickness of the various brain tissues were noted in all dose groups at PNDs 22 and 62. Statistically-significant decreases of morphometric measurement were noted in the hippocampus of males at all doses and females at 80 and 800 mg/kg/day. However, this finding may not be toxicologically significant since no dose-response and no further findings in the central and peripheral nervous system were seen. Other findings, with the exception of the folium pyramis (↓8-14%) in the ≥80 mg/kg males on PND 22, the frontal cortex (↓9-10%, left and right) in the 800 mg/kg females on PND 22 and (↓5-11%, left and right) in the 800 mg/kg males on PND 62, and the nucleus caudatus (↓6-7%, left and right) in the 800 mg/kg females on PND 62, no dose-dependence was observed.

The offspring LOAEL is 8 mg/kg/day, based on decreased auditory startle reflex response. The offspring NOAEL was not established.

This study is classified as **acceptable/non-guideline** and does not satisfy the guideline requirement (OPPTS 870.6300; OECD 426) for a developmental neurotoxicity study in rats due to inadequate positive control data.

4.2.3 Developmental Toxicity Studies

In a developmental toxicity study in rats, decreased fetal body weight and increased incidence of skeletal variations were seen in the presence of maternal toxicity at 100 mg/kg/day (LOAEL).

No developmental toxicity was seen in the developmental toxicity study in mice at the limit dose. The maternal toxicity NOAEL appears to be 200 mg/kg/day based on slightly decreased body weight gain during GD 6-9 at 1000 mg/kg/day.

The hazard database for topramezone contains eight developmental toxicity studies in the rabbit. The registrant conducted eight rabbit studies to determine the NOAEL for increased serum tyrosine levels as well as determine the NOAELs for systemic maternal and fetal developmental toxicity endpoints that are not based on tyrosine measurements.

The lowest maternal LOAEL observed in the numerous rabbit developmental toxicity studies was 0.5 mg/kg/day (MRID 45902210). This LOAEL is based on increased serum tyrosine levels. In this study a NOAEL was not established. A maternal NOAEL was not observed for increased serum tyrosine levels in any study. However, a maternal NOAEL of 5 mg/kg/day was observed in another study based on systemic toxicity; in this study tyrosine measurements were not performed (MRID 45902213). This study has the lowest maternal NOAEL for systemic toxicity among the eight rabbit developmental toxicity studies. Tyrosine levels were not measured for fetuses in any of the rabbit developmental studies. There was a clear developmental toxicity NOAEL of 0.5 mg/kg/day, based on skeletal variations observed at 5 mg/kg/day (MRID 45902210).

There are well established NOAELs and LOAELs for the standard endpoints for maternal and developmental toxicity in rabbits. Currently, it is not known what level of inhibition of the 4-HPPD enzyme results in an adverse effect. Therefore, the observation of enzyme inhibition in the absence of systemic toxicity in maternal animals or soft tissue or skeletal alterations in pups/offspring is being considered to be a biomarker of exposure, not an adverse effect. 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.

4.2.3.1 Developmental Toxicity Study in Rats

In a developmental toxicity study (MRID 45902207), topramezone in 0.5% (w/v) aqueous carboxymethylcellulose was administered orally via gavage in a dosing volume of 10 mL/kg bw to 25 presumed pregnant female Wistar rats/group at dose levels of 0, 100, 300, or 1000 mg/kg on GD 6 through 19. All dams were sacrificed on GD 20, and their fetuses were removed by cesarean and examined.

For maternal toxicity, there were no treatment-related effects on mortality, clinical signs, food

consumption, or gross pathology. There were statistically-significant decreases of body-weight gains in the 1000 mg/kg/day group at GD 6-8 (↓73%) and in all treated groups at GD 8-10 (↓28-36%) compared with the control. The overall (GD 0-20) body-weight gains were dose-dependently decreased in treated animals; however, corrected (for gravid uterine weight) body-weight gains did not show significant difference between treatment and control groups.

The maternal NOAEL was not established. The maternal LOAEL is 100 mg/kg/day based on decreased body-weight gains. The LOAEL could be lower because serum tyrosine was not evaluated.

For developmental toxicity, there were no abortions, premature deliveries, or complete litter resorption. Similarly, there were no effects of treatment on the number of resorption (early or late), number of fetuses (live or dead), post-implantation loss, or fetal sex ratio. There were no treatment-related external, visceral, or skeletal malformations. Decreased fetal body weights ($p \leq 0.01$) by 6-9% compared to controls were observed at doses ≥100 mg/kg/day. Increased incidences of the following skeletal variations that exceeded concurrent and historical controls were observed at doses ≥100 mg/kg/day: (i) supernumerary thoracic vertebrae; (ii) misshapen sacral vertebrae; (iii) supernumerary 14th rib with or without cartilage; and (iv) unossified sternebra. In addition, increased incidences of incomplete ossification of the thoracic centrum and basioccipital holes were observed at ≥300 mg/kg/day and increased incidences of the following skeletal variations were observed at 1000 mg/kg/day: (i) unossified hyoid and thoracic centrum; (ii) incomplete ossification of the cervical arch and pubis; and (iii) sacral arch cartilage, not connected.

The developmental LOAEL is 100 mg/kg/day based on decreased fetal body weights and increased incidences of skeletal variations. The developmental NOAEL was not established.

This study is classified **acceptable/guideline** (OPPTS 870.3700a) and satisfies the requirements for a developmental toxicity study in the rat.

4.2.3.2 Developmental Toxicity Study in Rabbits (8 studies are available)

Study #1. In a developmental toxicity study (MRID 45902210), topramezone in 0.5% (w/v) aqueous carboxymethylcellulose was administered by gavage at a dose volume of 10 mL/kg body weight to female New Zealand White [Hra:(NZW)SPF] rabbits (25/dose) at dose levels of 0, 0.5, 5, 50, or 450 mg/kg/day on GD 6 through 28. All does were sacrificed on GD 29; their fetuses were removed by cesarean and examined.

There were no treatment-related effects on maternal survival, body weight, or gross pathology. Increased incidence and frequency of scant and tan feces were observed at 450 mg/kg/day. Decreased body-weight gains (58%, $p \leq 0.01$) were observed on GD 20-24; the decrease was attributed to decreased gravid uterine weights (22%, $p \leq 0.01$). Decreased absolute food consumption was observed on GD 6-10 (5%, $p \leq 0.01$) and GD 10-29 (4-17%, not significant, NS) and throughout treatment (GD 6-29). Relative food consumption was decreased (NS) 4-15% on GD 6-29 and 8% throughout treatment. Increased serum tyrosine levels (≥127-570%)

were observed in all treated groups (≥0.5 mg/kg/day).

For maternal toxicity, the LOAEL is 0.5 mg/kg/day based on increased serum tyrosine level. The maternal NOAEL was not established.

For developmental toxicity, decreased litter weights (9-13%, $p \leq 0.05$) were observed at ≥50 mg/kg; fetal body weights were decreased in both sexes at 50 mg/kg (↓7-8%; NS) and 450 mg/kg (↓12%; $p \leq 0.05$). There were no treatment-related external, visceral, skeletal variations or malformations. Increased ($p \leq 0.01$) mean thoracic vertebrae ossification sites were noted in the 5, 50, and 450 mg/kg groups compared to concurrent controls. Decreased ($p \leq 0.01$) mean lumbar vertebrae ossification sites were noted in the 5, 50, and 450 mg/kg groups compared to concurrent controls. Increased ($p \leq 0.01$) mean caudal vertebrae ossification sites were observed in the 5 (NS), 50, and 450 mg/kg groups compared to concurrent controls. Increased ($p \leq 0.05$) mean number of pairs of ribs were noted in the 5, 50, and 450 mg/kg groups compared to concurrent controls. All of these observations fell outside the range of historical controls and were considered treatment-related.

The developmental LOAEL is 5 mg/kg/day based on alterations in skeletal ossification sites and increased number of pairs of ribs. The developmental NOAEL is 0.5 mg/kg/day.

This study is classified **acceptable/guideline (OPPTS 870.3700b)** and satisfies the requirements for a developmental study in the rabbit.

Study #2. In a developmental toxicity study (MRID 45902211), topramezone in 0.5% (w/v) aqueous carboxymethylcellulose was administered daily by oral gavage at a dose volume of 10 mL/kg body weight to 25 female New Zealand White [Crl:KBL (NZW)] rabbits/group on GD 6 through 28 at dose levels of 0, 5, 50, or 500 mg/kg. Blood was taken from all does on GD 28 for measurement of serum tyrosine levels. All does were sacrificed on GD 29; their fetuses were removed by cesarean section and examined. Skeletal examinations were not performed.

No effects of treatment were observed on maternal survival, clinical signs, body weights, body-weight gains, food consumption, or gross pathology. Significantly increased, tyrosine levels were observed in the sera of all treatment groups (↑6-12X). Increased tyrosine levels reached a plateau value at 50 mg/kg/day.

The maternal NOAEL was not observed. The maternal LOAEL was 5 mg/kg/day based on increased tyrosine level.

There were no treatment-related effects on the numbers of litters or fetuses (live or dead). Increased resorptions (early, late, and complete litter) were observed at 500 mg/kg (not significant), resulting in increased ($p \leq 0.05$) post-implantation loss compared to concurrent and historical controls. Increased incidences of unilateral absent kidney and ureter were observed in the 50 and 500 mg/kg fetuses compared to concurrent and historical controls. There were no treatment-related external malformations. There were no treatment-related external or visceral variations.

Mean gravid uterine weights were decreased ($p \leq 0.05$) at 500 mg/kg; however, fetal weights were comparable to controls. This decrease was considered to be due to a small decrease in the number of fetuses at this dose level.

Under the condition of this study, an increased incidence of unilateral absent kidney and ureter was observed at 50 mg/kg/day. However, a NOAEL/LOAEL cannot be established because fetal skeletal examination was not performed in this study; skeletal abnormality has been observed at lower doses in other developmental studies.

This study is classified as **Unacceptable/guideline (OPPTS 870.3700b)** because fetal skeletons were not evaluated for abnormalities and does not satisfy guideline requirements for a developmental toxicity study.

Study #3. The purpose of this study was to compare the effects of two different batches of topramezone on embryonic and fetal development. In this developmental toxicity study (MRID 45902212), two batches of topramezone in 0.5% (w/v) aqueous carboxymethylcellulose were administered daily by gavage at a dose volume of 10 mL/kg body weight to 25 female New Zealand White [Crl:KBL (NZW)] rabbits/group at dose levels of 0, 1.5, or 5.0 mg/kg on GD 6 through 28. All does were sacrificed on GD 29; their fetuses were removed by cesarean and examined.

No effects of treatment were observed on maternal survival, clinical signs, body weights, body-weight gains, food consumption, or gross pathology. Serum tyrosine levels were increased ($p \leq 0.01$) in both batches at 1.5 mg/kg (increase of 178-243%) and 5.0 mg/kg (increase of 504-563%). No differences were noted between Batches N17 and N26.

The maternal NOAEL was not observed. The maternal LOAEL is 1.5 mg/kg/day based on increased serum tyrosine level.

There were no treatment-related effects on the numbers of litters, fetuses (live or dead), resorptions (early, late or complete litter), or post-implantation loss. There were no treatment-related external, visceral, or skeletal malformations.

Increased incidences of absent kidney and ureter were observed in both batches at 1.5 mg/kg fetuses (0.6-1.6% fetuses; 5.0-8.7% litters) and 5.0 mg/kg fetuses (0.5-1.2% fetuses; 4.5-4.8% litters) compared to concurrent (0) and historical controls (0-0.5% fetuses; 0-4.2% litters). The Batch N26 findings were confined to single fetuses in each litter while the increased incidence in the Batch N17 fetuses was suggestive of a treatment-related finding. Similar findings were observed in another rabbit study (MRID 45902211) at doses of 50 and 500 mg/kg/day. Therefore, the absent kidney and ureter may be treatment-related. Increased fetal and litter incidences of supernumerary thoracic vertebrae were observed in both batches of 1.5 mg/kg and 5.0 mg/kg fetuses compared to concurrent and historical controls. Increased incidences of supernumerary 13th rib (with cartilage present) were observed in both batches of the 1.5 mg/kg and 5.0 mg/kg fetuses compared to concurrent and historical controls.

Decreased mean fetal weights were observed in both batches at 1.5 and 5.0 mg/kg/day; however,

statistical significance was achieved in the batch 26 only at 5.0 mg/kg/day. Increased incidences of incomplete ossification of the cervical centrum (with unchanged cartilage) were observed in the 5.0 mg/kg fetuses of both batches compared to concurrent and historical controls. Increased incidences of incomplete ossification of the hyoid bone (with cartilage present) were observed in the 5.0 mg/kg fetuses of both batches compared to concurrent and historical controls.

Under the condition of this study, no significant differences were noted between Batches N17 and N26 in maternal and developmental toxicities.

The developmental LOAEL is 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. The developmental NOAEL was not established.

This study is classified as **acceptable/non-guideline**.

Study #4. In a non-guideline developmental toxicity study (MRID 45902213), one batch of topramezone and 3 chromatographic fractions of topramezone in 0.5% (w/v) aqueous carboxymethylcellulose were administered by gavage at a dose volume of 10 mL/kg body weight to 25 female New Zealand White [Crl:KBL (NZW)] rabbits/group on GD) 6 through 28. Dose levels of 0, 1.5, or 5.0 mg/kg were used for batch N33; chromatography fractions (CFR) 1 and 2 were given at 1.5 mg/kg, while CFR 3 was administered at 0.5 mg/kg. All does were sacrificed on GD 29; their fetuses were removed by cesarean section and examined.

No effects of treatment were observed on maternal survival, clinical signs, body weights, body-weight gains, food consumption, or gross pathology. No differences were noted between Batch N33 and the 3 chromatographic fractions of Batch N17. Serum tyrosine level was not measured.

The maternal LOAEL was not observed. The NOAEL was 5.0 mg/kg/day. The LOAEL/NOAEL could be lower because serum tyrosine level was not evaluated.

There were no treatment-related effects on the numbers of litters, fetuses (live or dead), resorptions (early, late or complete litter), or post-implantation loss. There were no treatment-related external, visceral, or skeletal malformations and no effects on fetal growth or development.

Increased incidences of supernumerary thoracic vertebrae were observed in the 1.5 mg/kg N17/ CFR 1 and 2, and 1.5 and 5.0 mg/kg N33 fetuses compared to concurrent and historical controls. Increased incidences of supernumerary 13th rib (with cartilage present) were noted in the 1.5 mg/kg N17/ CFR 1 and 2, and 1.5 and 5.0 mg/kg N33 fetuses compared to concurrent and historical controls. The effects observed at 0.5 mg/kg/day for N17/CFR 3 were within the historical control ranges.

The purpose of this study was to ascertain the effects of three different CFRs isolated from a previously used batch N17 of topramezone on embryonic and fetal development and to compare them with the effects evoked by batch N33 of topramezone which has a greater purity compared to N17. However, the results did not achieve the goal because the study design and the dose

selection made it difficult to compare the effects among these treatments. No meaningful conclusion can be drawn from the study regarding the comparison of the effects between Batch N33 and the chromatographic fractions of Batch N17 in terms of maternal and prenatal developmental toxicity.

The developmental 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. The developmental NOAEL was not observed. No effect was observed for N17/CFR 3 at 0.5 mg/kg/day (the only dose tested). There was no evidence of teratogenicity.

This study is classified as **acceptable/non-guideline.**

Study #5. In a developmental toxicity study (MRID 46020301), topramezone in 0.5% (w/v) aqueous carboxymethylcellulose was administered by gavage at a dose volume of 10 mL/kg body weight to female New Zealand White [Crl:KBL (NZW)] rabbits (30/group) at dose levels of 0, 5, 50, or 450 mg/kg on GD 7 through 28. All does were sacrificed on GD 29; their fetuses were removed by cesarean and examined.

There were no treatment-related effects observed on maternal survival, clinical signs of toxicity, body weights, body-weight gains, food consumption, or gross pathology. No effects of treatment were noted on numbers of litters, number of live fetuses per doe, resorptions (early or late), fetal weight, placental weight, sex ratio, or postimplantation loss.

The maternal LOAEL was not observed. The maternal NOAEL is 450 mg/kg/day.

There were no dead fetuses and no treatment-related effects on early, late, or complete litter resorptions. Slight dose-dependent decrease of fetal weight was observed, though no statistical significance was achieved. The following findings were increased over concurrent and historical controls at 5, 50, and 450 mg/kg: (i) fluid-filled abdomen; (ii) pale liver; (iii) dark content of the stomach and intestines; (iv) unilateral ossification or incomplete ossification (with unchanged cartilage) of the centrum of the cervical vertebrae; (v) incomplete ossification of the thoracic centrum (with unchanged cartilage); (vi) supernumerary thoracic vertebrae; (vii) supernumerary 13th rib (with cartilage present); and (viii) incomplete ossification (with cartilage present) of the talus.

Additionally, the following findings were increased over concurrent and historical controls at 50 and 450 mg/kg: (i) increased incidences of infarct of the liver; (ii) unossified cervical centra (with unchanged cartilage); (iii) extra ossification site (with unchanged cartilage) of the sternebrae; (iv) unossified talus (with cartilage present); and (v) short 1st rib with cartilage not present. At 450 mg/kg, the following were increased over concurrent and historical controls: (i) incidences of small thymus; (ii) severely malformed bones of the skull; (iii) increased incidences of absent and misshapen caudal vertebrae; (iv) fused ribs with unchanged cartilage; (v) absent 1st rib; (vi) pale kidney; (vii) incidence of incomplete ossification of the interparietal bone; (viii) unilateral ossification (with dumbbell-shaped cartilage) of the centrum of the cervical vertebrae; (ix) incomplete ossification of the forepaw phalanx; and (x) incomplete ossification (with cartilage present) of the hindpaw phalanx.

The developmental LOAEL is 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). The developmental NOAEL was not established.

This study is classified **acceptable/guideline (OPPTS 870.3700b)** in conjunction with MRID 45902210 and satisfies the requirements for a developmental study in the rabbit.

Study #6. In a developmental toxicity study (MRID 46020302), topramezone was administered in 0.5% aqueous caroxymethylcellulose orally via gavage, in a dosing volume of 10 mL/kg, to 25 female Himalayan Chbb:HM rabbits/group, at dose levels of 0, 50, 150, or 450 mg/kg/day, on GD 7 through 28. All surviving does were sacrificed on GD 29, and their fetuses were removed by cesarean and examined. There were no treatment-related adverse effects observed from the cesarean section data.

At 450 mg/kg/day, body-weight gain decreased ($p \leq 0.01$) by 49% during Days 7-28. Body-weight gain from Day 7 until termination (corrected for gravid uterine weight) was decreased by 43% (not statistically significant [NS]). Food consumption was decreased ($p \leq 0.05$) by 22-30% at Days 19-20, 20-21, and 24-28, contributing to a decrease (NS) of 11% on Days 7-28 and 6% on Days 0-29. Three females, which were sacrificed following spontaneous abortion, consumed less than 10 g/day during the last third of the pregnancy. These three females were sacrificed after spontaneous abortions shortly before term (GD 28 and 29), and had markedly decreased body weights. In addition, five 450 mg/kg/day animals did not defecate for one or more days beginning at GD 22.

The maternal LOAEL was 450 mg/kg/day based on decreased body-weight gains and food consumption, increased incidences of abortion and lack of defecation. The maternal NOAEL was 150 mg/kg/day.

Increased incidences of short 1st rib (malformation) were observed in all treated groups at ≥50 mg/kg/day (with discontinuous cartilage) and at ≥150 mg/kg/day (with cartilage present). The total number of skeletal and visceral malformations were increased in all treated groups, but these effects were not clearly dose-dependent. The incidences of the following variations were increased compared to concurrent and historical controls: (i) incomplete ossification of cervical centrum, phalanx, and talus; (ii) unossified cervical centrum; (iii) extra ossification site between cervical centers; (vi) supernumerary thoracic vertebra; (vii) misshapen sacral vertebra; and (viii) supernumerary [13th] rib [with or without cartilage present]. An increased incidence of displaced cartilaginous parts of ribs was observed.

Increased incidences relative to the concurrent and historical controls were observed at ≥150 mg/kg/day: dilated aorta (malformation), small cervical arch (malformation), unossified talus (variation), and polyhydramnios (unclassified abnormality). Fetal weights were decreased in all treated groups (decrease of 8-18%) and were considered to be treatment-related.

Additionally, at 450 mg/kg/day, the following malformations were observed at increased

incidences relative to the concurrent and historical controls: enlarged ventricular chamber in the heart, three chambered heart (cor triloculare), small tongue (microglossia), and small thymus. One 450-mg/kg/day female fetus had a distended bladder (visceral unclassified) and dilated ureter (visceral variation), and these findings were not observed in concurrent and historical controls.

The developmental toxicity LOAEL was 50 mg/kg/day based on decreased fetal weight and increased incidence of visceral malformations, and skeletal malformations, variations, and unclassified abnormalities. The developmental toxicity NOAEL was not observed.

This study is classified **acceptable/guideline** (OPPTS 870.3700b; OECD 414) and satisfies the requirements for a developmental toxicity study in the rabbit.

Study #7. In a developmental toxicity study (MRID 46020303), topramezone (95.8% a.i.; Lot/Batch # N26) in 0.5% (w/v) aqueous carboxymethylcellulose was administered daily by oral gavage at a dose volume of 10 mL/kg body weight to 25 female New Zealand White (INRA A9077) rabbits/group at dose levels of 0, 0.5, 5, 50, or 450 mg/kg on GD 6 through 28. All does were sacrificed on GD 29; their fetuses were removed by cesarean section and examined.

No effects of treatment were observed on maternal survival, clinical signs, body weights, body-weight gains, food consumption, or gross pathology.

The maternal LOAEL was not observed. The maternal NOAEL is 450 mg/kg/day.

There were no treatment-related effects on the numbers of dead fetuses or resorptions (early, late or complete litter). Slightly lower fetal weights were observed in the 5, 50 and 450 mg/kg/day groups; however, no statistical significance was achieved. There were no treatment-related external, visceral, or skeletal malformations.

Increased presence of 27 pre-sacral vertebrae, a variation, was observed in the 5 (not significant), 50 ($p \leq 0.001$), and 450 ($p \leq 0.001$) mg/kg groups compared to concurrent and historical controls. Increased ($p \leq 0.001$) incidence of full supernumerary 13th rib, a variation, was noted in the 5, 50, and 450 mg/kg groups compared to concurrent and historical controls. Unossified 1st to 4th sternebrae, a variation, was observed in the 50 and 450 mg/kg groups compared to concurrent controls. Cartilage present in the ribs was observed in the 50 and 450 mg/kg groups compared to concurrent controls, and increased ($p \leq 0.01$) incidence of fused cartilage in the ribs was noted in the 50 and 450 mg/kg groups compared to concurrent controls. Additionally, increased ($p \leq 0.05$) incidence of incomplete ossification of the ribs was observed in the 450-mg/kg group compared to concurrent and historical controls.

The developmental LOAEL is 5 mg/kg/day based on increased presence of 27 pre-sacral vertebrae and increased incidences of full supernumerary 13th rib. The developmental NOAEL is 0.5 mg/kg/day.

This study is classified **acceptable/guideline (OPPTS 870.3700b)** and satisfies the requirements for a developmental study in the rabbit.

Study #8. In a developmental toxicity study (MRID 46020304), topramezone was administered in 0.5% aqueous carboxymethylcellulose orally via gavage, in a dosing volume of 10 mL/kg, to 25 female Himalayan Chbb:HM rabbits/group, at dose levels of 0, 50, 150, or 450 mg/kg/day, on GD 6 through 28. All surviving does were sacrificed on GD 29, and their fetuses were removed by cesarean and examined.

There were no treatment-related adverse effects observed on maternal mortality, clinical signs, body weight, food consumption, or gross pathology. There were no abortions, premature deliveries, or dead fetuses; and no effects of treatment on the number of litters, fetal body weight, or sex ratio. There were no other effects observed from the Cesarean section data to indicate treatment-related toxicity.

The maternal LOAEL was not observed. The maternal NOAEL is 450 mg/kg/day.

At ≥50 mg/kg/day, the incidence of extra sternebral ossification sites (skeletal malformation) increased dose-dependently. Full supernumerary (13^{th}) ribs (skeletal variation) increased dose-dependently ($p \leq 0.001$) in all groups. Additionally short supernumerary 13^{th} rib (skeletal variation) was observed ($p \leq 0.05$) more frequently; however, this effect was not clearly dose-dependent.

At ≥150 mg/kg, unossified rib(s) were observed, and cartilage was present in the cervical vertebra(e). At 450 mg/kg/day, the following variations/cartilage effects were increased compared to the controls: incomplete ossification of the frontal, parietal, cervical vertebra(e), and rib(s); unossified interparietal, 1^{st} metacarpal, and talus; cartilage present in the interparietal and metacarpal bone(s). Incomplete ossification of the 1^{st} to 4^{th} sternebra(e) was also observed at 450 mg/kg/day.

The developmental toxicity LOAEL is 50 mg/kg/day based on an increased incidence of extra sternebral ossification sites and supernumerary 13^{th} rib. The developmental toxicity NOAEL was not observed.

This study is classified **acceptable/guideline** (OPPTS 870.3700b; OECD 414) and satisfies the requirements for a developmental toxicity study in the rabbit.

4.2.3.3 Developmental Toxicity Study in Mice

In a developmental toxicity study (MRIDs 45902208), topramezone in 0.5% (w/v) aqueous carboxymethylcellulose was administered orally via gavage in a dosing volume of 10 mL/kg to 25 presumed pregnant Crl:CD-1®(ICR)BR mice/group at dose levels of 0, 30, 200, or 1000 mg/kg on GD 6 through 17. All dams were sacrificed on GD 18, and their fetuses were removed by cesarean section and examined. Clinical chemistry and organ weights were also evaluated.

No treatment-related effect was observed on mortality, clinical signs of toxicity, body weights, or gross pathology.

A decrease ($p \leq 0.01$) in body-weight gain was observed at 1000 mg/kg/day during GD 6-9; all

other measured body-weight gains in the treated groups (including for the overall study, and overall treatment period) were similar to the controls. Clinical chemistry showed an elevated alanine aminotransferase level ($p \leq 0.01$) at 1000 mg/kg/day with a dose-dependent response. An increase ($p \leq 0.05$) of relative liver weights was also observed at 1000 mg/kg/day. Serum tyrosine was increased ($p \leq 0.05$) dose-dependently at 30 (↑2-3X) and ≥200 (↑6-10X) mg/kg/day.

The maternal LOAEL is 30 mg/kg/day, based on increased serum tyrosine level. The maternal NOAEL was not established.

There were no abortions or complete litter resorptions. Similarly, there were no effects of treatment on the number of premature deliveries, resorptions (early or late), number of fetuses (live or dead), fetal sex ratio, or post-implantation losses. There were no treatment-related effects on external, visceral, or skeletal malformations, variations, or retardations.

The developmental LOAEL was not observed. The developmental NOAEL is 1000 mg/kg/day.

This study is classified **acceptable/guideline** (OPPTS 870.3700a) and satisfies the requirements for a developmental toxicity study in the mouse.

4.2.4 Reproductive Toxicity Study

In a two-generation reproduction toxicity study (MRID 45902214), topramezone was administered continuously in the diet to Wistar (CrlGlxBrlHan:WI) rats (25/sex/dose) at nominal dose levels of 0, 4, 40, 400, or 4000 ppm (equivalent to 0/0, 0.4/0.5, 4.2/4.6, 42.2/46.9, or 426.8/471.9 mg/kg bw/day [M/F]). The P animals were given test article diet formulations for 75 days prior to mating to produce the F1 litters. After weaning, F1 animals (25/sex/dose) were selected to become the parents of the F2 generation and were given the same concentration test formulation as their parents for 74 days prior to mating to produce the F2 litters. Developmental landmarks were not evaluated in the pups.

There were no treatment-related mortalities in either generation. Clinical signs of toxicity were limited to effects of the eyes (opacity of the cornea, chromodacryorrhea, cataracts and enlarged eye bulb). At termination, cloudiness of the cornea was confirmed macroscopically in the ≥40 ppm P females and F1 males and in the ≥400 ppm P males and F1 females. Microscopic examination revealed increased incidence and severity of minimal to marked/severe chronic keratitis in the eyes at ≥40 ppm in both sexes and both generations.

During pre-mating, there were no treatment-related effects on body weights, body-weight gains, or food consumption in the P generation males or females. In the F1 generation, body weights decreases (↓7-15%; $p \leq 0.05$) were observed in the males at ≥40 ppm during weeks 0-2 and at ≥400 ppm during weeks 3-5, and in the ≥400 ppm females during weeks 0-1. Decreased body-weight gains were observed in the ≥40 ppm males during week 0-1. During gestation and lactation, there were no treatment-related adverse effects on body weights, body-weight gains, or food consumption in either generation.

Increased absolute kidney weights ($p \leq 0.05$) were observed in both sexes in the P generation and in the males of the F1 generation at doses ≥40 ppm (↑2-13%) and in females at 40 ppm. Increased relative kidney weights (↑8-20%; $p \leq 0.05$) were observed in both sexes at doses ≥40 ppm in the P and F1 generations. Absolute and relative thyroid weights were increased (↑16-40%; $p \leq 0.01$) in the ≥40 ppm P generation males and in the F_1 females. In the F1 generation, increased incidences of flaky colloid were observed in the thyroid in the ≥4-ppm males (12-22/25 treated vs. 7/25 controls) and ≥40 ppm females (13-15/25 treated vs. 0/25 controls). Statistically- significant increases ($p \leq 0.05$) of absolute and relative liver weights were seen in the P generation males only. In the F1 generation, incidences of pelvic dilatation of the kidneys were increased in incidence over controls in the ≥40 ppm males (6-19/25 treated vs. 2/25 controls) and females (5-10/25 treated vs. 0/25 controls).

For parental toxicity, the LOAEL was 40 ppm (equivalent to 4.2/4.6 mg/kg/day [M/F]) based on decreased body weights and body-weight gains in males; increased kidney and thyroid weights in both sexes, and histopatholigical findings in the eyes, kidney, and thyroid of both sexes. The NOAEL was 4 ppm (equivalent to 0.4/0.5 mg/kg [M/F]).

There were no treatment-related effects on: the estrous cycle; sperm enumeration, morphology, or motility; pre-coital or gestation intervals; number of implantations; post-implantation loss; or mating, fertility, gestation, or live birth indices.

For reproductive toxicity, the LOAEL was not observed. The NOAEL for reproductive toxicity is 4000 ppm (equivalent to 426.8/471.9 mg/kg/day [M/F]).

An increased number of dead/cannibalized pups were observed at ≥400 ppm during PND 0-4 in the F1 (11-23 treated vs. 1 control) and F2 (51-75 treated vs. 5 controls) litters, resulting in a dose-dependently decreased ($p \leq 0.01$) viability index in the F1 (91-96% treated vs. 100% controls) and F2 (68-79% treated vs. 98% controls) litters.

In the F1 pups, pup weights for males and females and litter weights were decreased (↓11-13%; $p \leq 0.01$) at ≥400 ppm on PND 21. In the F2 pups, pup weights for males and females and litter weights were decreased (↓7-23%; $p \leq 0.05$) at ≥40 ppm generally throughout the post-natal period. Body-weight gains were decreased ($p \leq 0.05$): in the F1 generation at ≥400 ppm during PND 14-21 and 4-21 (↓9-24%) and at 4000 ppm during PND 4-7 (↓11-12%); and in the F2 generation at ≥40 ppm during PND 1-4, 14-21, and 4-21 (↓9-41%) and at ≥400 ppm during PND 4-7 and 7-14 (↓12-29%).

The number of days until preputial separation was dose-dependently increased ($p \leq 0.01$) in the ≥40 ppm males (44.9-45.8 days) compared to controls (42.8 days), although the body weight on the day of preputial separation was comparable to controls. In the females, there were no effects of treatment on time to sexual maturation (vaginal opening) or on the body weight on the day of vaginal opening.

Absolute and relative to body spleen weights were decreased ($p \leq 0.05$) in the: (i) ≥400 ppm F1 males (↓9-23%); (ii) ≥40 ppm F1 females (↓6-24%); and (iii) ≥4 ppm F2 males and females (↓9-38%). However, the group mean spleen weights for all F2 groups were within the range of

historical controls. Microscopic examinations were not performed on organs from the offspring. Thus, the decreased spleen weights were considered to be of equivocal toxicological significance.

The following macroscopic findings were noted in the offspring (vs. 0 concurrent controls, unless otherwise noted): (i) corneal opacity in the F1 pups at ≥400 ppm (0.9-1.5% pups; 8.7-13% litters); (ii) empty stomach in the 4000 ppm F1 offspring (5.5% pups; 4.2% litters); (iii) hydronephrosis in the ≥400 ppm F1 offspring and in the 4000 ppm F2 offspring (0.5-1.0% pups; 4.2-9.5% litters); (iv) dilated renal pelvis in the 4000 ppm F2 offspring (13% pups; 67% litters, $p \leq 0.01$) compared to concurrent controls (1.3% pups; 13% litters); (v) hydroureter in the 4000 ppm F2 offspring (1.0% pups; 9.5% offspring); (vi) discolored intestine in the ≥400 ppm F1 offspring and ≥40 ppm F2 offspring (0.4-4.6% pups; 4.2-24% litters); and (vii) small testis in the ≥400 ppm offspring in both generations (0.5-1.0% pups; 4.2-9.5% litters). The total percent offspring with macroscopic findings was increased ($p \leq 0.01$) in both generations at ≥400 ppm (6.2-26% pups; 38-90% litters) compared to controls (0.9-3.0% pups; 4.0-30% litters).

For offspring toxicity, the LOAEL was 40 ppm (equivalent to 4.2/4.6 mg/kg/day [M/F]) based on decreased pup body weights and body-weight gains in the F2 generation and increased time to preputial separation in the F1 males. The NOAEL for offspring toxicity was 4 ppm (equivalent to 0.4/0.5 mg/kg/day [M/F]).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

4.2.5 Additional Information from Literature Sources

No additional relevant toxicity studies from published literature were identified.

4.2.6 Pre- and/or Post-natal Toxicity

4.2.6.1 Determination of Susceptibility

There is no evidence of increased susceptibility following pre-/post-natal exposure to rats in the two-generation reproductive toxicity study. Increased incidences of skeletal variations and alterations in skeletal ossifications sites were observed in rat and rabbit developmental studies. There are data that suggest the skeletal variations are associated with 4-HPPD inhibitor herbicides. There is a potential of increased quantitative susceptibility following *in utero* and/or pre-/post-natal exposure in the developmental toxicity and developmental neurotoxicity studies in rats because NOAELs for parental or offspring systemic toxicity were not established. In a developmental toxicity study in rats, decreased fetal body weight and increased incidence of skeletal variations were seen in the presence of maternal toxicity at 100 mg/kg/day (LOAEL). Therefore, susceptibility could not be assessed in this study. However, the current NOAEL of 0.5 mg/kg/day for an acute RfD would provide a 200-fold lower dose based on the most sensitive endpoint. In a developmental neurotoxicity (DNT) study in rats, decreased auditory startle reflex was seen at the LOAEL of 8 mg/kg/day in the presence of maternal toxicity manifested as corneal opacity. Therefore, the susceptibility in this study could not be assessed. However, the

NOAEL for the chronic RfD is 0.4 mg/kg/day based on the most critical tyrosine-mediated effects which is 20-fold lower than the LOAEL for the DNT study. Based on the lack of increased susceptibility in the two-generation reproductive toxicity study and the NOAEL chosen for the acute and chronic RfD (based on the most sensitive endpoint), the risk assessment team decided that the apparent increase in quantitative susceptibility is not relevant for this risk assessment. Therefore, the special FQPA Safety Factor is reduced to 1x.

4.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility

The degree of concern is low for the quantitative susceptibility because the risk assessment was based on the most sensitive endpoint with a definitive NOAEL (rat carcinogenicity study). There are no concern or residual uncertainties for pre- and post-natal toxicity.

4.3 Recommendation for a Developmental Neurotoxicity Study

The registrant has submitted a developmental neurotoxicity study.

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Acute Reference Dose (aRfD)

4.4.1.1 Acute Reference Dose (aRfD) - General population including infants and children

An endpoint of concern attributable to a single oral dose was not identified for this population.

4.4.1.2 Acute Reference Dose (aRfD) - Females 13-50 years of age

Study Selected: Developmental Toxicity Study in Rabbits 870.3700b

MRID No.: 45902210

Executive Summary: See above section 4.2.3.2 developmental toxicity study in rabbits (study #1).

Dose and Endpoint Selection for Establishing aRfD: 0.5 mg/kg/day (NOAEL) based on alterations in skeletal ossification sites and increased number of pairs of ribs at 5 mg/kg/day (LOAEL).

Uncertainty Factor (UF): 100 (10x for interspecies extrapolation and 10x for intraspecies variations).

Comments about Study/Endpoint/UF: The study is appropriate for a single dose exposure with the effects of concern via the oral route and length of exposure for an acute dietary endpoint. The endpoints for risk assessment are based on alterations in skeletal ossification sites and increased number of pairs of ribs. These developmental effects are presumed to occur as a result of a

single dose at a critical time during gestation.

$$\textbf{Acute RfD} = \frac{0.5 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}} = 0.005 \text{ mg/kg/day}$$

4.4.2 Chronic Reference Dose (cRfD)

Study Selected: Carcinogenicity Study in Rats

MRID No.: 45902222

Executive Summary: In a carcinogenicity study (MRID 45902222), 50 Wistar rats/sex/dose were exposed to topramezone in the diet at concentrations of 0, 6, 60, 600, or 6000 ppm nominally (equivalent to 0/0, 0.4/0.5, 3.6/4.7, 36.4/50.8, and 381.5/524.1 mg/kg/day in males/females) for up to 24 months.

A dose-dependent increase of mortality was observed in males at Week 105: 6 (12%), 60 (16%), 600 (16%), and 6000 (24%) ppm vs. 8% in the concurrent controls; however, survival rates are within guideline requirements. No treatment-related effect on mortality was observed in females. Clinical observations showed corneal opacity in animals of both sexes at doses ≥60 ppm (20-88% vs. 0% in control). Ophthalmoscopic examination on Days 267 (females) and 282 (males) showed corneal pannus and opacity at ≥600 ppm in both sexes and in 60 ppm females (only animals with clinically observed corneal opacity were examined). On Days 722 (females) and 728 (males), an increased incidence of corneal pannus and opacity was observed in the 60 ppm group of both sexes vs. 0% in the controls and 6 ppm group (only the controls and the 6 and 60 ppm groups were examined).

Decreased body weight and body-weight gains were observed in males at ≥60 ppm, these decreases occurred late in the study, first observed on day 595 (6000 ppm) and day 651 (≥60 ppm). Statistically-significant decreases of body weight and body-weight gains in males at 60 and 600 ppm groups were observed on several days during the study. In females, decreased body weight and body-weight gains were observed at 600 and 6000 ppm.

Treatment-related increases ($p \leq 0.01$) of absolute and/or relative organ weight were observed in the following organs: (i) liver in ≥60 ppm males and ≥600 ppm females; (ii) kidneys in ≥60 ppm males and ≥600 ppm females. Gross pathology showed the following treatment-related gross lesions: (i) skin decubitus in all treated male groups (42-56% treated vs. 30% controls); (ii) enlarged iliac and popliteal lymph node in all treated male groups (22-50% treated vs. 16-18% controls); (iii) cloudiness in the cornea in ≥60 ppm males and females (16-88% treated vs. 0% controls); (iv) thyroid gland mass in ≥600 ppm males (18-24% treated vs. 4% controls) and enlarged thyroid in the 6000 ppm males (26% treated vs. 12% controls); (v) decreases in testes, epididymides, seminal vesicle, and prostate size (10-24% treated, each lesion vs. 0-4% controls) at 6000 ppm; and (vi) liver focus in the 6000 ppm females (68% treated vs. 38% controls).

Non-neoplastic microscopic pathology revealed: (i) focal follicular cell hyperplasia in the thyroid gland in all treated male groups (46-64% treated vs. 36% controls) and female groups (26-56% treated vs. 16% controls); (ii) minimal to slight diffuse follicular cell hypertrophy in the thyroid gland in all treated male groups (42-76% treated vs. 32% controls) and female groups (28-58% treated vs. 22% controls); (iii) minimal to severe loss of sperm in the epididymides of all treated male groups (10-18% treated vs. 4% controls); (iv) minimal to marked chronic keratitis in the ≥60 ppm males (16-82% treated vs. 0% controls) and females (14-88% treated vs.

0% controls); (v) minimal to severe hematopoiesis in the spleen in ≥60 ppm males (38-54% treated vs 32% controls); and (vi) minimal to marked diffuse degeneration in the pancreas in ≥600 ppm males (46-66% treated vs 0% controls) and ≥60 ppm females (10-38% treated vs 0% controls). In addition, increases were observed in the incidence of minimal to marked ulcerative skin inflammation in males (42-56% treated vs 32% controls) and pars distalis hyperplasia in females (16-26% treated vs 10% controls); however, the exact incidence at 6, 60, and 600 ppm is unknown, because all animals were not examined (incidence calculated as # affected/50 for all groups). Additionally, increased incidences of the following lesions were observed at 6000 ppm: (i) in the liver: focal necrosis in both sexes, hematopoiesis (equivocal) and centrilobular hypertrophy in males, and pigment storage in females; (ii) male reproductive system abnormalities: diffuse degeneration in the testes, seminal vesicles atrophy, and prostate gland atrophy and inflammation; (iii) bone marrow activation in the femur in both sexes and in the sternum of males; (iv) in the adrenal cortices, accessory adrenal tissue in both sexes and a focal fatty change in males; (v) pars distalis hyperplasia in males; (vi) focal degeneration in the sciatic nerves in both sexes; and (vii) mandibular lymph node hyperplasia in males. Because all animals in the 6, 60, and 600 ppm groups were not examined, it was unclear if the following lesions were observed at a higher incidence than controls at ≤600 ppm: adrenal cortices, male pituitary, sciatic nerves, mandibular lymph node, and female bone marrow activation.

For systemic toxicity, the LOAEL is 60 ppm (equivalent to 3.6/4.7 mg/kg/day), based on increased incidences of corneal opacity, decreased body weight and body-weight gains in males and histopathological evaluations [dose-dependent increases of the incidence in thyroid (follicular cell hyperplasia), pancreas (diffuse degeneration), liver (focal necrosis), and eyes (chronic keratitis) at doses ≥60 ppm] in both sexes. The NOAEL was 6 ppm (equivalent to 0.4/0.5 mg/kg/day).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4200a; OECD 451) for a carcinogenicity study in rats.

Dose and Endpoint for Establishing cRfD: 0.4 mg/kg/day (NOAEL) based on increased incidence of corneal opacity, decreased body weight and body-weight gains in males and histopathological evaluations [dose-dependent increases of incidences in thyroid (follicular cell hyperplasia), pancreas (diffuse degeneration), liver (focal necrosis), and eyes (chronic keratitis) at doses ≥60 ppm] in both sexes at 3.6 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100 (10x for interspecies extrapolation and 10x for intraspecies variations).

Comments about Study/Endpoint/Uncertainty Factor: There is a concern about the elevated tyrosine levels observed in treated rats and mice with the rat as the most sensitive species. However, no data could demonstrate at what level increases of tyrosine levels would result in detrimental (adverse) effects. It has been shown that the enzyme activities involved in the tyrosine metabolism of humans are very similar to those in mice, whereas the rat is significantly different. It is known that measurable effects of elevated tyrosine levels have been established in the target organs of the eye, liver, kidney, pancreas, and thyroid. In the carcinogenicity study, a NOAEL is established based on effects observed in these organs with the most sensitive species

of rats. The selected dose/endpoints are appropriate for the route and duration of exposure and are supported by a chronic toxicity study and a reproduction study in rats for the chronic dietary risk assessment.

$$\textbf{Chronic RfD} = \frac{0.4 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}} = 0.004 \text{ mg/kg/day}$$

4.4.3 Incidental Oral Exposure: Short-Term (1-30 days)

Study Selected: Carcinogenicity Study in Rats

MRID No.: 45902222

Executive Summary: See above chronic RfD.

Dose and Endpoint for Establishing cRfD: 0.4 mg/kg/day (NOAEL) based on 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 at 3.6 mg/kg/day (LOAEL) [histopathological evaluations showed dose-dependent increases of incidences in thyroid (follicular cell hyperplasia), pancreas (diffuse degeneration), liver (focal necrosis), and eyes (chronic keratitis) at doses ≥60 ppm].

Comments about Study/Endpoint/Uncertainty Factor: A rat subchronic oral toxicity study was not selected because the NOAEL of 1.1 mg/kg/day in this study based on degeneration of pancreas seen at 2.1 mg/kg/day (LOAEL) may not be protective of corneal effects seen in the subchronic neurotoxicity study (LOAEL=4.2 mg/kg/day) and in a developmental neurotoxicity study (LOAEL= 8 mg/kg/day). A NOAEL was not established in either study. The rat carcinogenicity study with a longer duration is appropriate because 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 the population of concern (infants and children). Further, the eye toxicity (effects of concern) was first observed in female on day 41, making this study and endpoint appropriate for the short- and intermediate-term duration.

4.4.4 Incidental Oral Exposure: Intermediated-term (1-6 Months)

Study Selected: Carcinogenicity Study in Rats

MRID No.: 45902222

Executive Summary: See above chronic RfD.

Dose and Endpoint for Establishing cRfD: 0.4 mg/kg/day (NOAEL) based on 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 at 3.6 mg/kg/day

(LOAEL) [histopathological evaluations showed dose-dependent increases of incidences in thyroid (follicular cell hyperplasia), pancreas (diffuse degeneration), liver (focal necrosis), and eyes (chronic keratitis) at doses ≥60 ppm].

Comments about Study/Endpoint/Uncertainty Factor: The study and endpoint are appropriate for the route and duration. See above section 4.4.3 for additional comments.

4.4.5 Dermal Absorption

Oral metabolism studies in rats indicated low oral absorption of topramezone. The excretion of the intact compound in feces range from 66.3 to 91.7% of the administered dose depending upon dose, sex and position of radiolabel. Based on this excretion profile in the feces, oral absorption ranged from 9 - 34%. For this risk assessment, the oral absorption is estimated to be 20%. Since an oral study is used for dermal risk assessment, the dermal absorption value (2.6%) was adjusted for low oral absorption. Therefore, the dermal-absorption factor was determined to be 13% for the extrapolation of an oral dose to a dermal equivalent dose.

The study is summarized below.

In a dermal-penetration study (MRID 45902307), [pyrazole-4-^{14}C] BAS 670H (>98%, batch/lot #706-1013) was administered to the shaved intact skin (10 cm^2) of four male CrlGlxBrlHan:WI rats/time point/dose at dose levels of 0, 0.004, 0.068, or 3.36 mg ai/cm^2. Exposure durations were 1, 4, 10, and 24 hours.

Recovery of the applied dose was acceptable, 95.9-105.5% for each group at each sampling interval. Following all exposure periods up to 24 hours, 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.

In all dose groups, skin residues ranged from 3.04-6.52% dose after 1 hour of exposure, and increased an additional 2% dose after 24 hours of exposure (4.99-8.73% dose). Only limited absorption of these skin residues was evident, with residues remaining in the skin accounting for 1.78-5.19% dose in animals exposed for 10 hours and sacrificed after 72 hours.

Of the selected tissues analyzed, concentrations of radioactivity were highest (less than 1% of the applied dose) in the kidneys and liver in all groups at each exposure interval.

4.4.6 Dermal Exposure (All Durations)

Study Selected: Carcinogenicity Study in Rats

MRID No.: 45902222

Executive Summary: See above chronic RfD.

Dose and Endpoint for Establishing cRfD: 0.4 mg/kg/day (NOAEL) based on 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 at 3.6 mg/kg/day (LOAEL) [histopathological evaluations showed dose-dependent increases of incidences in thyroid (follicular cell hyperplasia), pancreas (diffuse degeneration), liver (focal necrosis), and eyes (chronic keratitis) at doses ≥60 ppm].

Comments about Study/Endpoint/Uncertainty Factor: The rat 28-day dermal toxicity study (MRID 45902206) 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 NOAEL was 0.5 mg/kg/day using a dermal-absorption factor of 13%. 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. Further, the effects of concern were observed at day 41, making this study and endpoint appropriate for the short- and intermediate-term duration. Since an oral NOAEL was selected, 13% dermal-absorption factor should be used for route-to-route extrapolation.

4.4.7 Inhalation Exposure (All Durations)

Study Selected: Carcinogenicity Study in Rats

MRID No.: 45902222

Executive Summary: See above chronic RfD.

Dose and Endpoint for Establishing cRfD: 0.4 mg/kg/day (NOAEL) based on 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 at 3.6 mg/kg/day (LOAEL) [histopathological evaluations showed dose-dependent increases of incidences in thyroid (follicular cell hyperplasia), pancreas (diffuse degeneration), liver (focal necrosis), and eyes (chronic keratitis) at doses ≥60 ppm]. Further, the effects of concern were observed at day 41, making this study and endpoint appropriate for the short- and intermediate-term duration.

Comments about Study/Endpoint/Uncertainty Factor: In the absence of a repeated exposure inhalation study, an oral study is selected. Inhalation absorption is assumed to be 100%.

4.4.8 Margins of Exposure

Table 4.4.8 Summary of Target MOEs for Risk Assessment

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	100
Dermal	100	100	100
Inhalation	100	100	100

For Occupational Exposure: For short-term dermal and inhalation exposure risk assessments, a MOE of 100 is required.

For Residential Exposure: Not applicable. There are no residential uses proposed. If there were, the level of concern would be a MOE of 100.

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

No residential uses are proposed for topramezone at this time. Therefore, aggregate risk consists of exposure from food and drinking water sources only. Acute and chronic aggregate risks were assessed.

4.4.10 Classification of Carcinogenic Potential

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"**. This decision was based on the following considerations:

(i) No treatment-related tumors were seen in male or female mice when tested at doses (greater than the limit dose) that were adequate to assess carcinogenicity;

(ii) Treatment-related thyroid follicular cell tumors were seen in both male and female rats at 600 and 6000 ppm, which were considered to be adequate, and not excessive, to assess carcinogenicity;

(iii) There is no mutagenicity concern from *in vivo* or *in vitro* assays;

(iv) The non-neoplastic toxicological evidence (i.e., thyroid growth, thyroid follicular cell

hypertrophy/hyperplasia, thyroid hormonal changes) indicated that BAS 670H was inducing a disruption in the thyroid-pituitary hormonal status.

The mechanistic data for thyroid follicular cell tumor formation meet the criteria established by the Agency for the use of a margin of exposure approach for human cancer risk assessment. However, 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.

4.4.10.1 Carcinogenicity Study in Rats

Executive Summary: See chronic RfD section.

Discussion of Tumor Data: Male rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 6000 ppm dose group with the controls, for thyroid follicular cell adenomas and adenomas and/or adenocarcinomas combined, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 600 ppm dose group with the controls for thyroid follicular cell adenomas and adenomas and/or adenocarcinomas combined, both at $p<0.05$.

Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 6000 ppm dose group with the controls, for thyroid follicular cell adenomas and adenomas and/or adenocarcinomas combined, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 600 ppm dose group with the controls for thyroid follicular cell adenomas and adenomas and/or adenocarcinomas combined, and of the 60 ppm dose group with the controls for thyroid follicular cell adenomas and/or adenocarcinomas combined, all at $p<0.05$.

Adequacy of the Dose Levels Tested: In males, dosing was considered adequate and not excessive based on increased mortality at the high dose, clinical observations and histopathological evaluations. Increased mortality was observed at high dose (8%, 12%, 16%, 16%, or 24% for doses 0, 6, 60, 600, or 6000 ppm, respectively); however, the mortality did not exceed the guideline requirement. Decreased body weight (↓6-9%) and body-weight gains (↓7-11%) were observed at doses ≥60 ppm throughout the study. Dose-dependent increases of corneal opacity were observed at doses ≥60 ppm. Histopathological evaluations showed dose-dependent increases of incidences in thyroid (follicular cell hyperplasia), pancreas (diffuse degeneration), liver (focal necrosis), and eyes (chronic keratitis) at doses ≥60 ppm.

In females, dosing was considered adequate and not excessive based on slightly decreased body weight, body-weight gains, clinical observation, and histopathological evaluations. Slight decreases of body weights (↓3-8%) and body-weight gains (↓7-10%) were observed at doses ≥600 ppm throughout the study. Dose-dependent increases of corneal opacity were observed at doses ≥60 ppm. Histopathological evaluations showed dose-dependent increases of incidences in thyroid (follicular cell hyperplasia), pancreas (diffuse degeneration), liver (focal necrosis), and eyes (chronic keratitis) at doses ≥60 ppm.

4.4.10.2 Carcinogenicity Study in Mice

Executive Summary: In a carcinogenicity study (MRID 45902221), 50 C57BL/6J Rj mice/sex/dose were exposed to topramezone in the diet at concentrations of 0, 80, 800, or 8000 ppm nominally (equivalent to 0/0, 19/26, 194/256, and 1903/2467 mg/kg/day in males/females) for up to 78 weeks.

There were no treatment-related effects on clinical signs, food efficiency, ophthalmology, organ weights, or gross and histological pathology.

At ≥80 ppm, generally dose-dependent increases in magnitude and frequency of body weight decreases ($p \leq 0.05$) were observed (decrease of 2-8%), and corresponded to decreases ($p \leq 0.05$) in body-weight gains (decrease of 9-86%). Although significant decreases ($p \leq 0.05$) in body weights in the 80 ppm males were slight in magnitude (decrease of 2-4%) and less common than at the higher doses, slight decreases (often not statistically significant) were generally observed throughout the study, which contributed to the clearly adverse effect on body-weight gain. At 80 ppm, body-weight gain was decreased ($p \leq 0.05$) by ≥12% for more than half the study, by 43% on Day 14, and by 17% at termination on day 546.

At 8000 ppm, other effects were observed that were not clearly treatment-related or the toxicological significance was unclear. Survival was decreased in the females (76% treated vs 92% controls). However, four animals died very early in the study (between days 19-22) and one died during the necropsy period (day 552). These deaths may have been incidental; therefore, the effect on mortality is equivocal. Food consumption was generally decreased ($p \leq 0.05$) in the females at day 7 through day 119 (decrease of 9-27%, a transient effect); only sporadic, inconsistent differences ($p \leq 0.05$) were observed thereafter. Morphological variations were observed in the leukocytes of the males, including metamyelocytes, changes in the nucleus of neutrophils, juvenile lymphocytes, and monoblasts; however, the toxicological significance of these findings was unclear.

An increased incidence of central hepatocellular hypertrophy was observed in males only as follows: controls (6%), and 80 (2%), 800 (22%), and 8000 (38%) ppm. There was no increase in absolute liver weight in males; however, minor increases ($p \leq 0.05$) in relative to body liver weights was observed in all treated groups. In females, increased absolute liver weight and relative to body liver weights were observed at 800 and 8000 ppm (↑ 7-11%); however, no corroborated gross or histological hepatic lesions were observed.

The LOAEL is 80 ppm (equivalent to 19/26 mg/kg/day in males/females), based on decreased body weight and body-weight gains in males. The NOAEL was not established.

Discussion of Tumor Data: There were no significant compound-related tumors in male mice. Female mice had a significant increasing trend in histiocytic sarcomas of the hemolymphoreticular system at $p < 0.01$. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

Adequacy of the Dose Levels Tested: In males, dosing was considered adequate and not

excessive even the high dose exceeded the limit dose based on decreased body weight and body-weight gain, increased relative liver weight and increased incidences of hepatocellular hypertrophy in males.

In females, dosing was considered adequate and not excessive although the high dose was above 2x the limit dose. Increased mortality was observed at the high dose; however, no significant decreases in body weight and body-weight gains, or histopathological evaluations were observed.

4.4.11 Mutagenicity

Topramezone was not mutagenic in *Salmonella typhimurium* or *Escherichia coli* in a series of reverse mutation assays using the standard plate incorporation and preincubation protocols. Negative results were obtained with three different batches of the test material, and purity ranged from 97.7 to 99.3% (MRID 45902225 through 45902227). By contrast, a single batch (N 26) of the test material induced a reproducible and concentration-dependent mutagenic response in the nonactivated phase of plate and preincubation tests with *S. typhimurium* TA98 (MRID 45902228). This finding should be viewed with caution for the following reasons: 1) the response was seen at high concentrations including and exceeding the limit dose (2500-7000 µg/plate); 2) the batch of topramezone used in this study had the lowest percentage active ingredient (95.8% vs. 97.7-99.3% ai for the other batches) and 3) microbial tests performed with the three batches mentioned above were negative up to the limit dose. Therefore, the mutagenic effect was likely due to impurities in the test article. Topramezone was also not mutagenic in independently performed gene mutation assays in Chinese hamster ovary (CHO) cells up to insoluble and cytotoxic concentrations (MRID 45902230).

There was, however, evidence of concentration-related and reproducible clastogenicity in two trials of an initial *in vitro* chromosome aberration assay with Chinese hamster lung (V79) (MRID 45902232) and in a confirmatory assay performed three years later (MRID 45902233). Purity for both batches (Batches N 14 and 30786/22) used in these assays was 97.7 and 99.3%, respectively. In all cases, topramezone was positive up to S9-activated levels that were insoluble but not cytotoxic. The most frequently observed aberration was exchange. In contrast to the positive findings from the *in vitro* assays for chromosome damage, topramezone (Batch N 14, 97.7%) was neither clastogenic nor aneugenic when tested in excess of the limit dose in the bone marrow of NMRI mice (MRID No. 45902234). Although the registrant claimed that the results of a pharmacokinetic study indicate that the test material reaches the bone marrow, it was noted that the pharmacokinetic study in question was conducted in rats, not in mice. Therefore, no link can be made between the pharmacokinetic data and the micronucleus results. Nevertheless, topramezone tested negative in excess of the limited dose. Topramezone was also negative for induction of unscheduled DNA synthesis in primary rat hepatocytes (MRID 4590302).

It was concluded that topramezone induced a clastogenic response in cultured mammalian cells but this activity is not expressed in whole animals. The lack of a clastogenic effect *in vivo* casts doubts on the relevance of the in vitro response to a possible mutagenic mode of action for topramezone. Consequently, there is no concern for mutagenicity. The submitted assays satisfy the FIFRA guidelines for mutagenicity testing. No additional testing is required at this time.

Within the mutagenicity package, two studies were found on test material Reg. No. 388 010 which has a different CAS number than topramezone technical. Results for these studies were negative for gene mutations in Chinese hamster lung (V79) cells up to the limit concentration (MRID 45902231) and negative for micronucleus induction in the bone marrow of NMRI mice up to an intraperitoneal dose that represents 80% of the lethal dose (MRID 45902301).

Table 4.4.11 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.
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.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
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.
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.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
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.		

4.5 Special 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 special FQPA SF is 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 based on the following:

1. 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.

2. 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.

3. There are no residential uses of topramezone.

4.6 Endocrine Disruption

EPA is required under the 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 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).

Thyroid follicular cell hypertrophy was observed in a 28-day dermal toxicity study in rats. In a chronic rat study, thyroid hypertrophy was observed in male rats, and incidence of follicular cell adenomas were observed in a carcinogenicity study in rats.

In a two-generation reproductive toxicity study in rats, the increased time to preputial separation in the F_1 males and increased thyroid weights and microscopic findings in thyroids were observed. When additional appropriate screening and/or testing protocols being considered under HED's EDSP have been developed, topramezone may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

Topramezone is a new active ingredient. Therefore, public health information is not available.

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

6.1.1 Residue Profile

The results of the topramezone metabolism studies in corn, ruminants and poultry were similar in that the parent compound was not extensively metabolized. However, significant differences were observed in the metabolic pathways. In corn, the metabolism of topramezone involved the hydrolytic cleavage of the parent to form the acid metabolite M670H05. Further hydrolysis and cleavage resulted in the formation of M670H08, while desmethylation resulted in M670H03. After cleavage, the pyrazole ring appeared to undergo complete catabolism and reincorporation within the carbon backbone of natural products such as starch, soluble polysaccharides and fatty acids. The phenyl ring portion of the molecule also underwent degradation, resulting in the incorporation of radioactivity into natural products. In ruminants, the proposed metabolic pathway involved hydroxylation of the parent compound topramezone at the 4-position of the isoxazole ring to form M670H02. The isoxazole ring was then cleaved to form the cyano metabolite (M670H01). The linkage between the phenyl and pyrazole rings remained intact in all of the metabolites identified. In poultry, the proposed metabolic pathway also involved hydroxylation of the parent compound topramezone at the 4-position of the isoxazole ring to form M670H02. Further N-demethylation of M670H02 occurred and formed the desmethyl hydroxy metabolite M670H04. M670H04 was only detected in the phenyl-labeled liver. The pyrazole ring of topramezone could also be cleaved to form the acid metabolite M670H05. Similar metabolic pathways were also observed in rotational crops, with M670H05 and

M670H02 being the only metabolites identified. Topramezone *per se* is the residue of concern in crops and ruminants for purposes of tolerance enforcement and risk assessment. Additionally, M670H05 is a residue of concern in rotational crops. As a result of the proposed plantback restrictions, residues in rotational crops are not expected to result from the proposed uses.

BASF has proposed liquid chromatography (LC)/mass spectrometry (MS)/MS method No. D0007 for data-gathering and enforcement purposes for residues of topramezone and the free acid metabolite M670H05 in/on plant commodities and LC-MS/MS method D0104 for data-gathering and enforcement purposes for residues of topramezone and the metabolite M670H02 in/on livestock commodities. These methods will undergo a petition method validation (PMV) at Analytical Chemistry Laboratory/Biological and Economics Analysis Division (ACL/BEAD) (Memo S. Levy, 12/2/04; DP# 310773). **Successful completion of the PMV is necessary before the proposed methods can be employed for enforcement purposes.** As topramezone was not adequately recovered using any of the U.S. Food and Drug Administration (FDA) Multiresidue Methodologies (MRM) Test Protocols, MRMs would not be suitable for use as an enforcement method.

The petitioner submitted magnitude of the residue data for field corn, sweet corn, limited field rotational crops and lactating dairy cows. The field trial studies were conducted using the proposed application scenarios (with the exception of a 4.5X application rate) and in the regions suggested in OPPTS 860.1500 for establishment of a tolerance in/on the crops requested. No processing study was required as two field corn plots treated with topramezone at exaggerated rates (12-20X) produced no quantifiable residues. The field trial data were generated using adequately-validated analytical methods (storage intervals have also been validated) and resulted in no residues greater than the limit of quantitation (LOQ) in/on any RACs. In the lactating dairy cow feeding study, conducted at 4.9X, 13X and 47X, quantifiable residues were found only in liver and kidney (all levels). Based on the magnitude of the residue and processing studies, HED concludes that tolerances are appropriate for residues of topramezone *per se* in/on the following RACs:

Corn, field, forage	0.05 ppm	Corn, sweet, forage	0.05 ppm
Corn, field, grain	0.01 ppm	Corn, sweet, kernel plus cob with husks removed	0.01 ppm
Corn, field, stover	0.05 ppm	Corn, sweet, stover	0.05 ppm
Corn, pop, grain	0.01 ppm	Cattle, kidney*	0.05 ppm
Corn, pop, stover	0.05 ppm	Cattle, liver*	0.15 ppm

* includes: goat, horse, and sheep

A revised Section F is requested; no additional field trial or processing data are necessary. The rotational-crop plantback intervals (PBIs) listed on the proposed label are supported by the data submitted for rotational crops (confined and limited field).

6.1.2 Acute and Chronic Dietary Exposure and Risk

Residues of Concern in Plants & Livestock: Topramezone *per se* is the residue of concern in crops and ruminants for purposes of tolerance enforcement and risk assessment. As a result of the proposed plantback restrictions, residues of topramezone in rotational crops are not expected to result from the proposed uses.

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

Topramezone acute and chronic dietary risk assessments were conducted using DEEM-FCID™, Version 2.0 which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998.

Acute Dietary Exposure Results and Characterization

The Tier 1 acute 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 peak concentration for surface water generated by the PRZM - EXAMS model as a high-end estimate. An endpoint of concern attributable to a single dose was not identified in the hazard database for the general population (including infants and children), the acute risk analysis was performed only for females 13-49 years of age. The resulting acute dietary exposure and risk estimates using the DEEM-FCID model at the 95th percentile were 0.000068 mg/kg/day (1.4% of the aPAD) and are thus below HED's level of concern (<100%aPAD). **Since drinking water was included directly into the acute dietary analysis, the risk estimate represents acute aggregate risk from topramezone.**

Chronic Dietary Exposure Results and Characterization

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 risk estimates were less than 1.6% of the cPAD for the U.S. population and all population subgroups. The chronic dietary exposure and risk estimates (food + water) were estimated at 0.000023 mg/kg/day for the U.S. population (0.6% of the cPAD) and 0.000050 mg/kg/day (1.2% of the cPAD) for the most highly exposed population subgroup (children 3-5 years old) and are thus below HED's level of concern (<100%cPAD). **Since drinking water was included directly into the chronic dietary analysis, the risk estimate represents chronic aggregate risk from topramezone.**

Table 6.1.2 Summary of Dietary 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	N/A	0.000023	0.6
All Infants (< 1 year old)			0.000037	0.9
Children 1-2 years old			0.000042	1.1
Children 3-5 years old			**0.000050**	**1.2**
Children 6-12 years old			0.000038	0.9
Youth 13-19 years old			0.000029	0.7
Adults 20-49 years old			0.000019	0.5
Adults 50+ years old			0.000012	0.3
Females 13-49 years old	0.000068	1.4	0.000019	0.5

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 percent CT data, as well as refined drinking water estimates.

6.2 Water Exposure/Risk Pathway

Exposure concentrations of topramezone in drinking water were estimated using the PRZM Version 3.12 (May 24, 2001) and EXAMS Tier II simulation models for surface water and SCI-GROW for ground water. For surface water, estimates were made for ground and aerial applications. Five different corn scenarios were selected to estimate exposure in surface water.

Application rates were taken from the proposed label. Appropriate input parameters were selected from the physical and chemical properties (intrinsic properties) and from environmental fate studies submitted in support of registration for this chemical. Selection of physical chemical properties and environmental fate input parameters were in accordance with the recommendations given in *Guidance for Selecting Input Parameters in Modeling the Environmental Fate and Transport of Pesticides*, Version II, February 28, 2002.

Table 6.2 summarizes the estimated exposure concentrations (corrected for percent crop area (PCA)) of topramezone in surface and groundwater as a result of aerial or ground single application at the maximum proposed rate of 0.022 lb ai/acre (25 g/ha). The highest estimated concentrations were for Florida sweet corn. The topramezone concentrations represent, the 1-in-10-year annual exceedance probability for peak, yearly mean, and the overall mean for the Florida scenario. The PCA for corn is 0.46 (USEPA, 1999). There are no significant differences in exposure concentrations between aerial and ground applications, suggesting that exposure in

surface water is the result of runoff rather than by spray drift from application.

The simulation model SCI-GROW is not scenario-specific (i.e., it uses a generic scenario). Because topramezone is a weak acid, sorption may be influenced by pH and mineralogy of the soil. However, due to the limited range of soil pHs used by the registrant, a significant relationship was not observed.

Table 6.2 Summary of Estimated Surface and Ground Water Concentrations for Topramezone

Exposure Duration	Topramezone	
	Surface Water Conc., ppb [a]	Ground Water Conc., ppb [b]
Peak	0.77	0.0671
Average	0.14	

[a] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on applying a Percent Crop Area Adjustment to Tier 2 Surface Water Model Estimates for Pesticide Drinking Water Exposure Assessments. 12-07-99; maximum application rate of 0.022 lb ai/A, mean K_{ads} = 2.8 mL/g, aerobic soil metabolism half-life of 241.28 days.

[b] From the SCI-GROW model assuming a maximum seasonal use rate of 0.022 lb ai/A, a median K_{oc} of 105.5, and a aerobic soil metabolism half-life of 197.04 days.

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

There are no proposed or existing residential uses of topramezone.

6.3.1 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 (add) 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. Therefore, aggregate risk will consist of exposure from food and drinking water sources. Acute (females 13-49 years old only) and chronic aggregate risks were calculated. An endpoint of concern attributable to a single dose was not identified in the hazard database for the general population including infants and children.

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 6.1.2.

The Tier 1 acute 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 peak concentration for surface water generated by the PRZM - EXAMS model as a high-end estimate. An endpoint of concern attributable to a single dose was not identified in the hazard database for the general population (including infants and children), the acute risk analysis was performed only for females 13-49 years of age. The resulting acute dietary exposure and risk estimates (food + water) using the DEEM-FCID model at the 95th percentile were 0.000068 mg/kg/day (4.0% of the aPAD) and are thus below HED's level of concern (<100%aPAD).

7.2 Short-Term Aggregate Risk

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

7.3 Intermediate-Term Aggregate Risk

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

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 6.1.2.

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 risk estimates were less than 1.2% of the cPAD for the U.S. population and all population subgroups. The chronic dietary exposure and risk estimates (food + water) were estimated at 0.000023 mg/kg/day for the U.S. population (0.6% of the cPAD) and 0.000050 mg/kg/day (1.2% of the cPAD) for the most highly exposed population subgroup (children 3-5 years old) and are thus below HED's level of

concern (<100%cPAD). **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

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to topramezone and any other substances and topramezone does not appear to produce a toxic metabolite produced by other substances. However, EPA is aware of other herbicides that inhibit the 4-HPPD enzyme (i.e. mesotrione and isoxaflutole). Topramezone, isoxaflutole and mesotrione are known to cause tyrosinemia. To ensure that the potential cumulative effects from these pesticides are not of concern EPA examined three factors: (1) the extent to which the uses of these pesticides overlap; (2) the exposure assumptions used in the risk assessments for each of the pesticides; and (3) the risk characterization for each pesticide. As explained below, this analysis suggests both that the individual risk characterizations for each pesticide are highly overstated and that cumulative exposure to these pesticides, even if later determined to share a common mechanism, is unlikely to pose a risk of concern.

Pesticide uses. Topramezone, mesotrione, and isoxaflutole are broad-spectrum herbicides used to control grassy and broadleaf weeds in corn (the mesotrione label does not list grasses on the label). All three active ingredients are in the phenylpyrazolyl ketone class of chemicals and share the same mode of herbicidal action. They inhibit the 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) enzyme and thereby impair caroteniod biosynthesis in the chlorophyll synthesis pathway, leading to the breakdown in chloroplasts. Therefore no more than one of these active ingredients would be applied to the same field in the same growing season. Topramezone is used post-emergent, mesotrione is used pre- and post-emergent, and isoxaflutole is used pre-plant and pre-emergent. The current % crop treated (CT) information for field corn indicates a 5-10% CT for isoxaflutole and 10-15% CT for mesotrione. Sweet corn %CT is <2.5 for both chemicals. Maximum %CT projections for topramezone on field corn and sweet corn, made by assuming that it will surely not overtake the current leader(s) among herbicides on those crops (i.e. atrazine), are 68 and 60, respectively.

Exposure Assumptions. Highly-conservative assumptions were used for the aggregate (food + water) risk assessments for each individual assessment. First, it was assumed that 100 percent of the corn crop was treated with all three of the pesticides. Second, each of the exposure assessments assumed all corn in the diet would have residues present at the tolerance level. Residue data indicates that very low levels of residues were detected in the grain for all three pesticides.

Risk Characterization. Even with the highly-conservative assumptions the individual aggregate risk for each of the active ingredients is as follows: (1) The topramezone chronic dietary risk estimates (food + water) were <1% of the cPAD for the U.S. population and 1.2% of the cPAD for the most highly exposed population subgroup (children 3-5 years old); (2) The mesotrione chronic dietary risk estimates (food + water) were 15% of the cPAD for the U.S. population and 45% of the cPAD for the most highly-exposed population subgroup (all infants (< 1 year old)); and (3) The chronic dietary risk estimates (food + water) for residues of the 4-

HPPD inhibitors (isoxaflutole + RPA 202248) were 18% of the cPAD for the U.S. population and 40% of the cPAD for the most highly-exposed population subgroup (children 3-5 years old). In fact, even if one were to calculate the chronic dietary risk for all three herbicides by combining the individual exposures and using the most sensitive endpoint, the risk would not exceed the level of concern. These pesticides do not share a common acute adverse effect.

Accordingly, because the use patterns, exposure assumptions, and risk characterizations for the three pesticides do not suggest that any potential cumulative effect would be at a level of concern, EPA concludes it has adequately considered the potential cumulative effects of topramezone and the pesticides for which it may possibly share a common mechanism of toxicity.

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/Risk Pathway

9.1 Short/Intermediate/Long-Term Handler Risk

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) Aerial applicator (pilot)

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 in duration (1 - 30 days). The ExpoSAC maintains that it is possible for a commercial applicator to be exposed to intermediate-term exposures (1 - 6 months) by treating farm after farm for the same pest complex. HED 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 will 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 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 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 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 PPE as might be necessary.

Short- and intermediate-term handler risks were estimated. A dermal-absorption factor of 13% was use to calculate occupational risks. HED assumed 100% inhalation absorption. The level of concern for occupational pesticide handlers and agricultural workers is an MOE of $\leq$100.

Table 9.1 Estimated Handler Exposure and Risk from the Use of Topramezone on Corn

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 PHED 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 SC Herbicide.
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture," SOP No. 9.1. ExpoSAC; Revised 5 July 2000;
4. Average Daily Dose = Unit Exposure * Applic. Rate * Units Treated * absorption factor (13% 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.

Provided that mixer/loaders use protective gloves as specified on the proposed label, all MOEs are >100 and therefore do not exceed HED's level of concern.

9.2 Short/Intermediate/Long-Term Post-application Risk

There is a potential for post-application exposure of agricultural workers 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 TCs (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 9.2. In this case, the highest TC is associated with corn detasseling. However, the timing of topramezone makes it unlikely that workers would be exposed to topramezone during detasseling or scouting activities (topramezone is applied early postemergence, when weeds are approximately 6" tall). Therefore, HED used the TC of 400 cm^2/hr for scouting or irrigation activities for postapplication risk assessment.

Table 9.2 Summary of Highest TCs (cm^2/hr) For Post-application Activities in Corn

Post-application Activity	TC 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 TCs used in this assessment are from an interim TC SOP developed by the ExpoSAC using proprietary data from the ARTF database (SOP # 3.1). It is the intention of the ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on TCs. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to HED, and from studies in the published scientific literature.

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

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

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 $mg/\mu g$ * 1/70 kg bw

and where:

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

TC =400 cm^2/hr

0.022 lb a.i./A * 0.20 * $(1\text{-}0)^0$ * 4.54×10^8 $\mu g/lb$ * 2.47×10^{-8} A/cm^2 = 0.0493 $\mu g/cm^2$, therefore,

0.0493 $\mu g/cm^2$ * 400 cm^2/hr * 8 hr/day * 0.001 $mg/\mu g$ * 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.

9.3 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) REI (as listed on the proposed label) of 12 hours is adequate to protect occupational handlers and agricultural workers from post-application exposures to topramezone.

10.0 Data Needs and Label Requirements

Residue Chemistry

OPPTS 860.1340 Residue Analytical Methods

Plant commodity methods:

The proposed plant enforcement method needs to pass a PMV by Agency chemists at ACL/BEAD before the method can be deemed adequate for tolerance enforcement. Method D0007 has been forwarded to ACL/BEAD for the PMV (Memo S. Levy, 12/2/04; DP# 310773).

Livestock commodity methods:

The proposed livestock enforcement method needs to pass a PMV by Agency chemists at ACL/BEAD before the method can be deemed adequate for tolerance enforcement. Method D0104 has been forwarded to ACL/BEAD for the PMV (Memo S. Levy, 12/2/04; DP# 310773).

860.1550 Proposed Tolerances

The petitioner is requested to submit a revised Section F as specified in Section 6.1.1 of this document. HED determined that the tolerances proposed by the registrant for livestock RACs were too high.

References:

CARC Report:	Not finalized.
Residue Chemistry Summary:	Topramezone (BAS 670 H) in/on Corn. PP# 3F6568. Summary of Analytical Chemistry and Residue Data. G. Kramer. DRAFT. D310772
Dietary Analysis:	Topramezone (BAS 670 H) Acute and Chronic Dietary Exposure Assessments for a Petition for Tolerances on Corn. G. Kramer. D314719. 5/9/05.
Occupational Assessment:	BAS 670 H (TOPRAMEZONE) - Exposure/Risk Assessment for the Proposed Use of BAS 670 H On Corn (Field, Pop, Seed and Sweet). DRAFT.
Drinking Water Assessment:	Topramezone (BAS 670H) Herbicide. *Tier II Drinking Water Assessment.* J. Wolf, S. Termes.3/18/2005. D314642.

Appendix 1. Toxicological Data Requirements

The requirements (CFR 158.340) for food use of topramezone are presented below in Table A-1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A-1 Data Requirements (CFR 158.340) for Food Use of Topramezone

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	NA
870.3465	90-Day Inhalation	no	NA
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	no
870.6100b	90-Day Neurotoxicity (hen)	no	no
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Develop. Neuro	no	yes
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	no
	Subchronic Oral (rat)	no	no
	Six-month Oral (dog)	no	no

Appendix 2. Non-Critical Toxicology Studies

Executive summaries for studies not used for toxicity endpoint selection or FQPA assessment are as follows.

A-2.1 28-Day Dermal Toxicity – Rat (870.3200)

In a 28-day dermal toxicity study (MRID 45902206), topramezone (95.8% a.i.; Batch/Lot #: N26) in 0.5% (w/v) aqueous carboxymethylcellulose was applied to the shaved intact skin of Wistar rats (10/sex/dose) at dose levels of 0, 100, 300, or 1000 mg/kg bw/day (limit dose), 6 hours/day, 5 days/week for 4 weeks.

No treatment-related effects were observed in mortality, clinical signs, dermal effects, body weight, body-weight gain, food consumption, food efficiency, ophthalmoscopy, hematology, and clinical chemistry at any dose in either sex. No serum tyrosine level was measured.

Increased incidence of elevated ketone levels in the urine was noted at 100 mg/kg and above of both sexes. However, the results may be false positive due to the chemical treatment. The mode of action of the test material is inhibition of the enzyme p-hydroxyphenylpyruvate-dioxygenase, an enzyme involved in tyrosine catabolism in animals. The inhibition of this enzyme results in increased tyrosine levels in the blood and urine and leads to an excretion of large amounts of p-hydroxyphenylpyruvic acid (a keto-acid), which interferes with the reagent in the test strip method and causes false-positive results for ketone bodies in the urine.

Increased relative liver weights were observed in males only at doses ≥100 mg/kg. Histopathology examination revealed that one male of the 1000 mg/kg group showed a slight (grade 2) centrolobular hypertrophy of the liver cells which corroborated with the significantly increased mean relative liver weights. Increased relative thymus weight was observed in males at 1000 mg/kg. No morphologic alteration was noted that may explain the significantly increased mean relative thymus weight in males of the high dose group .

There is an increased incidence of slight thyroid follicular cell hypertrophy in the males at 300 and 1000 mg/kg. Two females at 1000 mg/kg also showed slight follicular cell hypertrophy.

For males, the LOAEL is 300 mg/kg/day based on thyroid follicular cell hypertrophy. The NOAEL is 100 mg/kg/day. For females, the LOAEL is 1000 mg/kg/day based on thyroid follicular cell hypertrophy and the NOAEL is 300 mg/kg/day. No serum tyrosine level was measured.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3200; OECD 410) for a 28-day dermal toxicity study in rats.

A-2.2 Subchronic Oral Toxicity - Mouse (870.3100)

In a subchronic oral toxicity study (MRID 45902202), topramezone (97.7% a.i., Batch/Lot #: N14) was administered to C57BL mice (10/sex/dose) in the diet at doses of 0, 125, 1000, or 8000

ppm (equivalent to 0/0, 37/51, 288/406, or 2289/3010 mg/kg/day [M/F]) for up to 91 days.

There were no adverse treatment-related effects observed on mortality, clinical signs, body weight, body-weight gain, food consumption, hematology, clinical chemistry, or gross or microscopic pathology at any dose in either sex. No serum tyrosine level was measured.

Increased relative liver weight was observed in females only at 1000 and 8000 ppm; however, there was no corroborative histopathological evidence for this finding, and it was considered adaptive effect. Decreased testes weights were observed in males at 125 and 1000 ppm. There was no dose-dependent responses and was considered incidental. Gross pathology showed increased incidence of erosion/ulcer in the glandular stomach in females at 1000 and 8000 ppm. However, the microscopic evaluation of the stomach showed that these erosions/ulcers also occurred with equal frequency in the control group and was not considered treatment-related.

Under conditions of this study, the LOAEL was not observed. The NOAEL is 8000 ppm (equivalent to 2289/3010 mg/kg/day in M/F).

This study is classified **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100; OECD 408) for a 90-day oral toxicity study in the mouse.

A-2.3 Subchronic Oral Toxicity- Rat (870.3100)

In a subchronic oral toxicity study (MRIDs 45902204 and 45902203), topramezone (99.3% a.i., Batch # 30786/22) was administered to 10 Wistar rats/sex/dose in the diet at dose levels of 0, 15, or 30 ppm (equivalent to 0/0, 1.1/1.3, and 2.1/2.5 mg/kg/day in males/females) for 13 weeks.

No treatment-related effect was observed on mortality, clinical signs, body weight, body-weight gain, food consumption, food efficiency, ophthalmology, hematology, urinalysis, organ weights, or gross pathology.

A minimal diffuse degeneration was observed in the pancreas of the 30 ppm males (2/10 treated vs 0/10 controls). The Sponsor stated that the lesions most resembled a chronic interstitial pancreatitis morphologically. This lesion was also observed in a previous subchronic toxicity and neurotoxicity study (MRID 45902201, concurrently submitted). Minimal to moderate flaky colloid was observed (vs 0/10 controls) in ≥15 ppm males (9-10/10) and females (1-3/10). There was no other histological thyroid lesion and no evidence of impairment of function; therefore, this effect was not considered adverse.

In the 30 ppm males, cholesterol was increased ($p \leq 0.01$) by 28%; and alkaline phosphatase was decreased ($p \leq 0.01$) by 21%. Corroborating evidence of adverse effect was absent for both parameters.

The LOAEL for males is 30 ppm (equivalent to 2.1 mg/kg/day), based on diffuse degeneration in the pancreas. The NOAEL is 15 ppm (equivalent to 1.1 mg/kg/day). The LOAEL for females was not established, the NOAEL is 30 ppm (2.5 mg/kg/day).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the rat.

A-2.4 Subchronic (8 week) Oral Toxicity - Dog (870.3150)

In a subchronic oral toxicity study (MRID 45902205), topramezone (95.2-95.8% a.i., Batch/Lot #s: N17 & N26) was administered to Beagle dogs (5/sex/dose) in a diet at doses of 0, 3000, 9000, or 25,000 ppm (equivalent to 0/0, 182/205, 535/624, or 1511/1712 mg/kg/day [M/F]) for up to 90 days.

No adverse treatment-related effects were observed on mortality, clinical signs, food consumption, hematology, clinical chemistry, gross or histopathology parameters.

Decreased body-weight gains were observed in males at 25,000 ppm throughout treatment with the terminal body weight decreased by 10% ($p \leq 0.05$). Food efficiency was decreased by 28-338% compared to controls in the 25000 ppm males throughout the study. No significant differences in body weights were observed at any dose in females; decreased body-weight gains were noted at all doses; however, no dose response was seen.

Urinalysis showed increased ketone level in the urine of all treated animals of both sexes. This finding may be a false positive due to excretion of p-hydroxyphenylpyruvic acid (a keto-acid) which interferes with the reagent of the test strip. Increased incidence of crystal (identified as magnesium complex of the parent compound) was seen in urine sediments of 25000 ppm males.

Absolute brain weight was decreased ($p \leq 0.01$) by 15-16% in the ≥9000 ppm females; however, the relative brain weight were comparable in all doses. In addition, as there was no corroborative histopathological evidence in the brains of these animals, this finding is of equivocal toxicological importance. Histopathology revealed inflammation in the urinary bladder of two male dogs at the 25000 ppm. All other histopathological evaluations were either incidentally as single case or were equally distributed over the dose groups.

The NOAEL for males is 9000 ppm (equivalent to 535 mg/kg/day), and the LOAEL is 25,000 ppm (equivalent to 1511 mg/kg/day) based on decreased body-weight gain, impaired food efficiency, and inflammation of the urinary bladder. The NOAEL for females is 25000 ppm (equivalent to 1712 mg/kg/day), the LOAEL for females is not established.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3150; OECD 409) for a 90-day oral toxicity study in the dog.

A-2.5 Chronic Oral Toxicity Study in Dogs (870.4100b)

In a chronic toxicity study (MRID 45902215), topramezone (95.8% a.i., Batch No.: N26) was administered to beagle dogs (5/sex/dose) in the diet at doses of 0, 3000, 9000, or 25,000 ppm for 209 days and 0, 2600, 7800, or 22,000 for study days 210-364 (equivalent to 0/0, 81/92, 248/287, and 688/780 mg/kg/day in males/females over the entire study). Because a NOAEL was not established in the initial study, a supplementary study (MRID 45902216) was performed. The

same test material (Batch No.: N26) was administered to 5 beagle dogs/sex/dose in the diet at doses of 0, 100, or 500 ppm (equivalent to 0/0, 2.9/3.1, and 15.3/15.4 mg/kg/day in males/females) for up to 12 months.

Two 25,000 ppm males died, one on Day 137 and the other on Day 280. The cause of death for both dogs were attributed to necrotizing cystitis and postrenal uremia. Observed clinical signs were limited to these two dogs that die. No other treatment-related adverse effects were seen on ophthalmology, food consumption, hematology, and clinical chemistry.

Slight decreases (NS) in body weight were frequently observed throughout the studies in males at ≥500 ppm and in females at ≥3000 ppm. This effect was clearly dose-dependent by Day 126 in the initial study and throughout the supplementary study. Cumulative body-weight gains were decreased in all treated animals throughout the studies. Overall body-weight gains (Day 0-364) were decreased in males at 3000 (↓9%, NS), 9000 (↓25%, NS), 25000 (↓34%, NS) ppm and in females at 3000 (↓14%, NS), 9000 (↓55%, $p \leq 0.05$), and 25,000 (↓29%, NS) ppm. Significant decreases ($p \leq 0.05$) were often observed in the 9000 ppm females from Day 77 to termination and in the 25,000 ppm females on Day 238. The effect on body-weight gain in the females was not clearly dose-dependent.

In the supplementary study, slight decrease (NS) of body weight and body-weight gains were observed in 500 ppm males compared to the control during the entire treatment period. Interestingly, increased body weight and body-weight gains (NS) were observed in females at 500 ppm. Overall (Days 0-364) body-weight gain was increased (NS) in the 100 and 500 ppm females by 5-46%. This increase (NS) may have been incidental as the effect of treatment in these studies is generally a decrease in body-weight gain. For these reasons, the effect on body-weight gain in the 100 and 500 ppm females was not considered adverse.

Although food consumption was limited and the ration was generally entirely consumed, food efficiency was affected as evidenced by the variation in body-weight gains. The average food efficiency (calculated by the reviewer) was decreased dose-dependently in the males of both studies; however, the decrease in the 100 ppm males was minor. Food efficiency was decreased in the ≥3000 ppm females, but the effect was not clearly dose-dependent. Food efficiency was not decreased in the 100 and 500 ppm females.

No significant treatment-related adverse effects were observed in hematology and chemistry parameters; however, serum tyrosine level was not measured in this study. Urinalysis showed increased ketone level in the urine in all treated animals. This finding may be a false positive due to excretion of p-hydroxyphenylpyruvic acid (a keto-acid) which interferes with the reagent of the test strip. Decreased urine pH values ($pH<6$) were observed in all treated animals compared with the controls ($pH>6$). Examination of urinary sediment revealed crystals (it was identified as magnesium complex of the parent compound). The study authors stated that due to the known solubility characteristics of the compound which is heavily dependent on pH level, it is possible that the limit of solubility was surpassed, as indicated by crystals of the compound in urine sediment. This finding was supported by high concentration of topramezone detected in the urine of treated animals. The quantity detected in the urine was not linearly proportional to the administered dose.

Histopathology examinations showed increased incidences of minimal to moderate thyroid C-cell hyperplasia in males (3-4/5 treated vs 1/5 controls). No dose-response was observed in females (3-5/5 treated vs 5/5 controls). It is known from other concurrently submitted studies that the compound affects the thyroid. Therefore, the thyroid c-cell hyperplasia is considered treatment-related.

Significant microscopic lesions were observed only in the two males of the 25000 ppm group that died: (i) renal/urinary system toxicity as evidenced by ureter dilation; urinary bladder cystitis; and pyelonephritis, perinephritis, and concretion in the kidney; (ii) ilium Peyer patch atrophy; (iii) brain glia cell reaction; (iv) indications of reproductive organ toxicity including hyperemia in the epididymides and prostatitis; (v) starry sky appearance of the thymus; (vi) serositis in the mesenteric lymph node; and (vii) hyperemia in the auxiliary lymph node.

One male dog of the 9000 ppm group showed multiple hemorrhages in the urinary bladder wall which corroborates with its gross pathological finding. This may be an indication for early toxic damage of the structures of the urinary bladder wall. The loss of the integrity of the transitional epithelium could lead to bacterial infection and other secondary effects.

All other histopathological evaluations were considered incidental as it occurred in single case or were equally distributed over the treated and control groups.

For males, the NOAEL is 100 ppm (equivalent to 2.9 mg/kg/day), and the LOAEL is 500 ppm (equivalent to 15.3 mg/kg/day) based on increased incidence of thyroid C-cell hyperplasia. For females, the NOAEL is 500 ppm (equivalent to 15.4 mg/kg/day), and the LOAEL is 3000 ppm (equivalent to 92 mg/kg/day) based on decreased body weights, body-weight gains, and food efficiency. No serum tyrosine level was measured.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.4100b, OECD 452) for a chronic oral toxicity study in dogs.

A-2.6 Chronic Oral Toxicity Study in Rats (870.4100)

In a chronic toxicity study (MRID 45902217), 20 Wistar (CrlGlxBrlHan:WI) rats/sex/dose were exposed to topramezone (95.2-95.8% a.i.; Lot/Batch Nos.: N17 and N26) in the diet at concentrations of 0, 6, 60, 600, or 6000 ppm (equivalent to 0/0, 0.4/0.5, 3.9/5.3, 42.0/53.2, and 422.6/535.0 mg/kg/day in males/females) for up to 364 days.

No treatment-related effect was observed on mortality, body weight, body-weight gains, food consumption, food efficiency, hematology, clinical chemistry, urinalysis, or neoplasia.

Clinical observations showed an increased incidence of corneal opacity in the right and/or left eye in the ≥60 ppm groups of both sexes. During ophthalmoscopic examination, an increased incidence of corneal pannus was observed in the ≥60 ppm groups of both sexes. Increased incidence of corneal opacity was observed in the ≥60 ppm females and in the ≥600 ppm males. Incidence and initial time observed was generally dose-dependent. Macroscopic examination showed a dose-dependent increased incidence of cloudiness of the cornea in the≥60 ppm groups

of both sexes.

Microscopic examination revealed a dose-dependent increase in incidence and severity of minimal to marked chronic keratitis, which typically corresponded to cloudiness of the cornea, in the ≥60 ppm groups of both sexes. In the thyroid, increased incidence of minimal to slight diffuse hypertrophy and focal follicular cell hyperplasia were observed in the ≥60 ppm groups of both sexes. The thyroid hypertrophy was increased in incidence and severity with dose; however, the hyperplasia was not clearly a dose-dependent effect, and severity was not reported. In the pancreas, a dose-dependent increase in incidence and severity of minimal to moderate diffuse degeneration was observed in ≥600 ppm males.

The LOAEL is 60 ppm (equivalent to 3.9/5.3 mg/kg/day in males/females), based on corneal opacity and pannus and chronic keratitis in both sexes, and thyroid hypertrophy in males. The NOAEL is 6 ppm (equivalent to 0.4/0.5 mg/kg/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements for a chronic oral study [OPPTS 870.4100, OECD 452] in rats.

A-2.7 Metabolism - Rat (870.7485)

In a rat metabolism study (MRIDs 45902305 and 45902306), ^{14}C-topramezone in 0.5% aqueous Tylose or Cremophor EL/CMC was administered to Wistar rats by gavage. In an initial plasma kinetics studies, a single oral dose of [pyrazole-4-^{14}C]-topramezone (Batch # 706-1013; radiochemical purity of ≥ 98%) was administered to 4 Wistar rats/sex/dose at nominal doses of 10, 100, 200, 400, or 500 mg/kg. In the main mass balance/excretion/metabolism studies, 4 rats/sex/dose were given [pyrazole-4-^{14}C]-topramezone as a single oral dose of 10 or 300 mg/kg, a repeated oral dose of 300 mg/kg (14 days unlabeled + 1 day radiolabeled), or 300 mg/kg [phenyl-U-^{14}C]-topramezone (Batch #714-1026; radiochemical purity of ≥ 98%). Tissue distribution time course and biliary excretion studies were also performed. Metabolites were identified and quantified in the urine, feces, bile, kidney, and liver in the main studies at 10 and 300 mg/kg. In an additional study, metabolite profiles were determined in urine and feces of rats given a single oral dose of 500 mg/kg.

Absorption of ^{14}C-topramezone following a single oral dose was rapid but limited, with the highest plasma concentrations observed at 1 hour (first time point measured). In the 10 mg/kg group, a second smaller peak in plasma concentration occurred at 8 hours post-dose. Plasma concentrations declined bi-phasically at 10 and 100 mg/kg and tri-phasically at ≥ 200 mg/kg. The change in AUC was proportional to dose in both sexes at ≤ 200 mg/kg and overproportional with dose at 400 and 500 mg/kg.

In the main mass balance/excretion studies, 94-103% of the dose was recovered after 168 hours, with ≤ 0.12% dose remaining in the tissues and <0.1% of the dose in exhaled air. The majority of the dose was recovered within 48 hours in the feces (73-91% dose) and urine (8-29% dose). In a separate experiment, bile was collected for up to 48 hours from rats and accounted for 19-32% dose at 10 mg/kg and 7-9% dose at 300 mg/kg. The pattern of excretion was similar between the sexes and dose groups, although urinary excretion was higher in the low dose groups than in the

high dose groups. Urinary excretion was also higher in females, while biliary excretion was higher in males.

At 168 hours post-dose, concentrations of radioactivity remaining in the tissues were generally similar between the sexes and across the dose groups. Concentrations were highest in liver and kidneys of all groups, and in the thyroid of rats from the single 300 mg/kg [^{14}C-pyrazole] dose group. Concentrations in the thyroid were also generally above levels in the blood for the other 300 mg/kg dose groups, but not the 10 mg/kg group. For the two groups dosed at 300 mg/kg with different ^{14}C-labels, concentrations in the adrenal glands, ovaries, uterus, bone marrow, and pancreas of the [^{14}C-phenyl] group were higher than in the [^{14}C-pyrazole] group, suggesting some differential distribution of metabolites. Repeated dosing at 300 mg/kg had no effect on the concentration of radioactivity in the tissues.

Similar findings in the relative distribution of radioactivity in tissues were observed in the time course study. Concentrations in the kidneys and liver were higher than in blood in both sexes at all time points in both the 10 and 300 mg/kg groups. Compared to levels in the blood, radioactivity was also higher in the ovaries and uterus beginning at 1 hour in the 10 mg/kg rats and beginning at 8 hours in the 300 mg/kg rats. In the thyroid, increases over blood levels were observed transiently in the low dose at 8 hours and consistently in the high dose beginning at 2 hours.

Radio-HPLC identified and quantified parent and up to four metabolites (M670H01, M670H02, M670H05, and M670H13) in the urine, feces, bile, liver, and kidney, and the identity of each compound was confirmed by LC/MS, LC/MS/MS, and /or NMR analysis. In the main study groups, parent and identified metabolites in excreta accounted for 91.8-104.5% dose, while unidentified compounds accounted for <1% dose.

In all groups, parent was the predominant compound identified in both urine (4.0-21.3% dose) and feces (66.3-91.7% dose). The primary metabolites in urine were M670H02 (1.0-5.3% dose) and M670H01 (0.2-1.2% dose), along with minor amounts (<0.5% dose) of M670H05 and M670H13. Metabolites identified in feces included M670H02 (1.3-3.1% dose) and M670H01 (0.6-6.7% dose). In the bile, parent was again the predominant compound identified, accounting for 3.4-13.7% of the dose, along with minor amounts of M670H02 (2.2-12.1% dose), M670H01 (0.2-1.3% dose), and M670H13 (<0.5% dose). In liver and kidneys sampled at T_{max} (1 hour) from both 10 and 300 mg/kg dose groups, the major compound identified was parent, accounting for 48.3-82.5% of the total radioactive residues (TRR), along with M670H02 (14.5-34.6% TRR) and M670H01 (0.9-14.0% TRR).

Regardless of sex, dose level, and the position of the ^{14}C-label, the overall metabolism of ^{14}C-topramezone in rats was similar. The ^{14}C-dose was excreted primarily as unchanged parent (82.7-98.3% dose), which was recovered primarily in the feces and to a lesser extent in the urine. Biotransformation of ^{14}C-topramezone was limited and primarily involved oxygenation of the isoxazole ring to form M670H02 (1.0-5.3% dose) and subsequent ring opening and loss of the acetic acid moiety to yield M670H01 (0.4-7.9% dose). A minor fraction of parent (<1% dose) was also hydrolyzed at methanone bridge to yield M670H13 and M670H05. The proposed pathway for biotransformation of ^{14}C-topramezone in rats is presented in Figure A-3.1.0.

This metabolism study in the rat is classified **acceptable/guideline** and satisfies the guideline requirement for a Tier 1 metabolism study [OPPTS 870.7485, OPP 85-1] in rats.

A-2.8 Special Study: 14-Day Dietary Study on Tyrosine - [rat and mouse]; Non-guideline

The purpose of these three non-guideline studies (MRIDs 45902218 through 45902220) was to measure the level of serum tyrosine and activity of hepatic tyrosine aminotransferase (TAT) in male CrlGlxBrlHan:WI rats and male C57BL/6JRj mice after 14 days of dietary exposure to topramezone. In the first study (MRID 45902218), 5 rats/dose and 15 mice/dose were fed topramezone (95.8% a.i.; Lot/batch # N26) continuously in the diet at nominal dose levels of 0, 6, 60, or 600 ppm (equivalent to 0, 0.6, 5.9, and 62.0 mg/kg bw/day in rats and 0, 1.7, 16.6, and 150.3 mg/kg bw/day in mice) for 14 days. Blood samples were taken for serum tyrosine analysis in 5 animals/species/dose after 1, 7, and 14 days; mice were sacrificed for blood sampling. Two subsequent studies were performed in order to determine a NOAEL for increased serum tyrosine levels and hepatic TAT activity in rats (MRID 45902219) and mice (MRID 45902220) in which 10 animals/species/dose were fed topramezone (99.3% a.i.; Lot/batch # 30786/22) continuously in the diet at nominal dose levels of 0, 1, 2, 3, 4, or 5 ppm (equivalent to 0, 0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg bw/day in rats and 0, 0.2, 0.5, 0.7, 0.9, and 1.2 mg/kg bw/day in mice) for 14 days. At termination: blood was collected for determination of serum tyrosine levels; liver tissue was sampled for measuring hepatic TAT activity; and a gross necropsy was performed. In all three studies, animals were observed for mortality and clinical signs of toxicity at least once daily. Body weights and food consumption were measured weekly. Body-weight gain, food efficiency, and test substance intake were calculated for each week.

There were no effects of treatment on survival, clinical signs, body weights, body-weight gains, food consumption, food efficiency, or gross pathology in any of the studies.

In the first study (MRID 45902218), serum tyrosine levels were increased (increase of 31-1362%; $p \leq 0.05$) in all treated groups of rats and mice. In mice, increases in serum tyrosine were dose-dependent. However, in rats, the dose-response reached a plateau at ≥60 ppm. At 6 ppm, increases over controls became more severe after Day 1, but at higher doses, these increases reached a plateau at Day 1.

In the subsequent studies at lower doses (MRIDs 45902219 and 45902220), serum tyrosine levels were increased ($p \leq 0.01$) in all treated groups (≥1 ppm) in both species, with greater increases in rats (increase of 532-808%) than in mice (increase of 55-104%). Similarly, tyrosine aminotransferase activity was increased ($p \leq 0.01$) in all treated groups (≥1 ppm) in rats (increase of 55-72%) and mice (increase of 24-35%).

The LOAEL was 1 ppm (equivalent to 0.1 mg/kg/day in rats and 0.2 mg/kg/day in mice) based on increased serum tyrosine levels and tyrosine aminotransferase activity. The NOAEL was not observed.

This study is classified as **acceptable/non-guideline**.

A-2.9 Special Study: Thyroid Hormone Study (diet) - Rats; Non-guideline

The objective of this study was to determine if topramezone impaire thyroid hormones and to determine the reversibility of any effects observed. In this non-guideline study (MRID 45902223), topramezone (95.8% a.i.; Lot/Batch #: N26) was administered in the diet to Wistar (CrlGlxBrlHan:Wi) rats (5/sex/dose) at concentrations of 0, 6, 60, 600, or 6000 ppm (equivalent to 0/0, 0.4/0.4, 3.6/4.3, 35.4/43.0, or 360.7/439.5 mg/kg/day in males/females) for up to 4 weeks. Additional groups of 5 rats/sex/dose were similarly treated for 4 weeks and then observed for recovery in a period of 4 or 13 weeks. Total triiodothyronine (T3), total thyroxine (T4), and thyroid-stimulating hormone (TSH) were measured in serum. The animals were sacrificed and necropsied, and only the thyroid gland was examined microscopically.

No significant treatment-related effects were observed on clinical observations, mortality, food consumption, or food efficiency.

Minor decreases (NS) in body weight were generally observed in all treated animals. Minor decreases (NS) in body weight were also generally observed during the recovery periods in the males; however, changes were inconsistent in the females. At the end of treatment, decreases (NS) in body-weight gain were observed in all treated males (↓11-65%), in the ≥60 ppm females in the main study (↓30-40%), and in the ≥6 ppm females in the recovery studies (↓9-55%). These decreases were not clearly dose-dependent.

Decreased total T4 levels ($p \leq 0.05$) were observed in ≥60 ppm male groups on treatment Days 14 and 28 (↓13-26%). TSH levels were increased ($p \leq 0.05$) in the ≥600 ppm males on Day 28 (↑20-54%). The increase of TSH was considered a compensatory response due to the negative feedback of decreased T4 level. After cessation of test substance administration, serum T4 and TSH concentrations returned to the control level during the recovery period of 4 or 13 weeks. No effect was seen in the T3 level.

Histopathological examination of the thyroid showed increased numbers and high grades of altered (flaky) colloid. The significance of this finding was not clear since these effects were seen more prominent during recovery period than at the end of the treatment period.

Slight increase of liver weight was seen in males and females at the 6000 ppm treatment period and was considered treatment-related. After 4 or 13 weeks of recovery period, the liver weights were returned to the control level indicating reversibility of the liver.

The data indicate that administration of topramezone in the diet at a dose of ≥60 ppm (equivalent to 3.6/4.3 mg/kg/day in males/females) resulted in decreased serum thyroxine(T4) levels and increased TSH levels in males. No effect level was 6 ppm (0.4mg/kg/day).

The study is classified as **acceptable/non-guideline**.

A-2.10 Special Study: Hepatic Enzyme Induction Study - [rat]; Non-guideline

The aim of this non-guideline study was to determine a possible hepatic enzyme induction after repeated oral dosing. In this study (MRID 45902224), BAS 760H (95.8% a.i.; Lot/batch # N26) was administered in the diet to Wistar rats (CrlGlxBrlHan:WI) (5/sex/dose) at nominal dose levels

of 0 or 6000 ppm (equivalent to 0/0 or 557.9/593.6 mg/kg bw/day [M/F]) for 28 days. At termination, the liver and thyroid gland of each rat was weighed. Enzyme activities of p-nitrophenol-glucuronyltransferase (pNP-GT), 4-methylumbelliferone-glucuronyltransferase (MUF-GT), and 4-hydroxybiphenyl-glucuronyltransferase (HOBI-GT) were measured in the liver.

There were no effects of treatment on survival, clinical signs, body weights, body-weight gains, food consumption, food efficiency, thyroid weight, or hepatic activities of pNP-GT or HOBI-GT. MUF-GT activity was increased (not significant) in the treated males (increase of 71%) and females (increase of 29%) compared to controls. Relative (to body) liver weights were increased (increase of 8%; $p \leq 0.05$) in the treated males compared to controls. There were no effects of treatment on liver weights in the females. **These findings are indicative of an adaptive response in the liver, including increased activity of the phase II enzyme, MUF-GT, in response to repeated exposure to the test substance in the diet for 28 days.**

This study is classified as **acceptable/non-guideline.**

Mutagenicity on Metabolite of Topramezone

A-3.0 Mutagenicity: Mammalian cells in culture gene mutation assay in Chinese hamster ovary cells; OPPTS 870.5300 [§84-2]; OECD 476

In independently-performed *in vitro* mammalian cell gene mutation assays (MRID No. 46244301), Chinese hamster ovary (CHO) cells were exposed to Reg. No. 4969168 (99.6%, Batch No. 01893-263, dissolved in dimethyl sulfoxide), (a metabolite of BAS 670 H) at six concentrations ranging from 12.5 to 400 µg/mL without or 62.5 to 1500 µg/mL with S9 activation (30% S9 in the S9 mix) in the first trial, and 9.38 to 300 µg/mL without S9 activation or 125 to 1500 µg/mL with S9 activation (10% S9 in the S9 mix) in the second trial. Cells were treated for 4 hours and cloned for mutant selection in both trials. The S9 was derived from Aroclor 1254-induced Sprague Dawley rat livers, and the test material was delivered to the test system in dimethyl sulfoxide; appropriate negative and positive controls were included.

Reg. No. 4969168 was insoluble at 400 µg/mL -S9 and ≥1000 µg/mL +S9, lethal at ≥400 µg/mL -S9 and cytotoxic at 1500 µg/mL +S9 (28% relative cell survival). Findings with the positive controls confirmed the sensitivity of the test system to detect mutagenesis. **There was, however, no indication that Reg. No. 4969168, (Metabolite of BAS 670 H) induced a mutagenic response, either in the presence of absence of S9 activation.**

The study is classified as **Acceptable/Guideline** and satisfies the requirements for an *in vitro* mammalian forward gene mutation study (84-2).

A-3.1 Mutagenicity: *Salmonella typhimurium/Escherichia coli*--mammalian microsome mutagenicity assay; OPPTS 870.5100 [§84-2]; OECD 471, 472

In independently performed microbial mutagenicity assays (MRID No. 46244302), histidine-deficient (*his* $^-$) strains of Salmonella typhimurium (TA1535, TA1537, TA98, and TA100) and tryptophan-deficient (*trp* $^-$) *Escherichia coli* strain WP2 *uvrA* were exposed for 48-72 hours to five

concentrations (20-5000 µg/plate) in the standard plate test and five concentrations (4-2500 µg/plate) of Reg. No. 4969168 (99.6%, Batch No. 01893-263) in the preincubation modification of the plate test in the presence and absence of S9 activation. The S9 fraction was derived from Aroclor 1254 induced Sprague Dawley rat livers and the test material was delivered to the test system in dimethyl sulfoxide (DMSO); the appropriate solvent and positive controls were included.

Reg. No. 4969168 was cytotoxic to all *Salmonella* strains and *E. coli* WP2 *uvr*A., causing a reduction in revertant colonies, the background lawn of growth and/ or the cell titres at 5000 µg/plate +/-S9 (plate incorporation) or 2500 µg/plate +/-S9 (preincubation). There was also evidence of test material insolubility at levels ≥2500 µg/plate +/-S9. Nonactivated and S9-activated positive controls induced the expected mutagenic response in the corresponding tester strain. **There was, however, no indication of a mutagenic response in any strain at any level up to cytotoxic concentrations either with or without S9 activation.**

The study is classified as **Acceptable/Guideline** and satisfies the requirements for FIFRA Test Guideline 84-2 for microbial gene mutation mutagenicity data.

A-3.2 Mutagenicity: *In vitro* mammalian cytogenetics: chromosome aberration assay in Chinese hamster lung (V79) cells; OPPTS 870.5375 [§84-2]; 473

In a series of independently conducted *in vitro* chromosome aberration assays (MRID No. 46244303), Chinese hamster lung (V79) cells were exposed for 4 hours to Reg. No. 4969168 (99.6%, Batch No. 01893-263, a metabolite of BAS 670 H) at concentrations ranging from 250-1000 µg/mL with or without S9 activation in the first trial or 250-750 µg/mL without S9 activation (Trial 2). All cells were harvested at 18 hours posttreatment. For the nonactivated phase of Trial 3, cells were dosed with 62.5-250 µg/mL continuously for 18 hours or exposed for 18 hours and harvested at 28 hours. With S9 activation, cells were treated with 250-750 µg/mL and harvested at 28 hours. Metaphases from all trials were analyzed for structural or numerical chromosome aberrations. The S9 was derived from Aroclor 1254-induced Sprague Dawley rat livers, and the test material was delivered to the test system in dimethyl sulfoxide; the appropriate solvent and positive controls were included.

Compound insolubility was reported at ≥500 µg/mL. The positive controls induced the expected high yield of metaphases with structural but not numerical chromosome aberrations. Reg 4969168 induced a powerful clastogenic effect [chromosome breaks and exchanges (predominantly ring chromosomes)] at concentrations of 500, 750 or 1000 µg/mL -S9 or 500 and 1000 µg/mL +S9 following a 4-hour exposure and an 18-hour cell harvest but not after a continuous treatment for 18-hour and harvest following treatment or a harvest at 28 hours (nonactivated conditions). Negative results were also obtained after a 4- hour treatment of cells with the S9-activated test material followed by a cell harvest at 28 hours. Increases in chromosome aberrations over the controls ranged from 11 to 29X at 500 or 1000 µg/mL -S9 (38.5 and 9.5% cells with aberrations and 16.5 and 3.0% exchanges at 500 and 1000 µg/mL -S9, respectively vs 2.0% and 0.0%, respectively for the concurrent solvent control cultures) or 3 to 7X at 500 or 1000 µg/mL +S9 (28.0 and 12.0% cells with aberrations and 10.0 and 5.5% exchanges at 500 and 1000 µg/mL +S9, respectively vs 4.0% and 0.0%, respectively for the concurrent solvent

control cultures).

The study authors claim that the response was the result of nonrandom chromosome breakage at fragile sites on chromosome pairs Nos. 3 and 4 at specific breakage sites. Sutherland (1988)[2] states that fragile sites on mammalian cells are chromosome loci which exhibit breaks and gaps when exposed to a variety of specific conditions in the tissue culture during the S phase of the cell cycle. HED notes that neither the pH nor the osmotic pressure of the culture medium were affected at the concentrations evaluated for cytogenetic activity. It was further noted that marked increases in gaps were seen at the levels inducing significant clastogenic effects and evidence of cytotoxicity (as indicated by the poor quality of available metaphases). When the treatment and/or harvest time was increased, however, there was no significant induction in chromosome breakage at concentrations producing good quality metaphases or metaphases with only a slight reduction in available metaphases. This suggests that the clastogenic response may be associated with test material cytotoxicity since the majority of induced aberrations (breaks and rings) are unstable and will not survive a second round of cell replication. Sutherland (1988) goes on to state that the induction of fragile sites involves direct or indirect pertubations of the intracellular pool of nucleotides by several conditions such as an excess of thymidine during DNA synthesis. Furthermore, Kuntz(1982)[3] lists an excess of thymidine triphosphate (dTTP) as an etiological agent for the enhancement of mutagenesis in Chinese hamster V79 cells. Thus, an excess of thymidine may be a possible mechanism of action (MOA) for the Reg No. 4969168-induced chromosome damage seen in this study. Nevertheless, the data in this study alone are not sufficient to support this MOA. There is, however, evidence of cytotoxicity as a possible secondary contributor to clastogenicity. **In light of the evidence that the parent compound, BAS 670 H is clastogenic in this *in vitro* mammalian cell test system, (see MRID No. 45902233), and the relationship of this metabolite to the parent compound is not known, it was concluded that the clastogenic activity of Reg. No. 4969168, the metabolite of BAS 670 H Reg can not be ruled out at this time.**

The study is, however, classified as **Acceptable/Guideline** and satisfies the guideline requirement for an *in vitro* mammalian cell cytogenetic assay (84-2).

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[2] Sutherland, G. R.:The role of nucleotides in human fragile site expression. Mut. Res., *200,* 207 - 213 (1988).

[3] Kunz, B. A.: Genetic effects of desoxyribonucleotide pool imbalance. Environ. Mut., 4: 695 - 725 (1 982)

Appendix 3. Metabolism Considerations

Table A-3.1.01 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Corn	Topramezone	Topramezone
	Rotational Crops	Topramezone + M670H05	not required
Livestock	Ruminant	Topramezone	Topramezone
	Poultry	tbd*	tbd
Drinking Water		Topramezone + M670H05	Not Applicable

*To be determined. Note: if future proposed uses significantly increase the dietary exposure to poultry, then the poultry feeding study should include analysis for metabolite M670H02.

A-3.1.02 Summary of Topramezone Metabolism Studies

Table A-3.1.02.1 Summary of Phenyl-Label (PH) and Pyrazole-Label (PY) Topramezone Metabolism Studies.

Commodity		%TRR Extractable		%Total Identified		Total TRR (ppm)		%TRR													
								Topramezone		M670H01		M670H02		M670H03		M670H04		M670H05		M670H08	
		PH	PY	PH	PY	PH	PY	PH	PY	PH	PY	PH	PY	PH	PY	PH	PY	PH	PY	PH	PY
Corn	Forage	78.8	65.3	51.2	23.6	0.534	0.294	40.4	16.9	-	-	-	-	3.0	3.1	-	-	6.6	-	1.2	3.6
	Stover	82.8	83.3	56.3	28.4	0.730	0.213	40.9	19.6	-	-	-	-	2.3	4.2	-	-	10.2	-	2.9	4.6
	Grain	83.1	77.3	5.5	2.5	0.107	0.032	2.1	2.5	-	-	-	-	-	-	-	-	3.4	-	-	-
Goat	Urine	100	100	96.8	99.5	NR[1]	NR	96.8	90.0	-	2.6	-	6.88	-	-	-	-	-	-	-	-
	Feces	64.8	83.0	59.9	72.9	NR	NR	59.9	72.9	-	-	-	-	-	-	-	-	-	-	-	-
	Kidney	87.8	92.1	84.0	90.1	0.352	0.282	83.2	79.5	0.35	0.68	0.41	9.95	-	-	-	-	-	-	-	-
	Liver	90.8	87.7	85.5	82.1	2.18	1.89	83.3	51.8	-	0.67	2.2	29.6	-	-	-	-	-	-	-	-
	Milk	-	34.5	-	27.6	0.002	0.007	-	25.3	-	0.88	-	1.18	-	-	-	-	-	-	-	-
Poultry*	Excreta (Day 1)	-	88.5	-	64.0	NA[2]	NR	-	64.0	-	-	-	-	-	-	-	-	-	-	-	-
	Excreta (Day 5)	86	-	70.1	-	NR	NA	59.5	-	-	-	10.6	-	-	-	-	-	-	-	-	-
	Liver	93.4	88.6	90.8	80.8	1.68	0.739	58.5	64.4	-	-	29.9	16.4	-	-	2.4	-	-	-	-	-
	Egg (Day 7)	58.9	-	31.7	-	0.002	NA	13.8	-	-	-	11.6	-	-	-	-	-	6.3	-	-	-
	Egg (Day 9)	52.8	-	23.2	-	0.002	NA	6.8	-	-	-	11.9	-	-	-	-	-	4.6	-	-	-

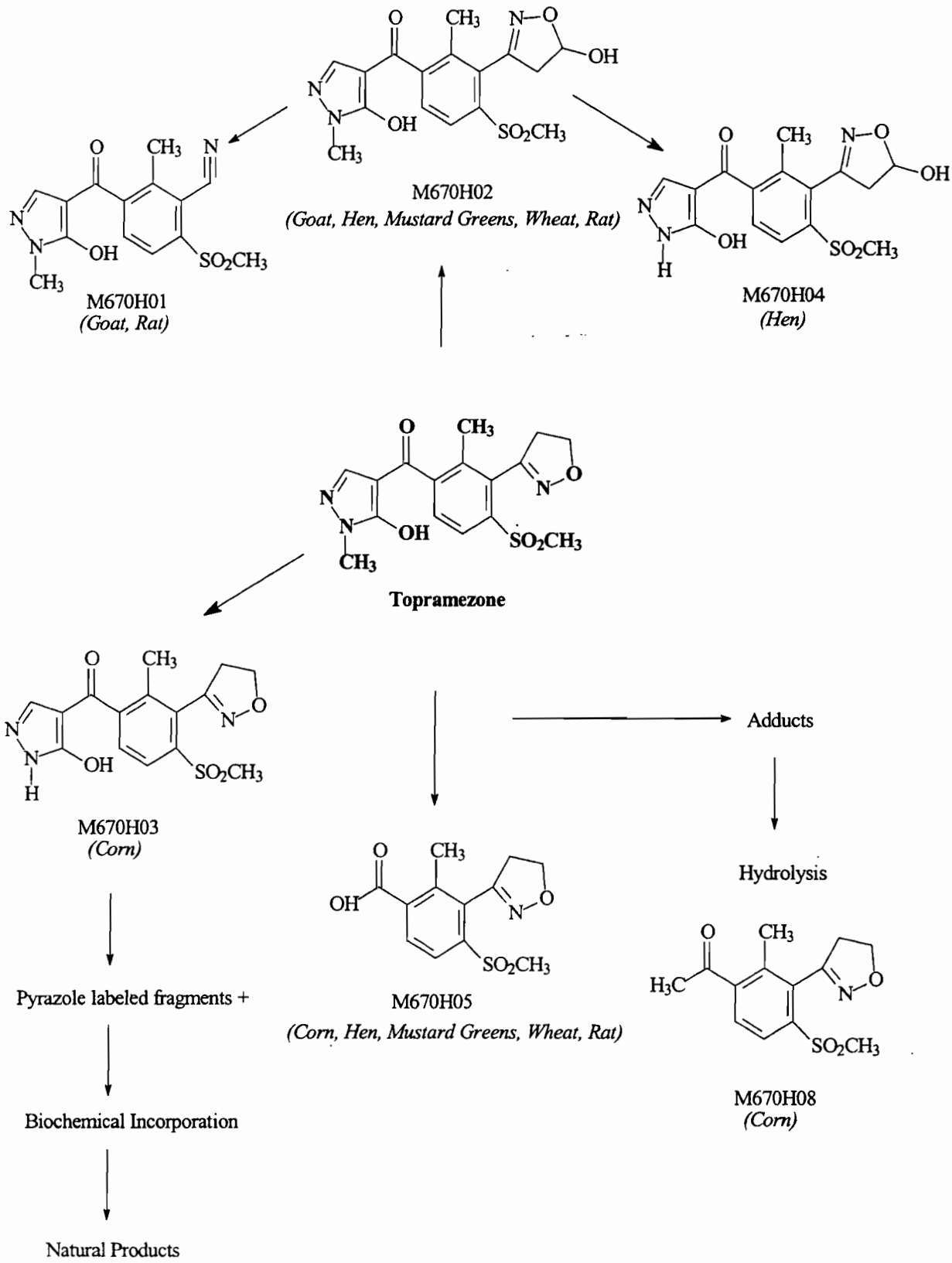
Commodity		%TRR Extractable		%Total Identified		Total TRR (ppm)		%TRR													
								Topramezone		M670H01		M670H02		M670H03		M670H04		M670H05		M670H08	
		PH	PY	PH	PY	PH	PY	PH	PY	PH	PY	PH	PY	PH	PY	PH	PY	PH	PY	PH	PY
Confined Rotational Crops (Soil aged for 34 days)	Wheat Forage	94.8	84.7	22.5	21.1	0.052	0.025	12.4	17.0	-	-	3.57	4.13	-	-	-	-	6.51	-	-	-
	Wheat Hay	82.5	81.6	20.0	21.3	0.132	0.075	11.2	21.3	-	-	2.91	-	-	-	-	-	5.96	-	-	-
	Wheat Straw	78.5	76.1	6.70	13.3	0.092	0.051	1.57	13.3	-	-	4.28	-	-	-	-	-	0.85	-	-	-
	Wheat Grain	107	117	61.2	64.4	0.021	0.007	16.3	64.4	-	-	-	-	-	-	-	-	45.0	-	-	-
	Mustard Greens	90.6	88.0	41.2	47.4	0.026	0.004	31.0	47.4	-	-	-	-	-	-	-	-	10.3	-	-	-
	Radish Top	-	-	-	-	0.010	0.002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Radish Root	-	-	-	-	0.003	0.001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Sorghum Forage[3]	-	-	-	-	0.004	0.001	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Sorghum Stover[3]	-	-	-	-	0.003	0.002	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Sorghum Grain[3]	-	-	-	-	0.002	0.002	-	-	-	-	-	-	-	-	-	-	-	-	-	-

1. NR = ppm values were not reported.
2. NA = commodity was not analyzed.
3. Soil aged for 99 days.

* Due to low TRRs, residues in muscle and fat were not characterized/identified.

Note: Metabolites which represent 10% or more of the TRR for a given commodity or part of a commodity are shaded.

Figure A-3.1.0 Combined metabolic pathways in plant, livestock and rat.



A-3.2.0 Nature of the Residue Studies in Plants

A-3.2.1.1 Executive Summary of Corn Metabolism Study

BASF conducted a corn metabolism study with [phenyl-U-^{14}C] topramezone and [pyrazole-4-^{14}C] topramezone. Topramezone was applied to corn plants at the 3-5 leaf growth stage (GS 13-15) at rates of 0.148 kg a.i./ha (0.132 lb a.i./A, 6.0X) for the pyrazole label or 0.146 kg a.i./ha (0.130 lb a.i./A, 5.9X) for the phenyl label as a single foliar application. The plants were grown in pots within a climate-controlled growth chamber, which was set to simulate the North American growing season. Immature plant samples were collected at 1, 9, 15 or 16, and 29 or 30 days after treatment (DAT). The corn forage samples were collected at the late dough stage (59-60 DAT), while stover and grain were harvested at maturity (77 DAT). Samples were analyzed within 5.1 months of harvest; thus, no storage stability data were collected or are necessary for this study.

The overall TRRs in treated corn samples were determined by both combustion/liquid-scintillation counting (LSC) and by calculation (the sum of the radioactive residues in the extracts and the remaining residues in the post-extraction solids (PES)). Chromatographic determinations of radioactivity were performed by high-performance liquid chromatography (HPLC), with MS providing confirmation. Major metabolites (>10% of the TRR) were identified by co-chromatography and MS, while minor metabolites (<10% of the TRR) were identified by co-chromatography alone.

Calculated TRRs in immature corn samples treated with [phenyl-U-^{14}C] label topramezone declined from 7.64 ppm at 1 DAT to 0.468 ppm at 30 DAT. The overall TRRs in forage (59-60 DAT), stover and grain (77 DAT) were 0.534 ppm, 0.730 ppm, and 0.107 ppm, respectively. The TRRs in immature whole corn samples treated with [pyrazole-4-^{14}C] label topramezone also declined, from 7.68 ppm at 1 DAT to 0.544 ppm at 29 DAT. The overall TRRs in forage, stover and grain were lower in pyrazole-label samples at 0.294 ppm, 0.213 ppm and 0.032 ppm, respectively.

A total of 74.9-81.7% of the TRRs (0.351-6.117 ppm) of phenyl-label immature corn plants were aqueous extractable. Of the 63.9-75.8% of the TRR identified (0.299-5.117 ppm), the parent topramezone accounted for the majority of residues (55.7-69.9% of the TRR; 0.264-4.255 ppm). The desmethyl metabolite M670H03 and the acid metabolite M670H05 were considered minor metabolites (<10% of the TRR each; ≤0.717 ppm). Residues characterized as a series of minor peaks/regions comprised 5.9-13.0% of the TRR (0.052-1.00 ppm). The unextractable residues (PES) accounted for 9.9-16.5% of the TRR (0.077-0.755 ppm), for an overall accountability ranging from 89.9-93.5%.

A total of 40.1-84.1% of the TRRs (0.218-6.46 ppm) of pyrazole-label immature corn plants were aqueous extractable. Of the 35.2-84.1% of the TRR identified (0.192-6.458 ppm), the parent topramezone was the predominant metabolite at 33.2-78.7% of the TRRs (0.181-6.05 ppm). The only other metabolite identified was M670H03 (see Table 3.4 for structures) at <6% of the TRR (≤0.412 ppm). Residues characterized as a series of minor peaks/regions comprised 4.9-11.4% of the TRR (0.026-0.137 ppm). The unextractable residues (PES) accounted for 5.8-33.1% of the

TRRs (0.18-0.475 ppm), for an overall accountability ranging from 71.3-89.9%.

A total of 78.8-82.8% of the TRRs (0.420-0.605 ppm) of phenyl-label forage and stover samples were aqueous extractable, while 83.1% of the TRR of grain (0.089 ppm) were extractable by acetonitrile (ACN):water. Of the 51.2-56.3% of the TRRs identified in forage and stover (0.273-0.412 ppm), the parent topramezone accounted for the majority of residues (40.4-40.9% of the TRR; 0.216-0.299 ppm). The metabolites M670H03, M670H05 and the methyl ketone metabolite M670H08 each comprised <11% of the TRR (≤0.075 ppm). Only 5.5% of the TRR was identified in grain (0.006 ppm), and there were more residues of M670H05 (3.4% of the TRR; 0.004 ppm) than parent (2.1% of the TRR; 0.002 ppm) identified. After exhaustive extraction/fractionation procedures, a total of 26.5-27.6% of the TRRs were characterized (0.147-0.193 ppm) in forage and stover. In grain, the majority of the residues were characterized (77.6% of the TRR, 0.083 ppm). The final unextractable residues in all matrices after fractionation accounted for 2.4-5.4% of the TRRs (0.005-0.029 ppm), for an overall accountability ranging from 84.1-87.9%.

A total of 65.3-83.3% of the TRRs (0.178-0.193 ppm) were extractable from the aqueous extract of pyrazole-label forage and stover samples, while 77.3% of the TRRs were extractable from the ACN:water extract of grain (0.025 ppm). Of the 23.6-28.4% of the TRR identified in forage and stover (0.061-0.07 ppm), the parent topramezone accounted for the majority of residues (16.9-19.6% of the TRR; 0.042-0.05 ppm). Each of the metabolites M670H03 and M670H08 comprised <5% of the TRR (≤0.011 ppm). Only 2.5% of the TRR was identified as topramezone in grain (0.001 ppm), with no metabolites identified. After exhaustive extraction/fractionation procedures, a total of 41.7-54.9% of the TRRs were characterized (0.117-0.123 ppm) in forage and stover. In grain, the majority of the residues were characterized (74.8% of the TRR, 0.024 ppm). The final unextractable residues in all matrices after fractionation accounted for 2.7-22.6% of the TRRs (0.006-0.066 ppm), for an overall accountability ranging from 86.4-97.2%.

Hydrolysis of grain PES indicated that radioactivity was incorporated into glucose. Saponification of oil indicated that radioactivity was also incorporated into the fatty acid constituents.

The metabolism of topramezone in corn involved the hydrolytic cleavage of the parent to form the acid metabolite M670H05. Further hydrolysis and cleavage resulted in the formation of M670H08, while desmethylation resulted in M670H03. After cleavage, the pyrazole ring appeared to undergo complete catabolism and reincorporation within the carbon backbone of natural products such as starch, soluble polysaccharides and fatty acids. The phenyl ring portion of the molecule also underwent degradation, resulting in the incorporation of radioactivity into natural products.

A-3.2.1.2 Tabular Summary of Corn Metabolism Study

Table A-3.2.1.2.1 Summary of Characterization and Identification of Radioactive Residues in Corn RAC Following Application of Phenyl-label Topramezone

Compound	Corn, forage TRR = 0.534 ppm		Corn, stover TRR = 0.730 ppm		Corn, grain TRR = 0.107 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
Total identified [1]	51.2	0.273	56.3	0.412	5.5	0.006
Topramezone	40.4	0.216	40.9	0.299	2.1	0.002
M670H03	3	0.016	2.3	0.017	—	—
M670H05	6.6	0.035	10.2	0.075	3.4	0.004
M670H08	1.2	0.006	2.9	0.021	—	—
Total characterized [2]	27.6	0.147	26.5	0.193	77.6	0.083
Final Extractable	78.8	0.42	82.8	0.605	83.1	0.089
Final Unextractable (PES) [3]	5.4	0.029	2.4	0.018	4.7	0.005
Accountability [4]	84.1%		85.3%		87.9%	

[1] If the metabolite was detected in the concentrated aqueous extract, and subsequently in the hydrolysed aqueous extract, the highest concentration value for the metabolite was used in determining the total identified.

[2] If characterized residues were detected in the concentrated aqueous extract , as well as in the hydrolysed aqueous extract, the highest concentration value for characterized residues was used in determining the total characterized.

[3] Residues remaining after exhaustive extractions.

[4] Accountability = (Final extractable + Final unextractable)/(calculated TRR) * 100.

Table A-3.2.1.2.2 Summary of Characterization and Identification of Radioactive Residues in Corn RAC Following Application of Pyrazole-label Topramezone

Compound	Corn, forage TRR = 0.294 ppm		Corn, stover TRR = 0.213 ppm		Corn, grain TRR = 0.032 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
Total identified [1]	23.6	0.07	28.4	0.061	2.5	0.001
Topramezone	16.9	0.05	19.6	0.042	2.5	0.001
M670H03	3.1	0.009	4.2	0.009	—	—
M670H05	—	—	—	—	—	—
M670H08	3.6	0.011	4.6	0.01	—	—
Total characterized [2]	41.7	0.123	54.9	0.117	74.8	0.0241
Final Extractable	65.3	0.193	83.3	0.178	77.3	0.0251
Final Unextractable (PES) [3]	22.6	0.066	2.7	0.006	18.8	0.006
Accountability [4]	88.1%		86.4%		97.2%	

[1] If the metabolite was detected in the concentrated aqueous extract, and subsequently in the hydrolysed aqueous extract, the highest concentration value for the metabolite was used in determining the total identified.

[2] If characterized residues were detected in the concentrated aqueous extract, as well as in the hydrolysed aqueous extract, the highest concentration value for characterized residues was used in determining the total characterized.

[3] Residues remaining after exhaustive extractions.

[4] Accountability = (Final extractable + Final unextractable)/(calculated TRR) * 100.

A-3.3.0 Nature of the Residue in Livestock

A-3.3.1.1 Executive Summary of Ruminant Study

BASF has conducted a goat metabolism study with [phenyl-U-^{14}C] topramezone and [pyrazole-4-^{14}C] topramezone. Topramezone was administered to two lactating dairy goats per label at feeding levels of 9.9 mg/kg (phenyl label, 130X) and 11.2 mg/kg (pyrazole label, 150X) by a single daily oral administration for 5 days. Milk was collected twice daily over the treatment period, and excreta was pooled and collected once daily. Tissue samples (muscle, bile, kidney, liver, fat and GI tract) were harvested upon termination, 21-23 hours after the final dose administration. The samples were assayed for TRRs by combustion and LSC. Extracts were characterized by thin-layer chromatography (TLC) and identified by HPLC. Confirmation of residue identification was performed by LC-MS/MS. Nuclear magnetic resonance (NMR) analysis elucidated the structures of the metabolites found in the goat urine samples. All samples other than milk were stored frozen and analysed within 4 months of collection; thus, no storage stability study was conducted. Milk was stored frozen and analysed within 11 months of collection, but no storage stability study was conducted due to low radioactivity levels.

The total applied dose recoveries of topramezone were 92.5% in pyrazole-label samples, of which 44.5% was found in the urine, 38.3% in the feces, 0.29% in the cage rinse (1.18 ppm), 2.67-5.27% in the GI tissue and contents (0.780-1.16 ppm), and negligible levels in bile (0.137 ppm). The dose recoveries in the edible tissues were predominantly in the liver at 1.28% of the administered dose (1.891 ppm), followed by kidney at 0.04% (0.282 ppm). The dose recoveries in fat, muscle and milk were <0.01% each (≤0.007 ppm). The total applied dose recoveries of topramezone were 81.9% in phenyl-label samples, of which 33.3% was found in the urine, 34.7% in the feces, 0.49% in the cage rinse (0.986 ppm), 1.20-10.2% in the GI tissue and contents (0.322-1.57 ppm), and negligible levels in bile (0.059 ppm). The dose recoveries in the edible tissues were again predominantly in the liver (1.96% of the administered dose; 2.18 ppm), followed by kidney (0.05% of the administered dose; 0.352 ppm). The dose recoveries in fat, muscle and milk were negligible at ≤0.002 ppm each.

A total of 87.7-90.8% of the TRRs (1.66-1.98 ppm) were extracted with methanol/ethyl acetate (EtOAc) from the pyrazole-label and phenyl-label liver samples. Of the 82.1-85.5% TRR identified (1.55-1.86 ppm), the parent topramezone accounted for 51.8-83.3% of the TRR (0.9799-1.817 ppm). The hydroxy metabolite M670H02 accounted for 29.6% of the TRR (0.560 ppm) in the pyrazole-label sample, but was a minor metabolite in the phenyl-label sample (2.2% of the TRR; 0.048 ppm). The cyano metabolite M670H01 was only identified in the pyrazole-label sample, at 0.67% of the TRR (0.013 ppm). Approximately 5.34-5.6% of the TRR (0.1057-0.1168 ppm) were characterized as fractions from the extracts. Approximately 3.16-3.73% of the TRR were unextractable (0.069-0.071 ppm), for an overall accountability ranging from 91.4-94.0%.

A total of 87.8-92.1% of the TRRs (0.259-0.309 ppm) were extracted with methanol/EtOAc from the pyrazole-label and phenyl-label kidney samples. Of the 84.0-90.1% TRR identified (0.2538-0.2955 ppm), the parent topramezone accounted for the vast majority of residues, at 79.5-83.2% of the TRR (0.224-0.293 ppm). M670H02 was identified as 9.95% of the TRR (0.028 ppm) in the

pyrazole-label sample, but accounted for only 0.41% of the TRR (0.0014 ppm) in the phenyl-label sample. M670H01 was identified in both labels, at 0.35-0.68% of the TRR (0.0012-0.0019 ppm). Approximately 1.96-3.88% of the TRRs (0.0056-0.0137 ppm) were characterized as either a single minor peak, or as fractions from the extracts. A total of 2.45-6.71% of the TRRs were unextractable (0.0086-0.0189 ppm), for an overall accountability ranging from 90.3-98.7%.

Only samples of pyrazole-label milk were analyzed. Approximately 34.5% of the TRR (0.002 ppm) was extractable from both the methanol/water extract and the acetone extract. Of the 27.6% of the TRR identified (0.00189 ppm), the parent topramezone accounted for 25.3% of the TRR (0.0018 ppm). M670H02 and M670H01 were minor metabolites at 0.88-1.18% of the TRR (0.00006-0.00008 ppm). Approximately 0.81% of the TRR (0.00006 ppm) was characterized as a series of minor peaks, while 6.03% of the TRR (0.0004 ppm) was found in the acetone extract.

One hundred percent of the TRRs were extractable in both the pyrazole-label and phenyl-label urine samples. Of the 99.5% of the TRR identified in the pyrazole-label sample, the parent topramezone was the predominant metabolite (90.0% of the TRR). M670H02 (6.88% of the TRR) and M670H01 (2.6% of the TRR) were considered minor metabolites. The parent topramezone was the only metabolite identified in the phenyl-label sample as 96.75% of the TRR. Approximately 0.48-3.25% of the TRR was characterized as a single minor peak in both labels.

A total of 64.8-83.0% of the TRRs were extracted from the methanol/water extract of both the pyrazole-label and phenyl-label feces samples. The only metabolite identified in both labels was the parent topramezone, at 59.9-72.9% of the TRR. Approximately 4.9-10.1% of the TRR was characterized as a series of minor peaks. Approximately 15.5-22.2% of the TRR was unextractable in the PES, for an overall accountability ranging from 87.0-98.5%.

The metabolic profiles of topramezone in goats were similar between the pyrazole and phenyl treatment groups. The proposed metabolic pathway proceeded from the hydroxylation of the parent compound topramezone at the 4-position of the isoxazole ring to form M670H02. The isoxazole ring was then cleaved to form the cyano metabolite (M670H01). The linkage between the phenyl and pyrazole rings remained intact in all of the metabolites identified.

A-3.3.1.2 Tabular Summary of Ruminant Study

Table A-3.3.1.2.1 Summary of Characterization and Identification of Radioactive Residues in Livestock Matrices Following Application of Pyrazole-label Topramezone at 11.2 ppm[1]

Compound	Urine		Feces		Kidney 0.282 ppm		Liver 1.891 ppm		Milk[2] 0.007 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Total identified	99.5	—	72.86	—	90.1	0.2538	82.1	1.553	27.6	0.0019
Topramezone	90.0	—	72.86	—	79.5	0.2239	51.8	0.9799	25.3	0.0018
M670H02	6.88	—	—	—	9.95	0.028	29.6	0.5603	1.18	0.00008
M670H01	2.6	—	—	—	0.68	0.0019	0.67	0.013	0.88	0.00006
Total characterized	0.48	—	10.1	—	1.96	0.0056	5.6	0.1057	6.84	0.00046
Total extractable	100	—	83.0	—	92.1	0.2594	87.7	1.659	34.5	0.002
Unextractable (PES)	0	—	15.5	—	6.71	0.0189	3.73	0.071	—	—
Accountability[3]	100%		98.5%		98.7%		91.4%		33.6%	

1 Identified residues quantitated by HPLC method 1, except for feces (HPLC method 3)
2 Identified metabolite residue%TRRs based on sum of fractions 9, 10 and 11.
3 Accountability = (Total extractable + Total unextractable)/(TRRs from combustion analysis) * 100

Table A-3.3.1.2.2 Summary of Characterization and Identification of Radioactive Residues in Livestock Matrices Following Application of Phenyl-label Topramezone at 9.9 ppm[1]

Compound	Urine		Feces		Kidney 0.352 ppm		Liver 2.182 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Total identified	96.8	—	59.9	—	84.0	0.2955	85.5	1.865
Topramezone	96.8	—	59.9	—	83.2	0.2929	83.3	1.817
M670H02	—	—	—	—	0.41	0.0014	2.2	0.048
M670H01	—	—	—	—	0.35	0.0012	—	—
Total characterized	3.25	—	4.9	—	3.88	0.0137	5.34	0.1168
Total extractable	100	—	64.8	—	87.8	0.3092	90.8	1.982
Unextractable (PES)	0	—	22.2	—	2.45	0.0086	3.16	0.069
Accountability[2]	100%		87.0%		90.3%		94.0%	

1 Identified residues quantitated by HPLC method 1
2 Accountability = (Total extractable + Total unextractable)/(TRRs from combustion analysis) * 100.

A-3.3.1.3 Executive Summary of Poultry Study

BASF has conducted a hen metabolism study with [pyrazole-4-^{14}C] topramezone and [phenyl-U-^{14}C] topramezone. Topramezone was orally administered to 10 Leghorn laying hens for each label at feeding levels of 12.3 mg/kg (pyrazole label, 1500X) or 13.4 mg/kg (phenyl label, 1700X) for 10 consecutive days. Eggs were collected twice daily, excreta was collected once daily, and cage rinse samples were collected on study day 0 and after termination. Tissue samples (liver, muscle, fat and GI tract/contents) were harvested upon termination, 21 - 23 hours after the final dose. The collected samples were assayed for TRRs by combustion and LSC. Samples were subjected to

solvent extraction to recover the maximum TRR for further chromatographic characterization and elucidation of the nature of residues. Metabolite identification/characterization of the matrices was achieved by HPLC and co-chromatography and/or comparison of retention times of reference standards or isolated metabolites. All livestock matrices were analyzed within 4 months of sampling. Therefore, no storage stability data were required for this study.

The total applied dose recovery was 94.09% for the pyrazole-label, of which 92.9% was found in excreta, 0.70% in the GI tract/contents (0.796 ppm) and 0.29% in cage rinse. The dose recovery in egg, muscle and fat was <0.005 ppm each (0.0% of the TRR), while virtually all the recoveries in edible tissues were in the liver (0.22% of the TRR; 0.739 ppm). For the phenyl-label, the total applied dose recovery was 93.1%, of which 91.4% was in excreta, 0.29% in cage rinse, and 1.07% in the GI tract/contents (1.318 ppm). The dose recovery in fat, muscle and egg were each ≤0.004 ppm each (0.0% of the TRR), while the vast majority of residues in edible tissues were found in the liver (1.680 ppm).

A total of 88.6-93.4% of the TRRs (0.656-1.568 ppm) were extractable from the methanol extract (phenyl-label) or methanol/water extract (pyrazole-label) of radiolabeled liver samples. Of the 80.8-90.8% of the TRR identified in both labels (0.597-1.525 ppm), the parent topramezone accounted for the majority of residues (58.5-64.4% of the TRR; 0.475-0.982 ppm). The hydroxy metabolite M670H02 accounted for 16.4-29.9% of the TRR in both labels (0.122-0.503 ppm), while the desmethyl hydroxy metabolite M670H04 was only detected in the phenyl-label sample (2.4% of the TRR; 0.04 ppm). Residues characterized as a series of minor peaks/regions comprised 2.6-7.8% of the TRR (0.043-0.059 ppm). The unextractable residues (PES) accounted for 3.7-7.9% of the TRR (0.059-0.062 ppm).

A total of 86.0-88.5% of the TRRs were extractable from the acetone:phosphate buffer extract of both the pyrazole-label and phenyl-label excreta samples. The parent topramezone was the only metabolite identified in the pyrazole label excreta (64.0% of the TRR). Of the 70.1% of the TRR identified in the phenyl-label excreta, 59.5% was identified as the parent topramezone, while M670H02 accounted for 10.6% of the TRR. Residues characterized as a series of minor peaks/regions comprised 15.9-24.5% of the TRR. The unextractable residues (PES) accounted for 3.4-6.3% of the TRR.

A total of 32.9-42.0% of the TRRs (0.0006-0.0007 ppm) were extractable from the ACN and water extracts of both the day 7 and day 9 phenyl-label egg samples. Of the 23.2-31.7% of the TRR identified (0.0004-0.0006 ppm), the parent topramezone accounted for 6.75-13.8% of the TRR (0.0001-0.0003 ppm). M670H02 accounted for 11.6-11.9% of the TRR (0.0002 ppm each) for both samples, while the acid metabolite M670H05 accounted for 4.6-6.3% of the TRR (0.0001 ppm each). Residues characterized as a series of minor peaks/regions comprised 9.65-10.2% of the TRR (0.0001-0.0002 ppm). The unextractable residues (PES) accounted for 21.1-23.0% of the TRR (0.0004 ppm each).

The metabolic pathway of topramezone in hens proceeded from the hydroxylation at the 4-position of the isoxazole ring to form the hydroxy metabolite M670H02. Further N-demethylation of M670H02 occurred and formed the desmethyl hydroxy metabolite M670H04. M670H04 was only detected in the phenyl labeled liver. The pyrazole ring of topramezone could

also be cleaved to form the acid metabolite M670H05.

A-3.3.1.4 Tabular Summary of Poultry Study

Table A-3.3.1.4.1 Summary of Characterization and Identification of Radioactive Residues in Livestock Matrices Following Application of Pyrazole-label Topramezone at 12.3 ppm using HPLC Method 1.

Compound	Excreta (Day 1) [1]		Liver (TRR = 0.739 ppm)	
	% TRR	ppm	% TRR	ppm
Total identified	64.0	—	80.8	0.597
Topramezone	64.0	—	64.4	0.475
M670H02	—	—	16.4	0.122
M670H04	—	—	—	—
M670H05	—	—	—	—
Total characterized	24.5	—	7.8	0.059
Total extractable	88.5	—	88.6	0.656
Unextractable (PES)	6.3	—	7.9	0.059
Accountability	94.8%		96.8% [2]	

[1] ppm values were not reported for excreta

[2] Accountability = (Total extractable (ppm) + Total unextractable (ppm))/(TRRs from combustion analysis (ppm)) * 100.

Table A-3.3.1.4.2 Summary of Characterization and Identification of Radioactive Residues in Livestock Matrices Following Application of Phenyl-label Topramezone at 13.4 ppm using HPLC Method 1.

Compound	Excreta (Day 5) [1]		Liver (TRR = 1.680 ppm)		Egg (Day 7) (TRR = 0.002 ppm)		Egg (Day 9) (TRR = 0.002 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Total identified	70.1	—	90.8	1.525	31.7	0.0006	23.2	0.0004
Topramezone	59.5	—	58.5	0.982	13.8	0.0003	6.8	0.0001
M670H02	10.6	—	29.9	0.503	11.6	0.0002	11.9	0.0002
M670H04	—	—	2.4	0.04	—	—	—	—
M670H05	—	—	—	—	6.3	0.0001	4.6	0.0001
Total characterized	15.9	—	2.6	0.043	27.2	0.0004	29.6	0.0006
Total extractable	86.0	—	93.4	1.568	58.9	0.001	52.8	0.001
Unextractable (PES)	3.4	—	3.7	0.062	21.9	0.0004	23.0	0.0004
Accountability	89.4%		97.0% [2]		70.0% [2]		70.0% [2]	

[1] ppm values were not reported for excreta

[2] Accountability = (Total extractable (ppm) + Total unextractable (ppm))/(TRRs from combustion analysis (ppm)) * 100.

A-3.4.0 Confined Rotational Crop Studies

A-3.4.1 Executive Summary of Rotational Crop Study

BASF conducted a confined accumulation study with [pyrazole-4-^{14}C] topramezone and [phenyl-U-^{14}C] topramezone. Topramezone was applied to bare soil at rates of 0.072-0.081 lb a.i./A (0.081-0.091 kg a.i./ha, 3.3-3.7X) for the phenyl-label, and 0.081-0.084 lb a.i./A (0.091-0.094 kg a.i./ha, 4.1-4.3X) for the pyrazole-label. Rotational crops were planted in open-bottom casks in four field plots with PBIs of 34 days (radish, mustard greens, and wheat), 99 days (mustard greens and sorghum) and 393 days (mustard greens only). Swiss chard was planted at the 34 day PBI, but the crop failed to grow. Due to climatic conditions, sorghum was planted at the 99 day PBI instead of wheat.

If the TRRs in a RAC sample were below 0.01 ppm, then no further planting of the crop was conducted. RAC samples with TRRs greater than 0.01 ppm were subjected to further analysis to characterize the radioactive residues. The range of overall TRRs in pyrazole- and phenyl-label crop RAC samples at the 34 day PBI were 0.0039-0.0256 ppm for mustard greens; 0.0021-0.0095 ppm in radish tops; 0.0010-0.0030 ppm in radish roots; 0.0753-0.1321 ppm for wheat grain; 0.0510-0.0920 ppm for wheat straw; 0.0249-0.0518 ppm for wheat forage; and 0.0073-0.0206 ppm for wheat hay. The range of overall TRRs in pyrazole- and phenyl-label crop RAC samples at the 99 day PBI were 0.001-0.004 ppm for sorghum forage; 0.0016-0.0032 ppm for sorghum stover; 0.0019-0.0021 ppm for sorghum grain; and 0.0025-0.0113 ppm for mustard green RACs. The overall TRRs in the phenyl-label mustard green RAC at the 393 day PBI was 0.003 ppm. All plant samples were analysed within 3 months of harvest; therefore, no storage stability data were generated.

A total of 88.0-90.6% of the TRRs (0.0034-0.0231 ppm) were extractable from the combined MeOH/water extracts of pyrazole-label and phenyl-label mustard greens from the 34 day PBI. The parent topramezone accounted for the majority of residues (31.0% of the TRRs; 0.0079 ppm) in the phenyl-label mustard greens, while the acid metabolite M670H05 accounted for 10.3% of the TRR (0.0026 ppm). The parent topramezone was the only metabolite identified in the pyrazole-label sample (47.4% of the TRR; 0.0018 ppm). Residues characterized as a series of minor peaks/regions comprised 40.6-49.3% of the TRRs (0.0016-0.0126 ppm). The unextractable residues (PES) accounted for 12.7-17.3% of the TRRs (0.0007-0.0033 ppm), for an overall accountability ranging from 103-105%.

A total of 76.1-117% of the TRRs (0.0085-0.1092 ppm) were extractable from the combined MeOH/water extracts in phenyl- and pyrazole-label wheat matrices (34 day PBI). The parent compound, topramezone, was either the predominant residue or the only residue identified in the pyrazole-label wheat matrices (13.3-64.4% of the TRRs; 0.0043-0.0160 ppm), and in phenyl-label forage and hay (11.2-12.4% of the TRRs; 0.0064-00.0147 ppm). M670H05 was the predominant metabolite identified in the phenyl-label grain (45.0% of the TRR; 0.0093 ppm). In the other radiolabeled wheat matrices, the metabolites M670H02 and M670H05 comprised less than 7% of the TRR (<0.01 ppm). After exhaustive extraction/fractionation procedures, a total of 45.5-72.3% of the TRRs were characterized in the phenyl-and pyrazole-label wheat RAC extracts (0.0038-0.0828 ppm). The final unextractable residues in all the wheat matrices after fractionation were

≤20.2% of the TRRs (≤0.0182 ppm), for accountabilities ranging from 92.4-126%.

The proposed metabolism of topramezone involved the hydrolysis of the parent to form the free acid M670H05. The pyrazole moiety was catabolized after cleavage, then reincorporated into natural products (as seen in the corn metabolism study). Parent-related adducts were formed from the des-methylation of the pyrazole ring. Hydroxylation of the isoxazole ring formed M670H02 (as seen in the goat metabolism study), then reincorporation into natural products occurred after further ring degradation.

The confined rotational crop data are classified as scientifically acceptable. The residue of concern was determined to be topramezone *per se* (Table 3.6.1). The total residues of concern were <0.01 ppm in radish and mustard greens planted at a 34-day PBI and sorghum planted at a 99-day PBI.

A-3.4.2 Tabular Summary of Rotational Crop Study

Table A-3.4.2.1 Summary of Characterization and Identification of Radioactive Residues in Rotational Crop Matrices Following Application of Radiolabeled Topramezone.

Compound	34-d PBI (Phenyl Label)		34-d PBI (Pyrazole Label)	
	% TRR	ppm	% TRR	ppm
Mustard Greens				
Topramezone	31.0	0.0079	47.4	0.0018
M670H02	—	—	—	—
M670H05	10.3	0.0026	—	—
Wheat Forage				
Topramezone	12.4	0.0064	17.0	0.0043
M670H02	3.57	0.0018	4.13	0.0010
M670H05	6.51	0.0034	—	—
Wheat Hay				
Topramezone	11.2	0.0147	21.3	0.0160
M670H02	2.91	0.0038	—	—
M670H05	5.96	0.0079	—	—
Wheat Straw				
Topramezone	1.57	0.0014	13.3	0.0068
M670H02	4.28	0.0039	—	—
M670H05	0.85	0.0008	—	—
Wheat Grain				
Topramezone	16.3	0.0034	64.4	0.0047
M670H02	—	—	—	—
M670H05	45.0	0.0093	—	—

A-3.5.0 Analytical Methodology

Method Name	Applicable Commodities	Analytes	Extraction Solvent(s)	Clean-up Step(s)	Determinative Step	LOQ, ppm	LOD, ppb
D0007	plant matrices	topramezone, M670H05	ACN, water	acid and base partitioning	LC-MS/MS	0.01-0.05	0.10
D0104	livestock tissues, milk, and eggs	topramezone, M670H02	water	partitioning with dichloromethane	LC-MS/MS	0.01-0.05	0.08

A-3.6.0 Summary of Magnitude of Residue (MOR) Studies

A-3.6.1 Plants

Table A-3.6.1.1 Summary of Residues from the Corn Field Trials (Field and Sweet) with Topramezone

Crop Matrix	Applic. Rate lb a.i./A	PHI (days)	Residues (ppm)				
			Mean	Std. Dev.	HAFT*	Min.	Max.
Topramezone							
Field Corn (proposed use = 0.022 lb ai/A total application rate, 45-day PHI)							
K+CWHR	0.088-0.092	29-64	<0.01	_	_	<0.01	<0.01
Forage	0.088-0.095	31-91	<0.05	_	_	<0.05	<0.05
Grain	0.088-0.095	59-128	<0.01	_	_	<0.01	<0.01
Stover	0.088-0.095	59-128	<0.05	_	_	<0.05	<0.05
Sweet Corn (proposed use = 0.022 lb ai/A total application rate, 45-day PHI)							
K+CWHR	0.088-0.091	35-49	<0.01	_	_	<0.01	<0.01
Forage	0.088-0.091	35-49	<0.05	_	_	<0.05	<0.05
Stover	0.088-0.091	57-92	<0.05	_	_	<0.05	<0.05
BAS 670 H 05							
Field Corn (proposed use = 0.022 lb ai/A total application rate, 45-day PHI)							
K+CWHR	0.088-0.092	29-64	<0.01	_	_	<0.01	<0.01
Forage	0.088-0.095	31-91	<0.05	_	_	<0.05	<0.05
Grain	0.088-0.095	59-128	<0.01	_	_	<0.01	<0.01
Stover	0.088-0.095	59-128	<0.05	_	_	<0.05	<0.05
Sweet Corn (proposed use = 0.022 lb ai/A total application rate, 45-day PHI)							
K+CWHR	0.088-0.091	35-49	<0.01	_	_	<0.01	<0.01
Forage	0.088-0.091	35-49	<0.05	_	_	<0.05	<0.05
Stover	0.088-0.091	57-92	<0.05	_	_	<0.05	<0.05

* HAFT = Highest Average Field Trial.

A-3.6.2 Livestock

Table A-3.6.2 Summary of Residue Data from Ruminant Feeding Study with Topramezone

Matrix	Feeding Level (ppm)	Residue Levels (ppm)*					
		n	Min.	Max.	Mean	Std. Dev.	R/F Ratio**
Milk	0.0	3	<0.01	<0.01			
	0.37 (4.9X)	3	<0.01	<0.01	—	—	—
	1.04 (14X)	3	<0.01	<0.01			
	3.57 (48X)	5	<0.01	<0.01			
Liver	0.0	3	<0.05	<0.05	—	—	—
	0.37 (4.9X)	3	0.484	0.608	0.555	0.064	1.50
	1.04 (14X)	3	0.808	1.296	1.129	0.278	1.09
	3.57 (48X)	3	1.588	1.882	1.782	0.168	0.499
Kidney	0.0	1	<0.05	<0.05	—	—	—
	0.37 (4.9X)	3	0.1436-	0.1876	0.159	0.025	0.430
	1.04 (14X)	3	0.1972	0.2080	0.204	0.006	0.196
	3.57 (48X)	3	0.3200	0.3500	0.332	0.016	0.0930
Fat	0.0	2	<0.05	<0.05			
	0.37 (4.9X)	NA	NA	NA	—	—	—
	1.04 (14X)	NA	NA	NA			
	3.57 (48X)	4	<0.05	<0.05			
Muscle	0.0	1	<0.01	<0.01			
	0.37 (4.9X)	NA	NA	NA	—	—	—
	1.04 (14X)	NA	NA	NA			
	3.57 (48X)	3	<0.01	<0.01			

NA - Not analyzed

* Residues of Topramezone *per se*, all values were <LOQ (0.05 ppm) for M670H02.

** Residue-to-feed ratio (mean residues divided by the feeding level)

A-3.6.3 Rotational Crops

Table A-3.6.3.1 Summary of Topramezone Residues from the Field Accumulation in Rotational Crops*

Crop Matrix	Applic. Rate lb ai/A	PHI (days)	Residues (ppm)				
			Mean	Std. Dev.	HAFT	Min.	Max.
28-29-day PBI							
Radish Root	0.089-0.091	54-57	<0.05	—	—	<0.05	<0.05
Radish Top		54-57	<0.05	—	—	<0.05	<0.05
Soybean Forage		62-64	<0.05	—	—	<0.05	<0.05
Soybean Hay		77-89	<0.05	—	—	<0.05	<0.05
Soybean Seed		127-159	<0.05	—	—	<0.05	<0.05
Sorghum Forage		113-122	<0.05	—	—	<0.05	<0.05
Sorghum Grain		127-172	<0.05	—	—	<0.05	<0.05
Sorghum Stover		127-172	<0.05	—	—	<0.05	<0.05
90-day PBI							
Radish Root	0.089-0.091	130-137	<0.05	—	—	<0.05	<0.05
Radish Top		130-137	<0.05	—	—	<0.05	<0.05
Spinach Leaves		137-154	<0.05	—	—	<0.05	<0.05
Winter Wheat Forage		137-320	<0.05	—	—	<0.05	<0.05
Winter Wheat Hay		354-363	<0.05	—	—	<0.05	<0.05
Winter Wheat Grain		385-397	<0.05	—	—	<0.05	<0.05
Winter Wheat Straw		385-397	<0.05	—	—	<0.05	<0.05

* Identical results were also obtained for the metabolite BAS 670 H 05

A-3.7.0 International Considerations

There are currently no established Codex, Canadian, or Mexican maximum residue limits (MRLs) for topramezone.

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