UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 07-SEP-2007

SUBJECT: PP#5F7009: **Tembotrione.** Human-Health Risk Assessment for Proposed Uses on Field Corn, Sweet Corn and Popcorn. PC Code 012808. DP# 325935. Decision # 362526.

Regulatory Action: Section 3 Registration
Risk Assessment Type: Single Chemical Aggregate

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TO: Eugene Wilson/Joanne Miller, PM Team 23
Registration Division (RD; 7505P)

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 the proposed uses of tembotrione, 2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-(trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione (designated by the company code AE0172747) in/on field corn, sweet corn and popcorn. The registrant is Bayer CropScience. This is the first food use request for tembotrione. This is a shared joint review with the Pest Management Regulatory Agency (PMRA) in Canada. It was recently registered in Austria for use on corn.

A summary of the findings and an assessment of human risk resulting from the proposed uses of tembotrione are provided in this document. The risk assessment and the hazard characterization were provided by Lisa Austin (RAB1), the residue chemistry data review, and the dietary risk assessment by George Kramer (RAB1), the occupational/residential exposure assessment by

Kelly Lowe (RAB1), and the drinking water assessment by William Eckel of the Environmental Fate and Effects Division (EFED).

Recommendation for Tolerances and Registration:

Pending submission of revised Sections B and F (see requirements under Section 10.0 Data Needs and Label Recommendations) and the submission of reference standards for tembotrione and its metabolite M5 (see requirements under Submittal of Analytical Reference Standards), there are no residue chemistry, occupational exposure or toxicology issues that would preclude granting a conditional registration for the requested uses of tembotrione on field corn, popcorn, and sweet corn. Registration should be made conditional pending the submission of additional information concerning the proposed enforcement methods (see requirements under Residue Analytical Methods), completion of a successful petition method validation (PMV) of the proposed enforcement methods for plant and livestock commodities by Agency chemists at the Analytical Chemistry Branch/Biological and Economics Analysis Division (ACB/BEAD), and chemical-specific dislodgeable foliar residue data.

The proposed uses and the submitted data support the following permanent tolerances for the combined residues of tembotrione and its metabolite M5 expressed as tembotrione equivalents, in/on the following corn commodities:

Corn, field, grain	0.02 ppm
Corn, field, forage	0.60 ppm
Corn, field, stover	0.45 ppm
Corn, sweet, kernel plus cob with husks removed	0.04 ppm
Corn, sweet, forage	1.0 ppm
Corn, sweet, stover	1.2 ppm
Corn, pop, grain	0.02 ppm
Corn, pop, stover	0.35 ppm

The proposed uses and the submitted data support the following tolerances for the combined residues of tembotrione and its metabolite M5, expressed as tembotrione equivalents in the following livestock commodities:

Cattle, liver	0.40 ppm
Cattle, meat byproducts, except liver	0.07 ppm
Goat, liver	0.40 ppm
Goat, meat byproducts, except liver	0.07 ppm
Horse, liver	0.40 ppm
Horse, meat byproducts, except liver	0.07 ppm
Sheep, liver	0.40 ppm
Sheep, meat byproducts, except liver	0.07 ppm
Poultry, liver	0.07 ppm

Data Gaps

Toxicology:
There are no toxicology data gaps.

Chemistry:

860.1340 Residue Analytical Methods

- To be acceptable as enforcement methods, LC/MS/MS Methods AE/03/01 for plant commodities and 00967 for livestock commodities should undergo successful PMVs by Agency chemists at ACB/BEAD.

- Both methods should be revised to include a calculation for the conversion of residues of the metabolite(s) to parent equivalents for quantitation.

- Separate confirmatory methods for Method AE/03/01 will not be requested provided that two ion transitions are monitored during MS/MS analysis for each analyte.

860.1650 Submittal of Analytical Reference Standards

Analytical standards for tembotrione and its metabolite M5 are currently not available in the National Pesticide Standards Repository. Analytical reference standards of tembotrione and its metabolite (including the deuterated internal standards) should be supplied, and supplies replenished as requested by the Repository.

860.1550 Proposed Tolerances

The petitioner is requested to submit a revised Section F specifying the following:

- The tolerance expression for plant commodities should be revised to include the combined residues of tembotrione and M5, expressed as tembotrione equivalents.

- The tolerance expression for livestock commodities should be revised to include the combined residues of tembotrione and its metabolite M5, expressed as tembotrione equivalents.

- The revised tolerances and commodity definitions presented in Appendix C: Tolerance Reassessment Summary and Table (summarized above).

Occupational and Residential Exposure:

875.2100 Chemical-specific dislodgeable foliar residue data.

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B.1 Metabolism Guidance and Considerations 101

1.0 Executive Summary

Tembotrione is a broad spectrum early and mid-postemergence herbicide. It is applied via groundboom equipment at an application rate of 0.082 lb ai/acre. The maximum application rate is 0.16 lb ai/acre (2 applications/season). Tembotrione belongs to the triketone class of herbicides and acts by inhibiting 4-hydroxyphenylpyruvate dioxygenase (HPPD) which leads to chlorophyll destruction by photooxidation and causes bleaching of emerging foliar tissue. In mammals, HPPD is a key enzyme in the catabolism of tyrosine. It catalyzes the conversion of 4-hydroxyphenylpyruvate (HPP) to homogentisate. Inhibition of HPPD leads to a reconversion of HPP to tyrosine and a consequent increase in blood tyrosine concentrations (tyrosinemia). There are no existing tolerances, uses, or exemptions for tembotrione. The field corn petition represents the first proposed use for tembotrione. There are currently no proposed residential uses of tembotrione. This is a joint shared review with PMRA in the U.S. It is currently registered in Austria.

Currently, there are three registered herbicides, isoxaflutole, topramezone, and mesotrione, and one new herbicide in the review process (pyrasulfatole) that are also HPPD inhibitors.

Toxicity/Hazard: Tembotrione has low acute toxicity via the oral, dermal and inhalation routes of exposure (Toxicity category III or IV). It is a dermal sensitizer but not an eye or dermal irritant.

The primary target organs were the eyes, liver and kidneys. In subchronic and chronic oral toxicity studies, corneal opacity, neovascularization, edema of the cornea, and keratitis of the eye were observed in the rat and dog. Liver effects (increased weight, hypertrophy, hyperplasia) were seen in the rat, mouse and dog. In the kidney, increased weight, and papillary mineralization were observed in the rat and mouse following chronic exposure.

The dog appeared to be more sensitive to hematological effects. In the subchronic and chronic dog toxicity studies hematological changes indicative of anemia were seen [decreased mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV)]. Similar hematological effects were also observed in the chronic toxicity study in the mouse.

Certain changes in multiple organs seen in the subchronic, chronic, dermal, and reproduction studies (e.g., microscopic changes in the thyroid gland, adrenal gland, and pancreas; increased number of corpora lutea in the ovary, and delayed preputial separation) may be due to various mechanisms including possible liver-pituitary-thyroid homeostatic disruption or inhibition of steroid synthesis.

In a combined chronic/carcinogenicity study, squamous cell carcinomas of the cornea and thyroid follicular adenomas were observed in male rats. The Cancer Assessment Review Committee (CARC) met on April 11, 2007 and classified tembotrione as "Suggestive Evidence of Carcinogenic Potential" based on the lack of carcinogenicity in mice, the observance of tumors in male rats only and the lack of mutagenicity. Therefore, quantification of carcinogenic potential is not required. The reference dose (RfD) would be protective of cancer effects. Evidence of neurotoxicity was seen in the subchronic and chronic toxicity studies in the dog (uncoordinated movement, disturbance in locomotion) and in the acute (decreased arousal,

decreased body temperature, decreased motor and locomotor activities) and developmental neurotoxicity (brain morphometric changes, decreased acoustic startle response) studies in the rat. In the developmental neurotoxicity study in rats, increased susceptibility was observed as fetal neurological effects and occurred at a dose that was lower than the dose at which maternal toxicity occurred (corneal opacity). There was no evidence of neurotoxicity in the subchronic neurotoxicity study in rats.

There was evidence of increased susceptibility of rabbits and rats to *in utero* and postnatal exposure to tembotrione in the developmental and 2 generation reproduction studies. In the developmental study in rabbits, fetal effects (delayed growth/skeletal development and skeletal variations/anomalies) occurred at a dose lower than that which caused maternal toxicity (mortality, few or no feces, abortion, decreased body weight and food consumption). Also, fetal effects (skeletal variations, decreased fetal body weight, runting) were observed at a dose lower than that which caused marginal maternal toxicity (decreased body-weight gains and food consumption) in the developmental study in rats. No teratogenic effects were observed in the rat and rabbit developmental toxicity studies. In the 2-generation reproduction study in rats, offspring effects (opacity, acute inflammation and neovascularization of the cornea, increased incidences of minimal extramedullary hematopoeisis in the spleen, delayed preputial separation, and decreased absolute brain weight) occur at the lowest dose in the presence of maternal toxicity (opacity, acute inflammation and neovascularization of the cornea). There were no reproductive effects.

Rat metabolism data indicate that tembotrione is well absorbed. More than 96% of the administered dose was recovered in urine and feces in 24 hours. Minor sex differences were observed in the routes of excretion. The primary routes of elimination were the urine in females and the urine and feces in males. The highest concentrations of radioactivity were found in the skin followed by the liver, kidneys, stomach (and contents) and carcass.

Males had higher mean blood, plasma maximum concentrations (C_{max}) and area under the concentration-time curves (AUC) values than females. At 5 mg/kg, saturation of the initial elimination/biotransformation processes was evident resulting in a slower initial elimination phase.

The parent molecule and 11 metabolites were identified and isolated from urine and feces. Metabolic profiles were qualitatively similar for both radiolabeled forms; however, profiles for the high and low doses were not the same and differences were noted between sexes. The primary step in the metabolism of tembotrione is the hydroxylation (oxidative pathway) of the cyclohexyl ring of the molecule.

Dose Response and Food Quality Protection Act (FQPA) Assessments: The tembotrione risk assessment team recommends that the 10X FQPA safety factor (SF) for the protection of infants and children be reduced to 1X since there is a complete toxicity database for tembotrione and exposure data are complete or are estimated based on data that reasonably account for potential exposures. The recommendation is based on the following: 1) The established acute RfD (aRfD, 0.0008 mg/kg) and chronic RfD (cRfD, 0.0004 mg/kg/day) are protective of any developmental and neurological effects observed at doses of 10 mg/kg/day in the developmental toxicity and 0.8 mg/kg/day in the developmental-neurotoxicity study (DNT), respectively. 2)

There are no residual uncertainties concerning pre- and postnatal toxicity. 3) There are no residual uncertainties with respect to exposure data. 4) The dietary food exposure assessment utilizes proposed tolerance-level residues and 100% crop treated (CT) information for all proposed commodities. By using this screening-level assessment, the acute and chronic exposures/risks will not be underestimated. 5) The dietary drinking water assessment utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations. 6) There are no registered or proposed uses of tembotrione which would result in residential exposure. A 100-fold uncertainty factor (UF) (10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated into the acute and chronic RfD. An additional 10X UF was applied to the aRfD due to lowest-observed adverse-effect level (LOAEL) to no-observed adverse-effect level (NOAEL) extrapolation in the DNT study. The acute population-adjusted dose (aPAD) and the chronic population adjusted dose (cPAD) are equal to the acute and chronic RfDs, respectively, divided by the FQPA SF (1X). Therefore, the acute and chronic PADs are equal to the acute and chronic RfDs. Tembotrione is classified as "suggestive evidence of carcinogenic potential" by all relevant routes of exposure based on adequate studies in two animal species; therefore, cancer risk assessments are not required. In estimating margins of exposure (MOEs), the level of concern (LOC) is for MOEs <1000 for the dermal and inhalation risk assessments. A 15% dermal-absorption factor and a 100% inhalation-absorption factor were used for use in the route-to-route extrapolation. The toxicological endpoints relevant to this assessment are summarized below.

acute dietary (general population, including infants and children)	NOAEL = 0.8 mg/kg/day	acute RfD and aPAD = 0.0008 mg/kg/day
chronic dietary	NOAEL = 0.04 mg/kg/day	chronic RfD and cPAD = 0.0004 mg/kg/day
short-term dermal	oral NOAEL = 0.8 mg/kg/day	LOC for MOEs <1000 (occupational)
intermediate-term dermal	oral NOAEL = 0.8 mg/kg/day	LOC for MOEs <1000 (occupational)
short-term inhalation	oral NOAEL = 0.8 mg/kg/day	LOC for MOEs <1000 (occupational)
intermediate-term inhalation	oral NOAEL = 0.8 mg/kg/day	LOC for MOEs <1000 (occupational)

Dietary Risk Estimates (Food + Water): Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The acute analysis assumed 100% crop treated (CT), DEEM™ 7.81 default processing factors, and tolerance-level residues for all foods. The entire distribution of estimated daily exposure values from the PRZM (Pesticide Root Zone Model)-EXAMS (Exposure Analysis Modeling System) run was incorporated in the acute probabilistic exposure analyses. The resulting acute dietary (food + water) risk estimates using the DEEM-FCID™ model at the 95th percentile (<77%, aPAD for all infants (<1 year old), the most highly-exposed population subgroup) were not of concern (<100% aPAD). A chronic dietary assessment assuming tolerance-level residues, DEEM™ 7.81 default processing factors, and 100% CT was also conducted. The highest estimate of chronic surface water exposure (1.05 ppb) was used for drinking water in this analysis. The chronic dietary risk assessment shows that for all included commodities, the chronic dietary risk estimates are not of concern (i.e., <100% cPAD). For the U.S. population the exposure for food and water utilized 22% of the cPAD. The chronic dietary risk estimate for the highest reported exposed population subgroup, children 3-5 years old, is

48% of the cPAD. Dietary cancer risk concerns due to long-term consumption of tembotrione residues are adequately addressed by the chronic exposure analysis using the cPAD.

Residential Exposure: The proposed new use is on an agricultural crop (e.g., corn); therefore, residential exposures are not expected and were not assessed.

Aggregate Risk: There are no uses of tembotrione that are expected to result in residential exposures. Therefore, the aggregate exposure assessment takes into consideration dietary food + water exposure only. The acute and chronic dietary estimates represent aggregate risk.

Occupational Exposure/Risk to Mixer/Loader and Applicators: Tembotrione is applied by ground equipment only (aerial application is prohibited on the label). Based upon the proposed use pattern, HED expects the most highly exposed occupational pesticide handlers are likely to be:

1) Mixer/loader using open-pour loading of liquids for groundboom applications (Pesticide Handlers Exposure Database, PHED)
2) Applicators using open-cab groundboom sprayer (PHED)

HED believes most exposure durations will be short-term (1-30 days). However, the HED Science Advisory Council for Exposure (ExpoSAC) maintains it is possible for commercial applicators to be exposed to intermediate-term exposure durations (1-6 months). In addition, the short- and intermediate-term toxicological endpoints are the same; therefore, the estimates of risk for short-term duration exposures are protective of those for intermediate-term duration exposures. Long-term exposures are not expected; therefore, a long-term assessment was not conducted.

No chemical-specific data were available to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (Ver 1.1, 1998) Surrogate Exposure Guide (August 1998). The proposed product label involved in this assessment directs applicators and other handlers to wear a long-sleeved shirt and long pants; socks, shoes and chemical-resistant gloves.

HED has determined that there are no risks of concern associated with the groundboom applicator scenario at baseline. However, HED has determined that there are risks of concern (i.e., MOEs <1000) associated with the mixer/loader scenarios at baseline and with the use of gloves, as directed by the label. If an extra layer of clothing is worn (i.e., a double layer), then the MOE is 910; and, if a closed mixing/loading system is utilized (i.e., engineering control), then the MOE is 1,400. HED has determined that the risks associated with a mixer/loader wearing a double layer of clothing are not of concern and **recommends that a double layer of clothing (*i.e.*, coverall) be added to the label under the personal-protective equipment (PPE) requirements for handlers**.

Occupation Post-application Risk: HED expects that postapplication exposure will occur since tembotrione is applied as a foliar spray. There is a potential for agricultural workers to have post-application exposure to pesticides during the course of typical agricultural activities in corn. Short-term exposures are expected for hand-weeding, scouting, and irrigation activities.

Estimates of exposure and risk result in a MOE >1000 on day 0 (restricted-entry interval (REI) = 12 hours) only for hand-weeding activities at the lowest transfer coefficient (TC; i.e., when corn is at a low crop height and minimal foliage development), and therefore, do not exceed HED's LOC. All of the other exposure activities result in risk that is of concern, with MOEs ranging from 250 to 630 on the day of application. Chemical-specific dislodgeable foliar data would be needed to further refine these estimates as well as information on specific re-entry activities occurring postapplication. Currently, the label requires a 12-hour REI; however, **HED recommends a 13-day REI for irrigation, scouting and hand-weeding activities**.

Environmental Justice Considerations: Potential areas of environmental justice concerns, to the extent possible, were considered in this human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://homer.ornl.gov/nuclearsafety/nsea/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under CSFII and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research: This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. The database listed below has been determined to require a review of its ethical conduct. It has received the appropriate review. It was concluded it does not violate current ethical standards.

Studies reviewed for ethical conduct: The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

The petitioner has submitted a draft label dated 11/5/06 for the 3.5 lb ai/gal suspension concentrate (SC) formulation (AE 0172747 Herbicide; File Symbol 264-xxx). Information pertaining to the proposed end-use product is listed in Table 2.1.1. A summary of the proposed use pattern on corn (field, pop, and sweet) is detailed in Table 2.1.2. The proposed rotational crop restrictions are listed in Table 2.1.3.

Table 2.1.1. Summary of Proposed End-Use Product.

Trade Name	Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Label Date
AE 0172747 Herbicide	264-xxx	34.5% (equivalent to 3.5 lb ai/gal)	SC	Field corn, silage corn, seed corn, sweet corn, and popcorn	Various annual broadleaf and grass weeds	Draft label submitted 11/5/06

Table 2.1.2. Summary of Proposed Directions for Use of Tembotrione (AE 0172747 Herbicide).

Application Timing	Single Application Rate (lb ai/A)	Max. Number of Applications per Season	Re-entry Interval (days)	Retreatment Interval (days)	Max. Seasonal Application Rate (lb ai/A)	PHI (days)
Corn (Field, Silage, Seed, Sweet, and Pop)						
Postemergence Broadcast foliar spray	0.082	2	13	14	0.16	45 days for forage; none listed for grain and stover
Use Directions and Restrictions: Applications must be made to corn from emergence through the V8 stage of growth; application to corn that is more mature than growth stage V8 (i.e., more than 8 visible leaf collars) is prohibited. Applications are to be made in a minimum of 10 gal/A using ground equipment. Aerial application and/or application through any type of irrigation system are prohibited. Use of an external spray adjuvant is required, and the adjuvant type is dependent on the weed spectrum. A 45-day pregrazing interval is proposed for corn forage.						

Table 2.1.3. Proposed Rotational Crop restrictions Listed on AE 0172747 Herbicide Label.

General: If a corn crop has been destroyed by hail or other means soon after an AE 0172747 Herbicide application, field corn, sweet corn, or popcorn may be replanted immediately after the application. Rotational intervals for all other crops following an AE 0172747 Herbicide application are presented in the chart below.

120 days	10 months	18 months
Small grains	Alfalfa	Cucurbits
	Canola	Dry beans
	Cotton	Sunflower
	Peas	Sugar beets
	Potatoes	All other crops
	Snap beans	
	Sorghum	
	Soybean	
	Tomato	

2.2 Structure and Nomenclature

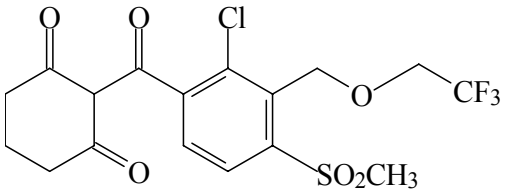
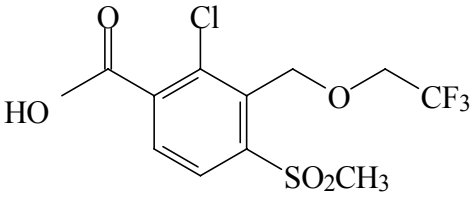
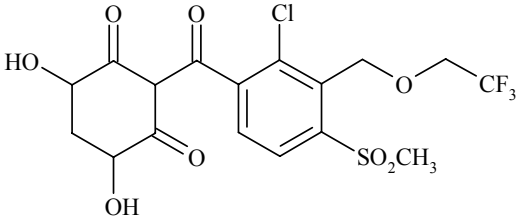
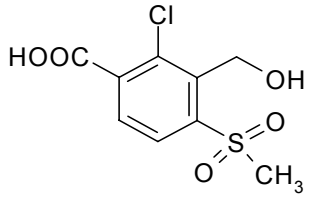
Table 2.2. Test Compound Nomenclature for Tembotrione and its Metabolites M6, M5, and M2.	
Compound: Tembotrione	Chemical Structure 
Proposed Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided
CAS name	2-Chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided

Table 2.2. Test Compound Nomenclature for Tembotrione and its Metabolites M6, M5, and M2.	
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-Chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 ºC	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH 4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

3.1.1.1 Studies available and considered (animal, human, general literature)

Acute- oral, dermal, inhalation, eye irritation, skin irritation, dermal sensitization, neurotoxicity.
Subchronic- 21/28-day dermal toxicity in rat, oral 90-day rat, oral 90-day mouse, oral neurotoxicity rat.
Chronic- oral rat (combined chronic/carcinogenicity), oral carcinogenicity in mice and oral dog.
Reproductive/developmental- oral developmental rat and rabbit, rat reproduction/fertility, rat DNT.
Other- dermal-penetration study, mutagenicity studies (*in vitro and in vivo*), metabolism/pharmacokinetics studies, blood coagulation study, tyrosine levels in pregnant rabbits study and HPPD-inhibition study parent versus metabolites.

3.1.1.2 Mode of action, metabolism, toxicokinetic data

Tembotrione is a broad-spectrum early and mid-postemergence herbicide that belongs to the triketone class of herbicides. It acts by inhibiting 4- HPPD, which leads to chlorophyll destruction by photooxidation and causes bleaching of emerging foliar tissue. In mammals, HPPD is a key enzyme in the catabolism of tyrosine. It catalyzes the conversion of 4-hydroxyphenylpyruvate (HPP) to homogentisate. Inhibition of HPPD leads to a reconversion of HPP to tyrosine and a consequent increase in blood tyrosine concentrations (tyrosinemia).

Rat metabolism data indicate that tembotrione is well absorbed. More than 96.3% of the administered dose was recovered in urine and feces in 24 hours. Sex differences were observed in the routes of excretion. The primary routes of elimination were the urine in females and the urine and feces in males. At the low dose, males excreted up to 24.4% and 70.4%; females up to 79.1% and 20% of the administered dose in the urine and feces, respectively. At the high dose, females excreted up to 63.7% and 28.5%; males up to 44.2 % and 49.1% of the dose in the urine and feces, respectively. The highest mean levels of radioactivity were extracted from the liver (1.7-3.5%) and kidneys (0.14-0.26%) at the low dose. At the high dose, the mean levels of radioactivity were extracted from the skin/fur (0.22-0.33%) and carcass. The highest concentrations of radioactivity were found in the skin followed by the liver, kidneys, stomach (and contents) and carcass.

Males had higher mean blood plasma maximum concentrations (C_{max}) and AUC values than females. In both sexes, the area under the AUC for both blood and plasma indicated a disproportionally higher mean systemic exposure at 1000 mg/kg than at 5 mg/kg (>200-fold) that was apparently due to a saturation of the initial elimination/biotransformation processes, resulting in a slower initial elimination phase.

The parent molecule and 11 metabolites were identified & isolated from urine and feces. Metabolic profiles were qualitatively similar for both radiolabeled forms; however, profiles for

the high and low doses were not the same and differences were noted between sexes. Females excreted the greatest quantity of the parent molecule in urine (44.1-59.4%). While low and high dose males eliminated 1.9-3.0% and 33.8%, respectively, in the urine. The metabolites found in the greatest quantities were 4-hydroxy-tembotrione and 5- hydroxy-tembotrione. Other identified metabolites found at <5% were the 4,5-dihydroxy, benzylic alcohol, dihydroxy-bezophenone, 4-hydroxy-benzylic alcohol, and ketohydroxy-hexanoic acid ([cyclohexyl-UL-^{14}C] only). Males excreted greater quantities of both major metabolites than females; except, at the high dose where 4-hydroxy-tembotrione was eliminated in approximately equal amounts in both sexes. The primary step in the metabolism of tembotrione is the hydroxylation (oxidative pathway) of the cyclohexyl ring of the molecule.

3.1.1.3 Sufficiency of studies/data

The toxicity database is complete for tembotrione and is adequate for the conduct of human health risk and assessment of children's susceptibility, as required by FQPA. All studies evaluated were deemed acceptable and met guideline criteria with few exceptions; however, there was enough adequate information available for each study for toxicity characterization that this does not constitute a data gap.

3.1.2 Toxicological Effects

Tembotrione has low acute toxicity via the oral, dermal and inhalation routes of exposure (Toxicity category III or IV). It is a dermal sensitizer but not an eye or dermal irritant.

The eye, liver and kidney are the primary target organs of tembotrione. In the subchronic, chronic and reproduction rat studies, and the subchronic dog study, corneal opacity, edema of the cornea, neovascularization, and keratitis were seen at various doses indicating ocular toxicity. Males appear to be more susceptible to ocular toxicity than females. Also, corneal opacity was completely reversible following subchronic and chronic exposures in rats and some neovascularizations were reversible following subchronic exposure in rats; but these effects were not reversible following chronic exposure. In the subchronic and chronic rat and mouse toxicity studies, and subchronic dog toxicity studies, liver toxicity was indicated at various doses by increased liver weights, gross and microscopic pathology, and increased serum alanine aminotransferase. In the subchronic, chronic, reproduction and dermal rat toxicity studies kidney toxicity (microscopic pathology, increased urinary ketone levels, decreased pH) was observed at various doses. In the chronic mouse toxicity study, kidney toxicity was also evident at the low and high dose (microscopic pathology, increased urinary ketone levels and decreased pH).

Thyroid gland toxicity was observed in the 21/28-day dermal toxicity study in the rat and chronic oral toxicity study in the dog. Dermal exposure (21/28-day study) resulted in colloid alteration and hypertrophic follicular epithelium in the thyroid gland in the rat. Also observed were degenerative changes in the pancreas, increased proteinacious material in the Ratche pouch in the pituitary gland and basophilic tubules in the kidneys. Pigmentation of the thyroid gland along with hematological changes and microscopic changes in the sciatic nerve were observed in the dog.

The dog was more susceptible than rodents to hematological effects. In the subchronic and

chronic dog studies changes indicative of anemia were seen (decreased MCH and MCV). Similar effects were also observed in the mouse.

Certain changes in multiple organs seen in the subchronic, chronic, dermal, and reproduction studies (e.g., microscopic changes in the thyroid gland, adrenal gland, and pancreas; increased number of corpora lutea in the ovary, and delayed preputial separation) may be due to various mechanisms including possible liver-pituitary-thyroid homeostatic disruption or inhibition of steroid synthesis.

Long-term dietary administration of tembotrione resulted in an increased incidence of thyroid adenomas and squamous cell carcinomas of the cornea in male rats. Since the incidence of thyroid adenomas was not statistically significant, they were considered unrelated to treatment. The levels of the doses tested were adequate. No tumors were noted in female rats or in male and female mice after long-term dietary administration of tembotrione. The HED CARC (April 11, 2007) classified tembotrione as **"Suggestive Evidence of Carcinogenic Potential"** by the oral route based on the occurrence of eye tumors in male rats; therefore, the quantification of cancer risk is not required.

Tembotrione did not show evidence of mutagenicity in *in vitro* or *in vivo* studies.

Evidence of neurotoxicity was noted in the subchronic and chronic toxicity studies in dogs. Uncoordinated movement, disturbance in locomotion and microscopic changes in the sciatic nerve were observed in the dog at the highest dose tested in the subchronic (124/111 mg/kg/day) and chronic studies (37.8/41.6 mg/kg/day, M/F). Neurotoxic effects were also seen in the acute neurotoxicity and developmental neurotoxicity studies in rats. In the acute neurotoxicity study, decreased arousal was observed on day 0 in male rats at the lowest dose tested 200 mg/kg. In females, decreased body temperature, motor and locomotor activities are observed on day 0 at the next dose (500 mg/kg). In the DNT study, brain morphometric changes and decreased acoustic startle response were observed in offspring at the lowest dose tested (0.8 mg/kg/day). These effects were observed at a dose lower than that which caused maternal toxicity (16.3 mg/kg/day, corneal opacity).

There was evidence of increased susceptibility following *in utero* and postnatal exposure in the developmental and 2-generation studies. Fetal effects were increased skeletal variations including delayed ossification and decreased fetal body weight and increased number of runts. These effects were observed at the lowest dose tested (25 mg/kg/day) and at a dose lower than that which caused marginal maternal toxicity (125 mg/kg/day, decreased body-weight gains and food consumption). In the rabbit developmental study, decreased growth and/or delayed development of the skeleton and increased incidences of skeletal variations and anomalies in fetuses occurred at the a dose (10 mg/kg/day) lower than that which caused maternal toxicity (100 mg/kg/day, few or no feces, late abortion, decreased body weight and food consumption). In the 2-generation reproduction study in rats, parental effects occur at the lowest dose tested (1.4/1.6 mg/kg/day, M/F) and include corneal opacity, acute inflammation and neovascularization of the cornea. Offspring effects occurred at the same dose and included similar eye effects as well as increased incidences of minimal extramedullary hematopoeisis in the spleen, delayed preputial separation, and decreased absolute brain weight. There were no effects on reproduction.

Rat metabolism data indicated that tembotrione is well absorbed. Greater than 96 % of the administered dose was recovered in urine and feces in 24 hours. The primary routes of elimination were the urine in females (63.7-79.1%) and the feces in males (49.1-70.4%). The highest mean levels of radioactivity were extracted from the liver (1.7-3.5%) and kidneys (0.14-0.26%) at the low dose. At the high dose, the mean levels of radioactivity were extracted from the skin/fur (0.22-0.33%) and carcass. No other tissue exceeded 0.06% of the administered dose. Males had higher mean blood plasma maximum concentrations (C_{max}) and AUC values than females. At 1000 mg/kg saturation of the initial elimination/ biotransformation processes occurred resulting in a slower initial elimination phase in both sexes. Metabolic profiles were qualitatively similar for both radiolabeled forms; however, profiles for the high and low doses were not the same and differences were noted between sexes. The major urinary and fecal metabolites were 4-hydroxy-tembotrione and 5- hydroxy-tembotrione. The primary step in the metabolism of tembotrione is the hydroxylation (oxidative pathway) of the cyclohexyl ring of the molecule.

3.1.3 Dose-Response Assessment

A summary of the toxicological endpoints and doses chosen for the relevant exposure scenarios for dietary and occupational human health risk assessments is provided in Tables 3.5.10a and 3.5.10b. The conventional interspecies extrapolation (10X) and intraspecies variation (10X) UFs were applied for all exposure scenarios. An additional 10X UF was applied for LOAEL to NOAEL extrapolation in the DNT study. The FQPA SF for increased susceptibility was reduced to 1x for all exposures scenarios.

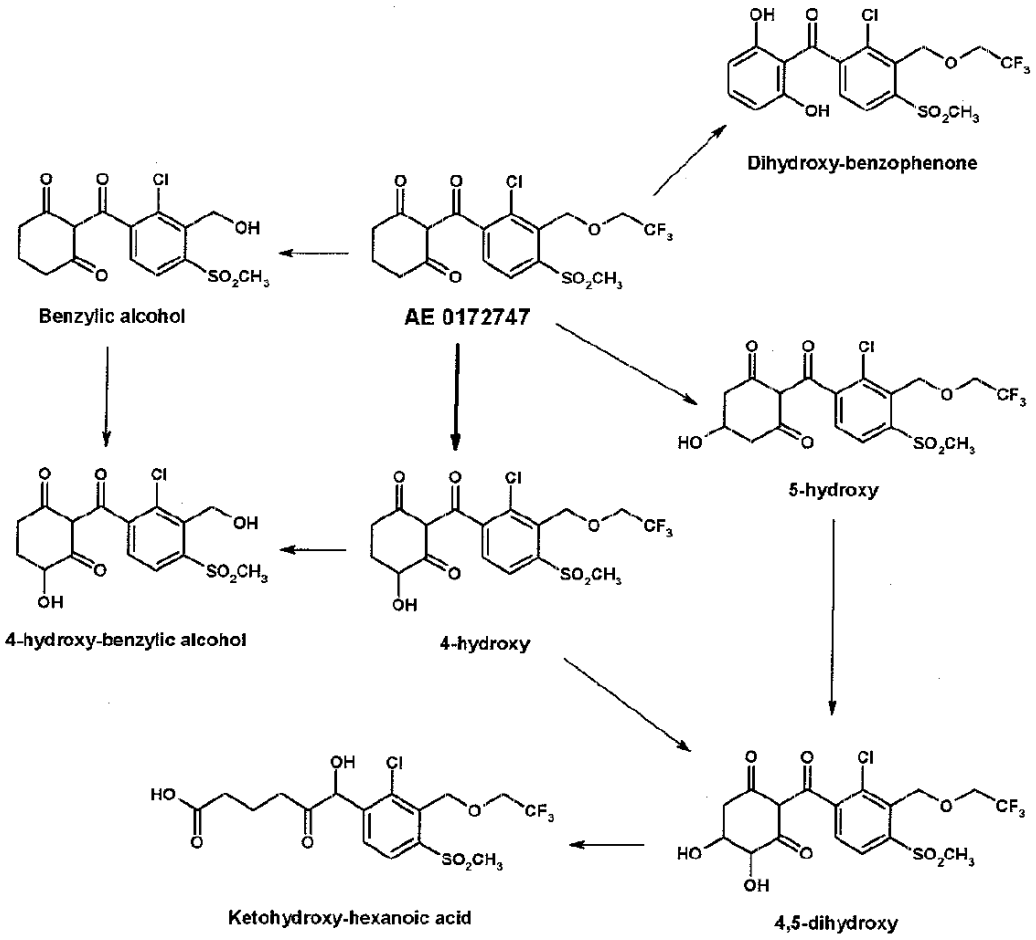
3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

The absorption and metabolism of tembotrione was investigated with the molecule labeled on either the phenyl or the cyclohexyl group at 5 mg/kg or 1000 mg/kg. Tembotrione was rapidly absorbed, extensively metabolized, and excreted. Total excretion of tembotrione was greater than 96% by 24 hours regardless of dose level or position of radiolabel. Sex differences were observed in the routes of excretion. The primary routes of elimination were the urine in females and the urine and feces in males. Males excreted up to 24.4% and 70.4% and females up to 79.1% and 20% of the administered dose in the urine and feces, respectively, at the low dose. Females excreted up to 63.7% and 28.5% and males up to 44.2 % and 49.1% of the dose in the urine and feces, respectively, at the high dose. The highest mean levels of radioactivity were extracted from the liver (1.7-3.5%) and kidneys (0.14-0.26%) at the low dose. At the high dose, the mean levels of radioactivity were extracted from the skin/fur (0.22-0.33%) and carcass. The highest concentrations of radioactivity were found in the skin followed by the liver, kidneys, stomach (and contents) and carcass. There was no evidence of bioaccumulation.

Males had higher mean blood, plasma maximum concentrations (C_{max}) and AUC values than females. In both sexes, the AUC for both blood and plasma indicated a disproportionally higher mean systemic exposure at 1000 mg/kg than at 5 mg/kg (>200-fold) that was apparently due to a saturation of the initial elimination/biotransformation processes, resulting in a slower initial elimination phase.

The parent molecule and 11 metabolites were identified and isolated. Metabolic profiles were qualitatively similar for both radiolabeled forms; however, profiles for the high and low doses were not the same and differences were noted between sexes. Females excreted the greatest quantity of the parent molecule in urine (44.1-59.4%). While low and high dose males eliminated 1.9-3.0% and 33.8%, respectively, in the urine. The metabolites found in the greatest quantities were 4- and 5- hydroxy-tembotrione. Other identified metabolites found at <5% were the 4,5-dihydroxy-tembotrione, benzylic alcohol, dihydroxy-benzophenone, 4-hydroxy-benzylic alcohol, and ketohydroxy-hexanoic acid ([cyclohexyl-UL-^{14}C] only). Males excreted greater quantities of 4- and 5- hydroxy-tembotrione than females; except, at the high dose where 4-hydroxy-tembotrione was eliminated in approximately equal amounts in both sexes. The primary step in the metabolism of tembotrione is the hydroxylation (oxidative pathway) of the cyclohexyl ring of the molecule (figure 1).

FIGURE 1. Proposed Metabolic Profile of Tembotrione in Rats



3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The toxicology database for tembotrione is adequate. The following acceptable studies are available:

Developmental toxicity in rats and rabbits (2)
Two-generation reproduction study in rats (1)
Developmental Neurotoxicity Study (1)
Acute and Subchronic Neurotoxicity Studies (2)

Executive summaries for each of these studies are provided in Appendix A.3.

3.3.2 Evidence of Neurotoxicity

Evidence of neurotoxicity was noted in the subchronic and chronic toxicity studies in the dog and the acute and developmental neurotoxicity studies in the rat. Uncoordinated movement, disturbance in locomotion and microscopic changes in the sciatic nerve were observed in the dog at the highest dose tested in the subchronic (124/111 mg/kg/day) and chronic studies (37.8/41.6 mg/kg/day, M/F). In the acute neurotoxicity study, decreased arousal was observed on day 0 in male rats at the lowest dose tested 200 mg/kg. In females, decreased body temperature, motor and locomotor activities were observed on day 0 at the next dose (500 mg/kg). In the DNT study, brain morphometric changes and decreased acoustic startle response are observed in offspring at the lowest dose tested (0.8 mg/kg/day).

3.3.3 Additional Information from Literature Sources

The literature search did not reveal relevant information.

3.3.4 Pre-and/or Postnatal Toxicity

3.3.4.1 Determination of Susceptibility

There is evidence of increased susceptibility in rabbit and rat fetuses to *in utero* exposure to tembotrione. In a developmental toxicity study in rabbits, decreased growth and/or delayed development of the skeleton and increased incidences of skeletal variations and anomalies in fetuses occurred at a dose (10 mg/kg/day) lower than that which caused maternal toxicity (100 mg/kg/day, few or no feces, late abortion, decreased body weight and food consumption). In a rat developmental toxicity study, increased skeletal variations including delayed ossifications and decreased growth and developmental effects as indicated by decreased fetal body weights and an increased number of runts occurred in fetuses at a dose (25 mg/kg/day) lower than the dose (125 mg/kg/day) that caused marginal maternal toxicity (decreased body-weight gains and food consumption). In addition, decreased post-weaning body weight (males), decreased acoustic startle response and brain morphometric changes were seen in rat fetuses at a dose (0.8 mg/kg/day, LDT) lower than the dose at which there was maternal toxicity (16.3 mg/kg/day, cornel opacity during lactation) in the rat neurotoxicity DNT. These studies indicate evidence of increased susceptibility however, the concern for the increased susceptibility seen in rat and rabbit developmental toxicity is low because a well characterized NOAEL protecting fetuses has been established. In addition, the developmental NOAELs for these studies are approximately 12 to 30 fold higher than the LOAEL used for the acute RfD. The effects seen in the developmental neurotoxicity study at the LOAEL of 0.8 mg/kg bw/day is considered as low toxicity since there was no clear dose response observed for morphometric changes in the offspring at termination. In fact, the brain morphometric measurements were lower at the dose compared to mid and the high dose. The decreased accoustic startle response observed in adult rats was statistically significant at the mid and high dose but not at the low dose. In addition, at the low dose there were large variations in the measurement of the acoustic startle response. Therefore, the FQPA factor of 10X applied for use of LOAEL to NOAEL is considered as protective of any residual susceptibility. In addition, the NOAEL (0.04 mg/kg/day) selected for the cRfD is lower (20X) than the dose at which developmental and neurological effects were observed.

3.3.4.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

There is evidence of increased susceptibility following in utero exposure in the rabbit (oral) and rat (oral) developmental toxicity studies occurring at 10 mg/kg/day and 25 mg/kg/day, respectively; and in the rat DNT study occurring at 0.8 mg/kg/day. However, the effects are well characterized and an additional 10X UF_L for extrapolation of the LOAEL to NOAEL was applied, which will be protective of developmental effects. Therefore, there are low concerns or residual uncertainties for pre- and post-natal toxicity. The NOAEL (0.04 mg/kg/day) selected for the cRfD is lower (20X) than the dose at which developmental and neurological effects were observed.

3.3.5 Recommendation for a Developmental Neurotoxicity Study

A DNT study was provided as part of the toxicity data package.

3.4 FQPA SF for Infants and Children

The tembotrione risk assessment team has recommended that the 10X FQPA SF be reduced to 1X for all exposure scenarios because there is a complete toxicity database for tembotrione and exposure data are complete or are estimated based on data that reasonably account for potential exposures. There was evidence of increased susceptibility of fetuses and offspring to developmental and neurological effects in the developmental toxicity and DNT studies (rabbits, rats), respectively. However, the established aRfD (0.0008 mg/kg) and cRfD (0.0004 mg/kg/day) are protective of any developmental and neurological effects observed at doses as low as 0.8 mg/kg/day in these studies. There are low concerns or residual uncertainties concerning pre- and postnatal toxicity. There are also no additional residual uncertainties with respect to exposure data. The dietary food exposure assessment utilizes proposed tolerance level or higher residues and 100% CT information for all commodities. By using these screening-level assessments, acute and chronic exposures/risks will not be underestimated. The dietary drinking water assessment utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations. There is no potential for residential exposure.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 aRfD - General Population (including females age 13-49)

Study Selected: Developmental Neurotoxicity/Rat

MRID No.: 46695725
Executive Summary: See Appendix A, Guideline [§ 870.3700]

Dose and Endpoint for Establishing aRfD: An offspring NOAEL was not established, based on decreased post-weaning body weight (males), decreased acoustic startle response on post-natal day (PND) 60 (males), and brain morphometric changes on PND 75 (males and females) at 0.8 mg/kg/day (LOAEL).

Comments on Study/Endpoint/UFs: The endpoint chosen, decreased acoustic startle response and brain morphometric changes were presumed to occur following a single exposure. An UF of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variation (10X) and an additional UF of 10X was applied to account for LOAEL to NOAEL extrapolation.

$$\textbf{aRfD} = \frac{0.8 \text{ mg/kg/day (LOAEL)}}{1000 \text{ (UF)}} = \textbf{0.0008 mg/kg}$$

3.5.2 cRfD

Study Selected: Chronic Toxicity/Carcinogenicity (Feeding)/Rat
MRID No.: 46695708
Executive Summary: See Appendix A, Guideline [§ 870.4300]

Dose and Endpoint for Establishing RfD: The NOAEL of 0.04 mg/kg/day was based on neovascularization and edema of the cornea and snow flake-like corneal opacity, unilateral or bilateral keratitis of the eye, decreased mean body weight and mean body-weight gain, increased total cholesterol, higher ketone levels and lower pH values, higher protein levels, increased kidney weight, kidney to body weight and kidney to brain weight ratios, chronic nephropathy and atrophy of the sciatic nerve observed in the male at 0.79 mg/kg/day (LOAEL).

UF(s): An UF of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variation (10X).

Comments about Study/Endpoint/UF: This study provided the lowest NOAEL in the database (most sensitive endpoint) and will also provide the most protective limits for human effects.

$$\textbf{cRfD} = \frac{0.04 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = \textbf{0.0004 mg/kg/day}$$

3.5.3 Incidental Oral Exposure (Short- and Intermediate-Term)

Study Selected: Developmental Neurotoxicity/ Rat

MRID No.: 46695725
Executive Summary: See Appendix A, Guideline [§ 870.3700]

Dose and Endpoint for Establishing aRfD: An offspring NOAEL was not established, based on decreased post-weaning body weight (males), decreased acoustic startle response on PND 60 (males), and brain morphometric changes on PND 75 (males and females) at 0.8 mg/kg/day (LOAEL).

Comments on Study/Endpoint/UFs: The endpoint chosen, because it was appropriate for the duration of exposure and the population of concern. An UF of 100 was applied to account for inter species extrapolation (10X) and intraspecies variation (10X) and an additional UF of 10X was applied to account for LOAEL to NOAEL extrapolation.

3.5.4 Dermal Absorption

Study Selected: Dermal Penetration Study/Rat

MRID No.: 46695730
Executive Summary: See Appendix A, Guideline [§ 870.7600]

Based on the dermal penetration study in rats, a dermal-absorption factor of 15% is appropriate for human risk assessment.

3.5.5 Dermal Exposure (Short-, Intermediate- and Long-Term)

Short- and Intermediate-term Dermal Exposure

Study Selected: Developmental Neurotoxicity/Rat

MRID No.: 46695725
Executive Summary: See Appendix A, Guideline [§ 870.3700]

Dose and Endpoint for Establishing aRfD: An offspring NOAEL was not established, based on decreased post-weaning body weight (males), decreased acoustic startle response on PND 60 (males), and brain morphometric changes on PND 75 (males and females) at 0.8 mg/kg/day (LOAEL).

Comments on Study/Endpoint/UFs: Since there is a developmental concern**,** the DNT was selected instead of a dermal toxicity study for this endpoint**.** Additionally**,** it was appropriate for the duration of exposure. An UF of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variation. The LOC for the MOE is <1000. The dermal-absorption factor is 15%, based on a dermal penetration study in rats.

Long-Term Dermal Exposure

Study Selected: Chronic Toxicity/Carcinogenicity (Feeding)/Rat
MRID No.: 46695708
Executive Summary: See Appendix A, Guideline [§ 870. 4300]

Dose and Endpoint for Establishing RfD: The NOAEL of 0.04 mg/kg/day was based on neovascularization and edema of the cornea and snow flake-like corneal opacity, unilateral or bilateral keratitis of the eye, decreased mean body weight and mean body-weight gain, increased total cholesterol, higher ketone levels and lower pH values, higher protein levels, increased kidney weight, kidney to body weight and kidney to brain weight ratios, chronic nephropathy and atrophy of the sciatic nerve observed in the male at 0.79 mg/kg/day (LOAEL).

UF(s): An UF of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variation (10X).

Comments about Study/Endpoint/UF: This study provided the lowest NOAEL in the database (most sensitive endpoint) and will also provide the most protective limits for human effects. The LOC for the MOE is <100. The dermal-absorption factor is 15%, based on a dermal penetration study in rats.

3.5.6 Inhalation Exposure (Short-, Intermediate- and Long-Term)

Short- and Intermediate-Term Inhalation Exposure

Study Selected: Developmental Neurotoxicity/Rat

MRID No.: 46695725
Executive Summary: See Appendix A, Guideline [§ 870.3700]

Dose and Endpoint for Establishing aRfD: An offspring NOAEL was not established, based on decreased post-weaning body weight (males), decreased acoustic startle response on PND 60 (males), and brain morphometric changes on PND 75 (males and females) at 0.8 mg/kg/day (LOAEL).

Comments on Study/Endpoint/UFs: Since there is a developmental concern and an inhalation toxicity study is not available, the DNT was selected for this endpoint. Additionally, it was appropriate for the duration of exposure. An UF of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variation (10X). The LOC for the MOE is <1000. HED assumes equivalent toxicity via the oral and inhalation routes.

Long-Term Inhalation Exposure

Study Selected: Chronic Toxicity/Carcinogenicity (Feeding)/Rat
MRID No.: 46695708
Executive Summary: See Appendix A, Guideline [§ 870.4300]

Dose and Endpoint for Establishing RfD: The NOAEL of 0.04 mg/kg/day was based on neovascularization and edema of the cornea and snow flake-like corneal opacity, unilateral or bilateral keratitis of the eye, decreased mean body weight and mean body-weight gain, increased total cholesterol, higher ketone levels and lower pH values, higher protein levels, increased kidney weight, kidney to body weight and kidney to brain weight ratios, chronic nephropathy and atrophy of the sciatic nerve observed in the male at 0.79 mg/kg/day (LOAEL).

UF(s): An UF of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variation (10X).

Comments about Study/Endpoint/UF: This study provided the lowest NOAEL in the database (most sensitive endpoint) and will also provide the most protective limits for human effects. The LOC for the MOE is <100. HED assumes equivalent toxicity via the oral and inhalation routes.

3.5.7 Levels of Concern for Margins of Exposure

Table 3.5.7. Summary of Levels of Concern for Risk Assessment.			
Route	**Short-Term (1-30 Days)**	**Intermediate-Term (1-6 Months)**	**Long-Term (>6 Months)**
Occupational (Worker) Exposure			
Dermal	1000[a]	1000	100[b]
Inhalation	1000	1000	100
Residential Exposure			
Dermal	1000	1000	100
Inhalation	1000	1000	100
Incidental Oral	1000	1000	100

[a] LOC = Interspecies extrapolation (10X), intraspecies variation (10X) and LOAEL to NOAEL extrapolation (10X) Ufs.

[b] LOC = Interspecies extrapolation (10X) and intraspecies variation (10X) UFs.

3.5.8 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. However, an aggregated exposure risk assessment incorporating residential exposures is not required since there are no residential uses for tembotrione at this time.

For oral exposure dietary exposure and water were aggregated. For occupational exposure dermal and inhalation exposure were combined since the effects of concern are the same and identified from the same study.

3.5.9 Classification of Carcinogenic Potential

On April 11, 2007, in accordance with the EPA Guidelines for Carcinogen Risk Assessment (March, 2005), the HED CARC classified tembotrione as **"Suggestive Evidence of Carcinogenic Potential"** based on the occurrence of squamous cell carcinoma in male rats. Therefore, quantification of carcinogenic potential is not required. The RfD is assumed to be protective of cancer effects.

3.5.10 Summary of Toxicological Doses and Endpoints for Tembotrione for Use in Human-Health Risk Assessments

Table 3.5.10a. Summary of Toxicological Doses and Endpoints for tembotrione for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA SFs	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL<0.8 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 10X (includes UF_L = 10X)	**Acute RfD** = 0.0008 mg/kg aPAD = 0.0008 mg/kg	Developmental neurotoxicity Offspring NOAEL was not established. Offspring LOAEL = 0.8 mg/kg/day based on decreased acoustic startle response on PND 60 (males), and brain morphometric changes on PND 75 (males and females).
Chronic Dietary (All Populations)	NOAEL=0.04 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X	**Chronic RfD** = 0.0004 mg/kg/day **cPAD** = 0.0004 mg/kg/day	Chronic/Carcinogenicity LOAEL = 0.79 mg/kg/day based on neovascularization and edema of the cornea and snow flake-like corneal opacity, unilateral or bilateral keratitis of the eye, decreased mean body weight and mean body-weight gain, increased total cholesterol, higher ketone levels and lower pH values, higher protein levels, increased kidney weight, kidney to body weight and kidney to brain weight ratios, chronic nephropathy and atrophy of the sciatic nerve.
Incidental Oral Short- and Intermediate-Term (1-30 days and 1-6 months)	NOAEL<0.8 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 10X (includes UF_L = 10X)	Residential LOC for MOE = 1000	Developmental neurotoxicity Offspring NOAEL was not established. Offspring LOAEL = 0.8 mg/kg/day based on decreased acoustic startle response on PND 60 (males), and brain morphometric changes on PND 75 (males and females).
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months)	NOAEL<0.8 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 10X (includes UF_L = 10X) Dermal-absorption rate = 15%	Residential and Occupational LOC for MOE = 1000	Developmental neurotoxicity Offspring NOAEL was not established. Offspring LOAEL = 0.8 mg/kg/day based on decreased acoustic startle response on PND 60 (males), and brain morphometric changes on PND 75 (males and females).

Table 3.5.10a. Summary of Toxicological Doses and Endpoints for tembotrione for Use in Dietary and Non-Occupational Human Health Risk Assessments.				
Dermal Long-Term (> 6 months)	NOAEL=0.04 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X Dermal-absorption rate = 15%	Residential and Occupational LOC for MOE = 100	Chronic/Carcinogenicity LOAEL = 0.79 mg/kg/day based on neovascularization and edema of the cornea and snow flake-like corneal opacity, unilateral or bilateral keratitis of the eye, decreased mean body weight and mean body-weight gain, increased total cholesterol, higher ketone levels and lower pH values, higher protein levels, increased kidney weight, kidney to body weight and kidney to brain weight ratios, chronic nephropathy and atrophy of the sciatic nerve.
Inhalation Short- and Intermediate-Term (1-30 days and 1-6 months)	NOAEL<0.8 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 10X (includes UF_L = 10X) Inhalation-absorption rate = 100%	Residential and Occupational LOC for MOE = 1000	Developmental neurotoxicity Offspring NOAEL was not established. Offspring LOAEL = 0.8 mg/kg/day based on decreased acoustic startle response on PND 60 (males), and brain morphometric changes on PND 75 (males and females).
Inhalation Long-Term (> 6 months)	NOAEL=0.04 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X Inhalation-absorption rate=100%	Residential and Occupational LOC for MOE = 100	Chronic/Carcinogenicity LOAEL = 0.79 mg/kg/day based on neovascularization and edema of the cornea and snow flake-like corneal opacity, unilateral or bilateral keratitis of the eye, decreased mean body weight and mean body-weight gain, increased total cholesterol, higher ketone levels and lower pH values, higher protein levels, increased kidney weight, kidney to body weight and kidney to brain weight ratios, chronic nephropathy and atrophy of the sciatic nerve.
Cancer (oral, dermal, inhalation)	Classification: "Suggestive Evidence of Carcinogenic Potential" based on the observance of squamous cell carcinomas in a rat carcinogenicity study. Quantification of cancer risk is not required.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 3.5.10b. Summary of Toxicological Doses and Endpoints for tembotrione for Use in Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**Point of Departure**	**UFs**	**LOC for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term and (Intermediate-Term (1-30 days and 1-6 months)	NOAEL<0.8 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 1X (includes UF_L = 10X) Dermal-absorption rate = 15%	Occupational LOC for MOE = 1000	Developmental neurotoxicity Offspring LOAEL = 0.8 mg/kg/day based on decreased acoustic startle response on PND 60 (males), and brain morphometric changes on PND 75 (males and females).
Inhalation Short- and Intermediate-Term (1-30 days and 1-6 months)	NOAEL<0.8 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 1X (includes UF_L = 10X) Dermal-absorption rate = 15%	Occupational LOC for MOE = 1000	Developmental neurotoxicity Offspring LOAEL = 0.8 mg/kg/day based on decreased acoustic startle response on PND 60 (males), and brain morphometric changes on PND 75 (males and females).
Cancer (oral, dermal, inhalation)	Classification: "Suggestive Evidence of Carcinogenic Potential" based on the observance of squamous cell carcinomas in a rat carcinogenicity study. Quantification of cancer risk is not required.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.6 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).

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

Public Health and Pesticide Epidemiology Data

No public health/epidemiology data were used in developing this risk assessment. Since tembotrione is a new chemical, data are not available.

5.0 Dietary Exposure/Risk Characterization

The following references apply to this section:
Residue Chemistry Summary - D325349, G. Kramer, 18-JUL-2007
Dietary Exposure - D335831, G. Kramer, 18-JUL -2007
Estimated Drinking Water Concentrations & Environmental Degradation - D335247, W. Eckel, 01-JAN-2007

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

The submitted metabolism data for corn, using test substances radiolabeled in the phenyl and cyclohexyl rings, are adequate to elucidate the nature of the residue in the subject crop. Tembotrione is metabolized in corn by hydroxylation of the cyclohexyl moiety to form the monohydroxy (M10) and dihydroxy (M5) metabolites, followed by cleavage to the benzoic acid derivative M6 (figure 2). The formation of M6 directly from the parent herbicide could not be ruled out. The metabolite M2 is formed by the subsequent cleavage of the trifluoroethoxy ether bond of M6.

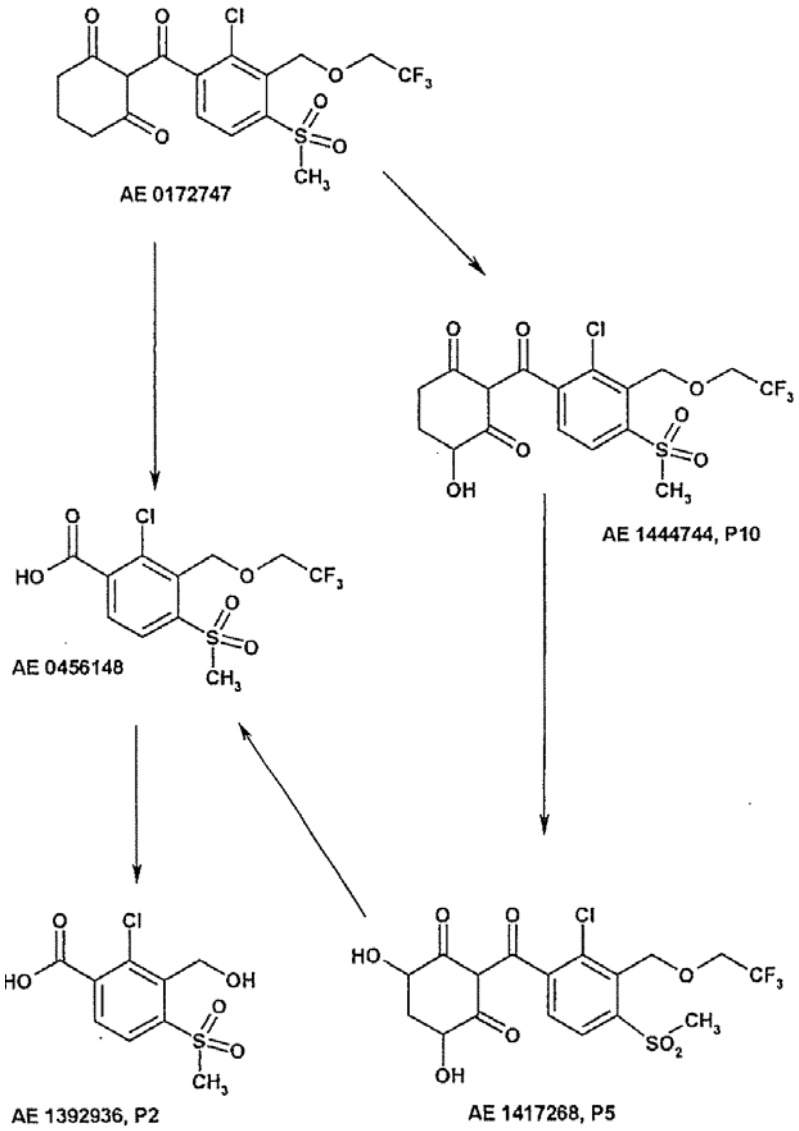
5.1.2 Metabolism in Rotational Crops

The metabolic profile of tembotrione in confined rotational crops involves cleavage of the complete cyclohexyl moiety from the parent compound leaving the benzoic acid moiety of the molecule, M6, and to a lesser extent subsequent cleavage of the ether bond to form M2. The two residue components identified in the study, M6 and M2, were also identified in the primary crop (corn) metabolism study. The metabolism of tembotrione in rotational crops appears to be consistent with the pathway observed in the corn metabolism study.

5.1.3 Metabolism in Livestock

The submitted cow and poultry metabolism data, using the parent compound radiolabeled in the phenyl and cyclohexyl rings, and the cow metabolism data using cyclohexyl-labeled M5 are adequate to satisfy data requirements. The livestock metabolism studies indicate that tembotrione and its M5 metabolite are not extensively metabolized. Only the parent was identified and confirmed in cow and poultry tissues, milk, and eggs; and only metabolite M5 was identified in the supplementary study.

FIGURE 2. Proposed Metabolic Profile of Tembotrione in Corn



Metabolites P2, P5 and P10 are presented in the text as M2, M5 and M10; AE045148, as M6.

5.1.4 Analytical Methodology

The petitioner has submitted several liquid chromatography/mass spectroscopy (LC/MS/MS) residue analytical methods for the determination of residues of the parent and its metabolites in/on corn and livestock commodities. Method AE/03/01 determines residues of tembotrione and its metabolites M6, M5, and M2 in/on corn commodities. Method 00967 determines residues of tembotrione and its metabolite M5 in meat, milk, and eggs. Method AE-003-A04-02 determines residues of tembotrione *per se* in beef tissues and milk. Method AE-004-A04-02 determines residues of tembotrione *per se* in poultry tissues (skin, muscle, and liver) and eggs (white and yolk). The validated limit of quantitation (LOQ) reported in the method submission is 0.010 ppm for all matrices. These methods were used as the data-collection methods in the analysis of samples for residues of concern from the various studies associated with the current petition. Each method has been adequately validated by the petitioner as well as by independent laboratories. Methods AE/03/01 and 00967 were also adequately radiovalidated using weathered samples obtained from metabolism studies.

HED has determined that Methods AE/03/01 and 00967 may be suitable enforcement methods for corn and livestock commodities, respectively, provided the methods pass successful PMVs by Agency chemists at ACL/BEAD and the petitioner addresses the following issues: The methods should be revised to include a calculation for the conversion of residues of the metabolite(s) to parent equivalents for quantitation. A separate confirmatory method for Method AE/03/01 will not be required provided that two ion transitions are monitored during MS/MS analysis for each analyte. Currently, Method No. 00967 reflects measurement of a second LC/MS/MS ion transition for each analyte. The petitioner has indicated that Method AE/03/01 will be superseded by Revision AE/03/01-01, in which a second ion transition is to be monitored.

5.1.5 Environmental Degradation

Tembotrione is not expected to be persistent in the environment, degrading primarily through aerobic biodegradation and photolysis. The primary metabolic profile of tembotrione in the environment involves cleavage of the complete cyclohexyl moiety from the parent compound leaving the benzoic acid moiety of the molecule, M6, and to a lesser extent subsequent cleavage of the ether bond to form M2. Other metabolites observed include AE 0968400, AE 1124336, glutaric acid, and AE 0941989 (see Appendix B: Metabolism Assessment, Table B.3).

5.1.6 Comparative Metabolic Profile

The primary route of metabolism in rats and a major route in corn was found to be hydroxylation (oxidative pathway) of the cyclohexyl ring of the molecule. The 4 and 6 positions were hydroxylated in corn while the 5 and 6 positions were hydroxylated in rats. The primary route of metabolism in corn, rotational crops, and the environment involves cleavage of the complete cyclohexyl moiety from the parent compound leaving the benzoic acid moiety of the molecule, M6, and to a lesser extent subsequent cleavage of the ether bond to form M2. Metabolism of tembotrione was not observed in the livestock studies.

5.1.7 Toxicity Profile of Major Metabolites and Degradates

The following toxicity data were submitted for metabolites M6, M2 and M5.

M6 has low acute toxicity via the oral and dermal routes of exposure (Toxicity Category III). It is an eye irritant (Toxicity Category III) but not a dermal irritant (Toxicity Category IV).

In a subchronic oral toxicity rat study, M6 caused an increase in the incidence of hematopoiesis of the spleen at the high dose (1436.3 mg/kg/day) in females. Effects were not observed in males up to the highest dose tested (1203.8 mg/kg/day). There is no evidence of mutagenicity in *in vitro* studies.

M2 has low acute toxicity via the oral route of exposure (Toxicity Category III). Additional acute toxicity studies were not provided. There is no evidence of mutagenicity in *in vitro* studies.

M5 has low acute toxicity via the oral route of exposure (Toxicity Category III). Additional acute toxicity studies were not provided.

In a subchronic toxicity study in the rat, M5 caused pancreatic toxicity (acinar degeneration/ apoptosis) in both sexes, hepatotoxicity (increase weight, enlargement with prominent lobulation, hypertrophy) in males at 586 mg/kg/day (HDT) and increase serum triglycerides and eye lesions (white area in eye, corneal opacity, neovascularization, edema of the cornea, keratitis) in females at 718 mg/kg/day (HDT). Also, there was one mortality due to a hemorrhagic syndrome in a male rat.

M5 is positive for the gene mutation assay in mouse lymphoma cells; other assays (gene mutation assay in bacteria and chromosome aberrations assay in human lymphocytes) are negative. Since additional mutagenic studies were not available, the mutagenic potential of the metabolite M5 is inconclusive.

In a special single dose oral study in rats, tembotrione and M5 caused a 20- and 5-fold increase, respectively, in plasma tyrosine levels at 10 mg/kg in male rats. M2 and M6 did not cause elevated tyrosine levels in the plasma. Cleavage of the phenyl and cyclohexyl rings appears to eliminate the ability to inhibit HPPD.

5.1.8 Pesticide Metabolites and Degradates of Concern

Table 5.1.8. 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	Primary Crop	Tembotrione + M5	Tembotrione + M5
	Rotational Crop	Tembotrione + M5	Not Applicable
Livestock	Ruminant	Tembotrione + M5	Tembotrione + M5
	Poultry	Tembotrione + M5	Tembotrione + M5
Drinking Water		Tembotrione	Not Applicable

Plants and Livestock: The available toxicity data for M2, M5 and M6 (the major metabolites in plants) show that the metabolites are considerably less toxic than the parent. Since there is limited data for M5 and it retains some potential to inhibit HPPD due to its structural similarity to the parent compound, the M5 metabolite is considered as toxic as the parent in this risk assessment. M2 and M6 were excluded as residues of concern since they lack the potential to inhibit HPPD and are structurally unrelated to the parent compound. Therefore, residues of concern in the tolerance expression and risk assessment for plants are tembotrione and its metabolite M5. Metabolism of tembotrione was not observed in the livestock studies. However, M5 was included as a residue of concern in the tolerance expression and risk assessment for livestock to account for transfer of residues from feed commodities.

Water: M2, AE 0968400, and M6 are the major environmental degradates. M2 and M6 were excluded as residues of concern for the reasons discussed above. AE 0968400 is structurally similar to M6 and can thus be excluded as a residue of concern. Therefore, the residue of concern in the risk assessment for drinking water is tembotrione only.

5.1.9 Drinking Water Residue Profile

Table 5.1.9. Summary of Estimated Surface Water and Groundwater Concentrations for Tembotrione.		
	Tembotrione *per se*	
	Surface Water Conc., ppb[a]	**Groundwater Conc., ppb [b]**
Acute	5.84	0.0139
Chronic (non-cancer)	1.05	0.0139
Chronic (cancer)	0.72	0.0139

[a] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on 0.082 lbs a.i./acre per application with a 14 day minimum interval between applications and two applications per season. The highest peak concentration came from the Florida corn scenario; the highest yearly average and 30-year average, from the North Dakota scenario.

[b] From the SCI-GROW model assuming a maximum seasonal use rate of 0.082 lbs ai/A, a K_{oc} of 20 mL/g, and a half-life of 10.45 days.

5.1.10 Food Residue Profile

The submitted magnitude of the residue data for the RACs of field corn, popcorn, and sweet corn are adequate. There are adequate storage stability data to validate the storage conditions and intervals of samples collected from the field trials.

An acceptable corn processing study is available. The corn study shows that following processing of field corn grain bearing quantifiable residues, total residues of tembotrione and its metabolite (as parent equivalents) concentrated slightly in meal (1.2x processing factor) but did not concentrate in oil (0.02x), flour (0.80x), grits (1.0x), or starch (0.02x). A tolerance for corn meal need not be established as the recommended RAC tolerance will cover any expected residues in corn meal as a result of the proposed use. A processing study on rotated wheat was also submitted. The wheat study shows that total residues of tembotrione and its metabolites were below the method <LOQ of 0.010 ppm in/on rotated wheat grain following treatment of the primary crop at 5x. As residues in the RAC were <0.010 ppm, data on the processed commodities of wheat as a rotated crop are not required.

Adequate dairy cow and poultry feeding studies have been submitted; these studies are acceptable for determining tolerance levels for livestock commodities. Based on the submitted data, HED has concluded that the tolerances, expressed as tembotrione and its metabolite M5, are required for some livestock commodities (meat byproducts).

A summary of the recommended tolerances for the current petition are listed in Appendix C: Tolerance Reassessment Summary. The petitioner should submit a revised Section F reflecting the recommended tolerances and commodity definitions presented in Appendix C.

The Agency's *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* was utilized for determining appropriate tolerance levels for field corn forage, field corn stover, popcorn stover sweet corn forage, and sweet corn stover; see Appendix II for tolerance calculations. The Agency's tolerance spreadsheet was not used to determine tolerance levels for the remainder of various corn commodities since greater than 95% of the treated samples bore individual or total residues below the LOQ.

A tolerance for corn aspirated grain fractions is not needed because the proposed use on field corn involves applications prior to the crop's reproductive stage. Tolerances for the processed commodities of corn are not needed because the submitted corn processing study shows that residues do not concentrate. Residues of tembotrione and its metabolite are not likely to concentrate in the processed commodities of rotated wheat grain because residues of tembotrione and its metabolites were nonquantifiable following treatments at 5x the proposed seasonal rate. Tolerances for inadvertent residues of tembotrione in/on rotational crops are not needed because the limited field rotational crop trials show that residues were below the LOQ in/on various rotational crop commodities.

5.1.11 International Residue Limits

There are no Codex, Canadian, or Mexican maximum residue limits (MRLs) established for residues of tembotrione in crops or livestock commodities.

5.2 Dietary Exposure and Risk

5.2.1 Acute Dietary Exposure/Risk

The acute analysis assumed 100% CT, DEEM™ 7.81 default processing factors, and tolerance-level residues for all foods. For drinking water, the entire distribution of estimated daily exposure values from the PRZM-EXAMS run was incorporated in the acute probabilistic exposure analyses. The resulting **acute dietary (food + water) risk estimates were <32% of the aPAD for the general U.S. population and <77% of the aPAD for all infants (<1 year old, the most highly-exposed population subgroup) at the 95th percentile; less than HED's LOC (100% aPAD).** Even though the entire distribution of estimated daily drinking water exposure values was incorporated, this analysis is still conservative since tolerance-level residues, DEEM™ 7.81 default processing factors, and 100% CT were assumed. Also, the distribution of estimated daily drinking water exposure still assumes 100% CT and the maximum application rate. The 95th percentile is thus the appropriate LOC.

5.2.2 Chronic Dietary Exposure/Risk

A conservative chronic dietary assessment assuming tolerance-level residues, DEEM™ 7.81 default processing factors, and 100% CT was also conducted. The highest estimate of chronic surface water exposure (1.05 ppb) was used for drinking water in this analysis. The chronic dietary risk assessment shows that for all included commodities, the **chronic (non-cancer) dietary risk estimates are below HED's LOC (i.e., <100% cPAD).** For the U.S. population the exposure for food and water utilized 22% of the cPAD. The chronic dietary risk estimate for the highest reported exposed population subgroup, children 3-5 years old, is 48% of the cPAD.

5.2.3 Cancer Dietary Risk

Dietary cancer risk concerns due to long-term consumption of tembotrione residues are adequately addressed by the chronic exposure analysis using the cPAD.

Table 5.2. Summary of Dietary (Food and Drinking Water) Exposure Risk for Tembotrione.				
Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.000255	32	0.000090	22
All Infants (<1 year old)	**0.000618**	77	0.000159	40
Children 1-2 years old	0.000445	56	0.000172	43
Children 3-5 years old	0.000444	55	**0.000192**	**48**
Children 6-12 years old	0.000335	42	0.000141	35
Youth 13-19 years old	0.000261	33	0.000104	26
Adults 20-49 years old	0.000192	24	0.000075	19
Adults 50+ years old	0.000147	18	0.000056	14
Females 13-49 years old	0.000197	25	0.000075	19

The values for the highest exposed population for each type of risk assessment are bolded.

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

The acute and chronic dietary exposure analyses were based on tolerance-level residues and the assumption of 100% CT. Anticipated residues and percent CT estimates were not incorporated into the assessments.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

The following reference applies to this section:
Occupational and Residential Exposure - D326301, K. Lowe, 29-Mar-2007.

As tembotrione is a new active ingredient with no registered or proposed residential uses, a quantitative non-occupational exposure assessment was not performed.

6.1 Other (Spray Drift, etc.)

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 tembotrione. The Agency 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, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The

Agency has completed its evaluation of the new database 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, the Agency 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

Aggregate exposure and risk assessments were assessed by incorporating the drinking water directly into the dietary-exposure assessment for the following scenarios: acute and chronic aggregate exposure (food + drinking water). Short-, intermediate-, and long-term aggregate-risk assessments were not performed because there are no registered or proposed uses of which result in residential exposures. A cancer aggregate-risk assessment was not performed because dietary cancer risk concerns due to long-term consumption of tembotrione residues are adequately addressed by the chronic exposure analysis using the cPAD.

See section 8.0 for further discussion on the effects of HPPD inhibition.

8.0 Cumulative Risk Characterization/Assessment

Tembotrione, mesotrione, pyrasulfotole, isoxaflutole and topramezone belongs to a class of herbicides that inhibit the liver enzyme HPPD, which is involved in the catabolism (metabolic breakdown) of tyrosine (an amino acid derived from proteins in the diet). Inhibition of HPPD can result in elevated tyrosine levels in the blood, a condition called tyrosinemia. HPPD-inhibiting herbicides have been found to cause a number of toxicities in laboratory animal studies including ocular, developmental, liver and kidney effects. Of these toxicities, it is the ocular effect (corneal opacity) that is highly correlated with the elevated blood tyrosine levels. In fact, rats dosed with tyrosine alone show ocular opacities similar to those seen with HPPD inhibitors. Although the other toxicities may be associated with chemically-induced tyrosinemia, other mechanisms may also be involved.

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

HPPD inhibitors (*e.g.,* Nitisinone) are used as an effective therapeutic agent to treat patients suffering from rare genetic diseases of tyrosine catabolism. Treatment starts in childhood but is

often sustained throughout patient's lifetime.–The human experience indicates that a therapeutic dose (1 mg/kg/day dose) of Nitisinone has an excellent safety record in infants, children and adults and that serious adverse health outcomes have not been observed in a population followed for approximately a decade. Rarely, ocular effects are seen in patients with high plasma tyrosine levels; however, these effects are transient and can be readily reversed upon adherence to a restricted protein diet. This indicates that an HPPD inhibitor in it of itself cannot easily overwhelm the tyrosine-clearance mechanism in humans.

Therefore, exposure to environmental residues of HPPD-inhibiting herbicides are unlikely to result in the high blood levels of tyrosine and ocular toxicity in humans due to an efficient metabolic process to handle excess tyrosine. In the future, assessments of HPPD-inhibiting herbicides willl consider more appropriate models and cross species extrapolation methods. Therefore, EPA has not conducted cumulative risk assessment with other HPPD inhibitors (HED Doc. D 341612; dated 7/02/07).

Therefore, a cumulative risk assessment was not performed for tembotrione.

9.0 Occupational Exposure/Risk Pathway

The following reference applies to this section:

Occupational and Residential Exposure Assessment - D326301, K. Lowe., 29-March-2007

Uses are proposed in/on field corn, sweet corn and popcorn. Tembotrione is applied as an early (prior to the 8-leaf stage of growth) post-emergent herbicide. Occupational handler and post-application exposure may occur as a result of the proposed uses. Application methods, rates and use pattern are described in Table 2.1.2. Aerial application and/or application through any type of irrigation system are prohibited. Use of an external spray adjuvant is required, and the adjuvant type is dependent on the weed spectrum. Use sites carry a 45-day PHI for forage. Re-treatment interval is 14 days. The label indicates a REI of 12-hours. Corn (field, sweet and popcorn) may be treated twice a season.

HED believes most exposure durations will be short-term (1-30 days). However, the ExpoSAC maintains it is possible for commercial applicators to be exposed to intermediate-term exposure durations (1-6 months). In addition, the short- and intermediate-term toxicological endpoints are the same; therefore, the estimates of risk for short-term duration exposures are protective of those for intermediate-term duration exposures. Long-term exposures are not expected; therefore, a long-term assessment was not conducted.

9.1 Short-/Intermediate-Term Occupational Handler Risk

Tembotrione is applied by ground equipment only (aerial application is prohibited on the label). Based upon the proposed agricultural uses, HED expects the most highly exposed occupational pesticide handlers are likely to be:
1) mixer/loader using open-pour loading of liquids for groundboom spraying
2) applicator using open-cab ground-boom sprayer

No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED Surrogate Guide (August, 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 for "baseline" and the use of protective gloves or other PPE as might be necessary. The proposed product label involved in this assessment directs applicators and other handlers to wear a long-sleeved shirt and long pants; socks, shoes and chemical-resistant gloves.

Daily dermal or inhalation handler exposures are estimated for each applicable handler task with the application rate, the area treated in a day, and the applicable dermal or inhalation unit exposure using the following formula:

Daily Exposure (mg ai/day) = UE (mg ai/lb ai handled) x AR (lbs ai/area or volume) x AT (area or amount/day)

Where:

Daily Exposure	=	Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
UE	=	Unit exposure value (mg ai/lb ai) derived from August 1998 PHED Surrogate Guide;
AR	=	application rate (lb ai/A or lb ai/gal); 0.082 lb ai/A and
AT	=	Area treated (A/day) or 200A.

The daily dermal or inhalation dose is calculated by normalizing the daily exposure by body weight and adjusting, if necessary, with an appropriate dermal- or inhalation- absorption factor using the following formula:

Average Daily Dose (mg/kg/day) = Daily Exposure (mg ai/day) x (Absorption Factor (%/100) / Body Weight (70 kg)

Where:

Average Daily Dose	=	Absorbed dose received from exposure to a pesticide in a given scenario (mg pesticide active ingredient/kg body weight/day);
Daily Exposure	=	Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
Absorption Factor	=	A measure of the amount of chemical that crosses a biological boundary such as the skin or lungs (% of the total available absorbed); and
Body Weight	=	Body weight determined to represent the population of interest in a risk assessment (kg).

Non-cancer dermal and inhalation risks for each applicable handler scenario are represented by a MOE, which is a ratio of the NOAEL to the daily dose. All MOE values were calculated using the formula below:

MOE= 0.8 mg/kg/day / Average Daily Dose (mg/kg/day)

A total MOE was calculated because the dermal and inhalation toxicological endpoints of concern are based on the same adverse effects and dose level. The total (dermal + inhalation) MOE values were calculated using the formula below:

Total MOE = NOAEL / Dermal + Inhalation Dose

Occupational Handler Non-cancer Risk Summary

Short- and intermediate-term handler risks were estimated. HED assumes inhalation toxicity as equivalent to oral toxicity and 15% dermal absorption (based on a dermal penetration study in rats). Short-term dermal and inhalation exposures were summed and compared to the short-term NOAEL of 0.8 mg/kg/day identified for short-term dermal and inhalation risk assessment. Intermediate-term dermal and inhalation exposures were summed and compared to the NOAEL of 0.8 mg/kg/day identified for intermediate-term dermal and inhalation risk assessment. The MOE is $\geq$1000 as a result of LOAEL to NOAEL extrapolation. Exposure and risk estimates are presented in Table 9.1 below. HED has determined that there are no risks of concern associated with the groundboom application scenario at baseline. However, HED has determined that there are risks of concern (i.e., MOEs <1000) associated with the mixer/loader scenarios at baseline. and with the use of gloves, as directed by the label. If an extra layer of clothing is worn (i.e., a double layer), the MOE is 910 and if a closed mixing/loading system is utilized (i.e., engineering control), the MOE is 1,400. HED has determined that the risks associated with a mixer/loader wearing a double layer of clothing are not of concern and **recommends that a double layer of clothing (*i.e.*, coverall) be added to the label for PPE**.

Table 9.1. Tembotrione Occupational Dermal and Inhalation Exposures and Risks.							
Exposure Scenario	Crop or Target	App Rate (lb ai/acre)[a]	Area Treated Daily (acres)[b]	Unit Exposures Dermal and Inhalation (mg/lb ai)	Doses (mg/kg/day)[c]	Short-and Intermediate-term MOEs	Combined MOEs[d]
Mixer/Loader							
Mixing/Loading Liquids Concentrates for Groundboom Applications (open pour)	Field and silage corn, seed corn, sweet corn, popcorn	0.082	200	Dermal Baseline[e]: 2.9 PPE – SL w/gloves[g]: 0.023 PPE – DL w/gloves[h]: 0.017 Engineering control[i]: 0.0086	Dermal Baseline: 0.1 PPE – SL w/gloves: 0.00081 PPE – DL w/gloves: 0.0006 Engineering control: 0.0003	Dermal Baseline: **7.8** PPE – SL w/gloves: **990** PPE – DL w/gloves: 1,300 Engineering control: 2,600	Baseline Dermal and Inhalation: **7.8** PPE – SL w/gloves + Baseline Inhalation: **730** PPE – DL w/gloves + Baseline Inhalation: **910** Engineering control + Baseline Inhalation: 1,400
				Inhalation Baseline[f]: 0.0012	Inhalation Baseline: 0.00028	Inhalation Baseline: 2,800	
Applicator							
Applying Sprays via Ground-boom Equipment (open cab)	Field and silage corn, seed corn, sweet corn, popcorn	0.082	200	Dermal Baseline: 0.014	Dermal Baseline: 0.00049	Dermal Baseline: 1,600	Baseline Dermal + Inhalation: 1,200
				Inhalation Baseline: 0.00074	Inhalation Baseline: 0.00017	Inhalation Baseline: 4,600	

a Application rate = maximum application rate from label (0.082 lb ai/acre).
b Amount handled per day values are HED estimates of acres treated per day based on Exposure SAC SOP #9 "Standard Values for Daily Acres Treated in Agriculture," industry sources, and HED estimates.
c Dose (mg/kg/day) = Unit exposure(mg/lb ai) x App Rate (lb ai/acre) x Area Treated (acres/day) x %Absorption (15% dermal and 100% inhalation) / Body weight (70 kg).
d Combined MOE = NOAEL or LOAEL (mg/kg/day) / (Dermal + Inhalation Dose (mg/kg/day))
e Baseline Dermal: Long-sleeve shirt, long pants, and no gloves.
f Baseline Inhalation: no respirator.
g PPE - SL w/ gloves: Single layer plus chemical-resistant gloves.
h PPE – DL w/gloves: Double layer plus chemical-resistant gloves.
i Engineering control: closed mixing/loading system

9.2 Short-/Intermediate-Term Postapplication Risk

HED expects that postapplication exposure will occur since tembotrione is applied as a foliar spray. Since no postapplication data was submitted in support of this registration action, exposures during postapplication activities were estimated using dermal TCs from the HED ExpoSAC Policy Number 3.1: Agricultural TCs, August 2000, summarized in 9.2.1 below. It is anticipated that because of the label restriction that this product will not be applied to corn that is more mature than the 8-leaf stage of growth, that the most likely postapplication activities will be hand-weeding, scouting, and irrigation. In addition, the following assumptions were also used:

Assumptions:

- Application Rate = 0.082 lb ai/A
- Exposure Duration = 8 hours per day
- Body Weight = 70 kg
- Dermal Absorption = 15%
- Fraction of a.i. retained on foliage is assumed to be 20% (0.2) on day zero (= % dislodgeable foliar residue, DFR, after initial treatment). This fraction is assumed to

further dissipate at the rate of 10% (0.1) per day on following days. These are default values established by HED's ExpoSAC.

Daily dermal exposures were calculated on each postapplication day after application using the following equation:

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

Where:

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

Note that the ($TR_{(t)}$) input may represent levels on the day of application in the case of short-term risk calculations. Once daily exposures are calculated, the calculation of daily absorbed dose and the resulting MOEs use the same algorithms that are described above for the handler exposures. These calculations are completed for each day or appropriate block of time after application.

Occupational Postapplication Noncancer Risk Summary

Table 9.2.2 presents a summary of occupational postapplication risks associated with use of tembotrione. HED has determined that risks are not of concern (i.e., MOEs >1000) on day 0 (REI = 12 hours) only for hand-weeding activities at the lowest TC (i.e., when corn is at a low crop height and minimal foliage development). All of the other exposure activities have risks of concern, with MOEs ranging from 250 to 630 on the day of application. Chemical-specific dislodgeable foliar data would be needed to further refine these estimates. Currently, the label requires a 12-hour REI; however, **HED recommends a 13-day REI for irrigation, scouting and hand-weeding activities.**

Table 9.2.1. Postapplication Activities and Dermal TCs.

Proposed Crops	Policy Crop Group Category	TCs (cm^2/hr)	Activities
Corn	Field / row crop, tall	100	Hand-weeding
		400	Scouting
		1,000	Irrigation, Scouting, Hand-weeding

Table 9.2.2. Summary of Occupational Postapplication Risks for Tembotrione.				
Crop Grouping	Application rate (lb ai/acre)	TC (cm^2/hr)	Days after Application to Reach LOC	MOE at Day 0
			LOC = 1000	
Corn	0.082	100 (Hand-weeding)	0 (12 hours)	2,500
		400 (Scouting)	5	**630**
		1,000 (Irrigation, Scouting, Hand-weeding)	13	**250**

10.0 Data Needs and Label Recommendations

10.1 Toxicology

There are no toxicology data gaps.

10.2 Residue Chemistry

860.1340 Residue Analytical Methods

- To be acceptable as enforcement methods, LC/MS/MS Methods AE/03/01 for plant commodities and 00967 for livestock commodities should undergo successful PMVs by Agency chemists at ACL/BEAD.

- Both methods should be revised to include a calculation for the conversion of residues of the metabolite(s) to parent equivalents for quantitation.

- Separate confirmatory methods for Method AE/03/01 will not be requested provided that two ion transitions are monitored during MS/MS analysis for each analyte.

860.1650 Submittal of Analytical Reference Standards

Analytical standards for tembotrione and its metabolite M5 are currently not available in the National Pesticide Standards Repository. Analytical reference standards of tembotrione and its metabolite (including the deuterated internal standards) should be supplied, and supplies replenished as requested by the Repository.

860.1550 Proposed Tolerances

The petitioner is requested to submit a revised Section F specifying the following:

- The tolerance expression for plant commodities should be revised to include the combined residues of tembotrione and M5, expressed as tembotrione equivalents.

- The tolerance expression for livestock commodities should be revised to include the combined residues of tembotrione and its metabolite M5, expressed as tembotrione equivalents.

The appropriate levels are specified in Appendix C: Tolerance Reassessment Summary and Table.

10.3 Occupational and Residential Exposure

875.2100 Chemical-specific dislodgeable foliar residue data.

HED requests further information from the registrant on specific re-entry activities that take place postapplication.

HED recommends the following label changes based on the results of the exposure assessment:

- Add coveralls to the **PPE** requirements for handlers.
- Change the REI to 13 days.

References:

Tembotrione: Section 3 Registration Request for Uses on Corn (Field, Pop, and Sweet). Summary of Analytical Chemistry and Residue Data. PP#5F7009. G. Kramer. D325349.

Tembotrione: Acute and Chronic Dietary (Food and Drinking Water) Exposure and Risk Assessment for Residues on Corn and Livestock Commodities. PP#5F7009. G. Kramer. D335831.

Tembotrione: Occupational and Residential Exposure/Risk Assessment for the New Use on Field and Silage Corn, Seed Corn, Sweet Corn and Popcorn. K. Lowe. D326301

Drinking Water Assessment for Tembotrione. W. Eckel. D335247.

Tembotrione: Evaluation of the Carcinogenic Potential of Tembotrione. J. Kidwell. TXR 0054606.

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for use on food for tembotrione are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

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	-
870.3465 90-Day Inhalation	no	-
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
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	no	yes
870.6200b 90-Day Neuro. Screening Battery (rat)	no	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) Subchronic Oral (rat) Six-month Oral (dog)	-	-

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile - Test Substance				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral [rat]	46695618	LD_{50} > 2000 mg/kg	III
870.1200	Acute dermal [rat]	46695623	LD_{50} > 2000 mg/kg	III
870.1300	Acute inhalation [rat]	46695626	LC_{50} >4.57 mg/L	IV
870.2400	Acute eye irritation [rabbit]	46695628	Non-irritating	IV
870.2500	Acute dermal irritation [rabbit]	46695631	Non-irritating	IV
870.2600	Skin sensitization [Guinea Pig]	46695634	Dermal Sensitizer	N/A

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	46695638 (2002) Acceptable/guideline 0, 1.25, 75, 1500, 7000 ppm M: 0, 0.07, 4.45, 86.4, 413 mg/kg/day F: 0, 0.09, 5.59, 107.2, 465 mg/kg/day	NOAEL=M/F: 0.07/0.09 mg/kg/day LOAEL=M/F: 4.45/5.59 mg/kg/day based on neovascularization and opacity of the cornea and increased urinary ketones in both sexes; increased cholesterol, absolute liver weights, and diffuse centrilobular hepatocellular hypertrophy in males; and decreased absolute and relative thymus weights in females.
870.3100	90-Day oral toxicity (rat)	466995639 (2005) Acceptable/guideline 0, 6, 20, 40 ppm M: 0, 0.30, 0.98, 2.20 mg/kg/day F: 0, 0.35, 1.18, 2.68 mg/kg/day	NOAEL =M/F: 0.30/0.35 mg/kg/day LOAEL = M/F: 0.98/1.18 mg/kg/day based on snowflake-like corneal opacity and keratitis of the eyes in males and corneal opacity, neovascularization and edema of the cornea in females.
870.3100	90-Day oral toxicity (mouse)	466995640 (2003) Acceptable/non-guideline 0, 35, 350, 3500, 7000 ppm M: 0, 5.9, 64, 631, 1317 mg/kg/day F: 0, 7.3, 75.6, 783, 1833 mg/kg/day	NOAEL =M/F: 64/75.6 mg/kg/day LOAEL =M/F: 631/783 mg/kg/day based on decreased uterine weights and increased corpora lutea in the ovary in females and serum alanine aminotransferase activity , liver weights, hepatocellular hypertrophy, dark livers, macroscopic erosive/ulcerative lesion in the stomach and/or dark intestinal content in both sexes.
870.3150	90-Day oral toxicity (dog)	46695643 (2004) Acceptable/guideline 0, 125, 750, 4500/2250 ppm M: 0, 4.5, 26.7, 124/111 mg/kg/day F: 0, 4.5, 28.5, 124/111 mg/kg/day	NOAEL =M/F: 26.7/28.5 mg/kg/day LOAEL = 124/111 mg/kg/day based on clinical signs of toxicity including uncoordinated movement, disturbance in locomotion , decreased body weights and body-weight gains, effects on hematology and clinical chemistry, increased liver weights, and microscopic effects on the liver and peripheral nerves in both sexes; vacuolation of the adrenal glands in males, bilateral corneal opacity in males, and decreased food consumption in females.
870.3200	21/28-Day dermal toxicity (rat)	46695644 (2005) Acceptable/guideline 0, 250, 500, 1000 mg/kg/day	NOAEL was not established LOAEL = 250 mg/kg/day based on colloid alterations and hypertrophic follicular epithelium in the thyroid gland; and degenerative changes in the pancreas in both sexes and increased proteinacious material in the Rathke pouch in the pituitary and basophilic tubules in the kidneys of males.
870.3200	21/28-Day dermal toxicity (rat)	46695645 (2005) Acceptable/guideline 0, 50, 250, 1000 mg/kg/day	NOAEL was not established in males; NOAEL=F: 50 mg/kg/day LOAEL = M: 50 mg/kg/day based on colloid alterations in the thyroid gland and degenerative changes in the pancreas. LOAEL=F: 250 mg/kg/day based on degenerative changes in the pancreas.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3250	90-Day dermal toxicity (species)	N/A	
870.3465	90-Day inhalation toxicity (species)	N/A	
870.3700a	Prenatal developmental in (rat)	46695646 and 46695647 (2003) Acceptable/guideline 0, 25, 125, 500 mg/kg/day	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 125 mg/kg/day based on decreased body-weight gains and food consumption. **Developmental** NOAEL was not established. LOAEL = 25 mg/kg/day based on increased skeletal variations including delayed ossifications and decreased growth and developmental as indicated by decreased fetal body weights and an increased number of runts.
870.3700b	Prenatal developmental in (rabbit)	46695703 (2003) acceptable/guideline 0, 1, 10, 100 mg/kg/day	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day based on mortality, clinical signs of toxicity (i.e., few or no feces), abortion, decreased body weight and food consumption. **Developmental** NOAEL = 1 mg/kg/day LOAEL = 10 mg/kg/day based on decreased or delayed growth and/or development of the skeleton and increased incidences of other skeletal variations and anomalies.
870.3800	Reproduction and fertility effects (rat)	46695704 (2005) Acceptable/guideline 0, 20, 200, 1500 ppm M: 0, 1.4, 13.3, 100.4 mg/kg/day F: 0, 1.6, 15.8, 119.3 mg/kg/day	**Parental/Systemic** NOAEL was not established. LOAEL = M/F: 1.4/1.6 mg/kg/day based on effects on the eyes, including corneal opacity, acute inflammation, and neovascularization. **Reproductive** NOAEL = M/F 100.4/119.3 mg/kg/day LOAEL was not established. **Offspring** NOAEL was not established. LOAEL = M/F: 1.4/1.6 mg/kg/day based on effects on the eyes, including corneal opacity, acute inflammation, and neovascularization; increased incidences of minimal extramedullary hematopoeisis in the spleen, delayed preputial separation, and decreased absolute brain weight.
870.4100b	Chronic toxicity (dog)	46695705 (2005) Acceptable/guideline 0, 75, 300, or 1200 ppm M: 0, 2.5, 9.0, 37.8 mg/kg/day F: 0, 2.5, 10.2, 41.6 mg/kg/day	NOAEL was not established in males. LOAEL= M: 2.5 mg/kg/day based on the increased number of digestion chambers of the sciatic nerve. NOAEL=F: 10.2 mg/kg/day LOAEL= F: 41.6 mg/kg/day based on decreases in MCH and MCV, increased platelet counts, changes in erythrocyte morphology and pigmentation of the thyroid gland.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4300	Chronic/ Carcinogenicity (mouse)	46695706 (2005) Acceptable/guideline 0, 30, 300, 1000, or 3000 ppm M: 0, 4, 43, 146, 440 mg/kg/day F: 0, 5, 54, 179, 552 mg/kg/day	NOAEL was not established. LOAEL =M/F: 4/5 mg/kg/day based on based on gallstones, eosinophilic cytoplasmic alteration, subepithelial mixed cell infiltrate, and dilatation in/of the gallbladder; hepatocellular vacuolation, hepatocellular hypertrophy, and increased liver weight in males and females; and papillary mineralization of the kidney and changes in hematological parameters indicative of anemia in females. **No evidence of carcinogenicity**
870.4300	Chronic/ Carcinogenicity (rat)	46695707 (2005) Unacceptable/guideline 0, 0.10, 1.05, 134, 280 mg/kg/day	NOAEL =F: 0.10 mg/kg/day LOAEL = F: 1.05 mg/kg/day based on keratitis of the eye and biliary hyperplasia/fibrosis. **No evidence of carcinogenicity**
870.4300	Chronic/ Carcinogenicity (rat)	46695708 (2005) Acceptable/guideline 0, 20, 200, or 800 ppm M: 0, 0.04, 0.79, 8.3, 31.7 mg/kg/day	NOAEL=M: 0.04 mg/kg/day LOAEL =M: 0.79 mg/kg/day based on neovascularization and edema of the cornea and snow flake-like corneal opacity, unilateral or bilateral keratitis of the eye, decreased mean body weight and mean body-weight gain, increased total cholesterol, higher ketone levels and lower pH values, higher protein levels, increased kidney weight, kidney to body weight and kidney to brain weight ratios, chronic nephropathy and atrophy of the sciatic nerve. **Evidence of carcinogenicity:** There was a slight increase in neoplastic lesions; i.e., squamous cell carcinoma of the cornea in the 200 and 800 ppm groups (7% and 3%, respectively), when compared to controls (0%). This change was considered to be a result of the keratitis of the eye.
870.5100	*In vitro* Bacterial Gene Mutation	46695709 (2005) Acceptable/guideline 0, 50, 150, 500, 1500 and 5000 ug/plate	There was no evidence of induced mutant colonies over background.
870.5300	*In vitro* Gene mutation in Chinese Hamster V79	46695713 (2005) Acceptable/guideline 0, 250, 500, 1000, 1400, 1500, 1600 ug/mL	There was no evidence of induced mutant colonies over background.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5375	*In vitro* Mammalian Cytogenetics chromosomal aberration assay Human Lymphocytes	46695717 (2005) Acceptable/Guideline 0, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10 mM	Equivocal because structural aberrations and polyploidy observed in the absence of excessive cytotoxicity at 3306 ug/mL with metabolic activation was not reproduced.
870.5395	*In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus assay in mice	46695721 (2005) Acceptable/Guideline 500, 1000 and 2000 mg/kg	There was no increase in the frequency of micronucleated immature erythrocytes in mouse bone marrow.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5550	Other Effects: Unscheduled DNA Synthesis in primary rat hepatocytes/mammalian cell cultures	46695722(2005) Acceptable/Guideline 0, 1000 and 2000 mg/kg	There was no increase in the frequency of micronucleated immature erythrocytes in mouse bone marrow.
870.6200a	Acute neurotoxicity screening battery	46695723(2005) Acceptable/Guideline 0, 200, 500, 2000 mg/kg	NOAEL was not established in males LOAEL=M: 200 mg/kg based on decreased arousal (sluggish with some exploratory movement) in the open field on day 0 NOAEL= F: 200 mg/kg LOAEL= F: 500 mg/kg based on urine staining, red nasal discharge, decreased body temperature on day 0, decreased motor and locomotor activity on day 0.
870.6200b	Subchronic neurotoxicity screening battery (rat)	46695724(2005) Acceptable/Guideline 0, 20, 250, 2500 ppm M: 0, 1.33, 16.4, 160 mg/kg/day F: 0, 1.75, 21.0, 224 mg/kg/day	NOAEL= M/F: 16.4/21.0 mg/kg/day LOAEL= M/F: 160/224 mg/kg/day based on decreased body weight and body-weight gain in both sexes.
870.6300	Developmental neurotoxicity (rat)	46695725(2005) Acceptable/Guideline 0, 10, 200, or 1500 ppm 0, 0.8, 16.3, and 118 mg/kg/day	Maternal NOAEL= 0.8 mg/kg/day Maternal LOAEL=16.3 mg/kg/day based on corneal opacity during lactation. Offspring NOAEL was not established. Offspring LOAEL= 0.8 mg/kg/day based on decreased post-weaning body weight (males), decreased acoustic startle response on PND 60 (males), and brain morphometric changes on PND 75 (males and females).

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (rat)	46695726 (2005) Acceptable/guideline 5 and 1000 mg/kg	Tembotrione was rapidly absorbed, extensively metabolized, and excreted. Total excretion of tembotrione was 96.3-102.7% by 24 hours regardless of dose level or position of radiolabel. Sex differences were observed in the routes of excretion. The primary routes of elimination were the urine in females and the urine and feces in males. Males excreted up to 24.4% and 70.4% and females up to 79.1% and 20% of the administered dose in the urine and feces, respectively, at the low dose. Females excreted up to 63.7% and 28.5% and males up to 44.2 % and 49.1% of the dose in the urine and feces, respectively, at the high dose. The highest mean levels of radioactivity were extracted from the liver (1.7-3.5%) and kidneys (0.14-0.26%) at the low dose. At the high dose, the mean levels of radioactivity were extracted from the skin/fur (0.22-0.33%) and carcass. The highest concentrations of radioactivity were found in the skin followed by the liver, kidneys, stomach (and contents) and carcass. There was no evidence of bioaccumulation. The parent molecule and 11 metabolites were identified & isolated. Metabolic profiles were qualitatively similar for both radiolabeled forms; however, profiles for the high and low doses were not the same and differences were noted between sexes. Females excreted the greatest quantity of the parent molecule in urine (44.1-59.4%). While low and high dose males eliminated 1.9-3.0% and 33.8%, respectively, in the urine. The metabolites found in the greatest quantities were 4-hydroxy--tembotrione and 5- hydroxy--tembotrione. Other identified metabolites found at <5% were the 4,5-dihydroxy, benzylic alcohol, dihydroxy-bezophenone, 4-hydroxy-benzylic alcohol, and ketohydroxy-hexanoic acid ([cyclohexyl-UL-^{14}C] only). Males excreted greater quantities of both metabolites than females; except, at the high dose where 4-hydroxy--tembotrione was eliminated in approximately equal amounts in both sexes. The primary step in the metabolism of tembotrione is the hydroxylation (oxidative pathway) of the cyclohexyl ring of the molecule.
870.7600	Dermal penetration (rat)	46695730 (2005) Acceptable/guideline 6.6, 66, 660 ug/cm^2	Dermal absorption is 15%

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	Effects on blood coagulation parameters with and without vitamin K1	46695731 (2005) Acceptable/non-guideline 1000 mg/kg 1000 mg/kg and 10 mg/kg vitamin K1	Alterations in clotting parameters were mediated by effects on vitamin K1 clotting factors.
	Effect on blood tyrosine levels in pregnant rabbits	46695732 (2004) Acceptable/non-guideline 0, 10 mg/kg/day	Blood tyrosine levels in treated animals were significantly elevated relative to controls for all intervals measured during treatment.
	Inhibition of 4-Hydroxyphenylpyruvate Dioxygenase in Rats and *In Vitro*	46695733 and 46695734 (2005) Acceptable/non-guideline *In vivo*: 0, 10 mg/kg *In vitro*: 0, 30, 60, 120 uM	*In vivo*: AE0172747 increased plasma tyrosine levels by 20-fold, AE1417286 increased plasma tyrosine levels by 5-fold, AE0456148 and AE1392936 did not affect plasma tyrosine levels relative to controls. *In vitro*: Rank of species by their ability to produce 4- HPLA after inhibition of HPPDase in (from most to least produced): mouse, human, rabbit, rat and dog.

Table A.2.3 Subchronic Toxicity Profile for Metabolites of Tembotrione			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
AE 1417268			
870.3100	90-Day oral toxicity (rat)	46695641 and 46695637 (2005) Acceptable/guideline 0, 200, 1500, 9000 ppm M: 0, 12.7, 95.7, 586 mg/kg/d F: 0, 15.6, 115, 718 mg/kg/d	NOAEL=M/F; 95.7/115 mg/kg/d LOAEL=M/F: 586/718 mg/kg/d based on acinar degeneration/ apoptosis in the pancreas of both sexes, death due to a hemorrhagic syndrome in one male, increased absolute and relative liver weights, enlarged liver with prominent lobulation and hepatocellular hypertrophy in males; and increased serum triglycerides and eye lesions in females.
AE0456148			

Table A.2.3 Subchronic Toxicity Profile for Metabolites of Tembotrione			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	46695642 (2005) Acceptable/guideline 0, 15, 150, 1500, 15,000 ppm M: 0, 1.19, 12.34, 120.19, 1203.8 mg/kg/d F: 0, 1.63, 16.08, 162.49, 1436.3 mg/kg/d	NOAEL= M: 1203.8 mg/kg/d LOAEL was not established. NOAEL=F: 162.49 mg/kg/d LOAEL = F: based on increased incidence of hematopoiesis of the spleen.

A.3 Executive Summaries

870.3100 90-Day Oral Toxicity - Rat

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 46695638*)* AE0172747 (97.4% a.i., batch # LE356) was administered to Wistar (AF) Rj:WI (IOPS HAN) rats10/sex/dose in the diet at dose levels of 0, 1.25, or 7,000 ppm (equivalent to M/F: 0/0, 0.07/0.09, or 413/465 mg/kg bw/day) and 15/sex/ dose at 75 or 1,500 ppm (equivalent to M/F: 4.45/5.59, or 86.4/107.2 mg/kg bw/day) for 90 days. Five animals/sex from the 75 and 1,500 ppm groups were maintained untreated for 4 weeks to observe reversibility of potential ophthalmological effects.

There were no treatment related effects observed in urinalysis.

One male in the 7000 ppm group was sacrificed moribund on day 64. Clinical signs of toxicity included white area on the eye, ocular discharge and damaged eyes in 1500 ppm (6/10) and 7000 ppm (8/10) males and sores and/or crusts on the skin in 7000 ppm males (7/10). Neovascularisation and corneal opacity occurred at an increased incidence in males at 75 (2/15), 1500 (4/15) and 7000 ppm (2/10); and in females at 75 (1/15), 1500 ppm (3-4/15) compared to 0/10 in controls. These effects were observed at a higher frequency in males compared to females. Also, the frequency of appearance of corneal opacity increased with treatment duration. However, neovascularization (2/5 in 1500 ppm males) observed in males and in females corneal opacity and neovascularization were reversible following a 4 week recovery period in the 75 and 1500 ppm groups. Hair loss was observed in both sexes in the 7000 ppm group (7/10).

At 1,500 ppm, body-weight gain was significantly reduced for males during days 1-15 (↓19%, $p<0.01$) and 1-29 (↓12%, $p<0.05$). At 7,000 ppm in both sexes, body weight was significantly reduced throughout treatment by 13-19% in males ($p<0.001$) and 9-11% in females ($p<0.01$). Body-weight gain was significantly ($p<0.001$) reduced by 29% in males and 24% in females. At 1,500 ppm, food consumption was significantly reduced for males during the first week of treatment (↓14%, $p<0.01$). Food consumption was reduced throughout treatment by 7-36% in males and 10-32% in females at 7,000 ppm.

No hematological effects were observed in females at any dose level. Blood clotting parameters (mean activated partial thromboplastin and mean prothrombin times) were significantly elevated at $\geq$ 1500 ppm (21-41%). RBC, MCH and HCT were significantly reduced in 7000 ppm males by 9-21%.

A treatment related increase in cholesterol was observed in males in a dose-dependent manner that reached significance at $\geq$75 ppm [1.25 ppm (14%), 75 ppm (22%, $p<0.01$), 1500 ppm (32%, $p<0.001$), 7000 ppm (80%, $p<0.001$)] and increased significantly by 34% ($p<0.01$) in females at 7000 ppm.

Urinary pH significantly ($p<0.01$) decreased at $\geq$ 1500 ppm (5.95-6.00) versus controls (6.65) in males and at 75 and 1500 ppm (5.25, 10%, $p<0.05$; 5.15, 10%, $p<0.01$), respectively, versus controls (5.75) in females. A treatment related increase in ketone levels (grades 2 and 3) was noted in both sexes at $\geq$75 ppm when compared to controls.

Relative brain weight was significantly ($p<0.01$) increased in both males and females by 11 and 12%, respectively, at 7000 ppm. Absolute brain weight decreased significantly ($p<0.001$) by 6% in 7000 ppm males only and was comparable to controls in females. In males, absolute liver weight was significantly increased by 20% ($p<0.01$) in 75 and 1500 ppm and by 18% ($p<0.05$) in 7000 ppm groups. Relative liver weight significantly ($p<0.001$) increased dose-dependently by 21-38% in males; and in 7000 ppm females by 19%. These effects were considered treatment related since hepatic effects were observed in other studies. Absolute thymus weight decreased in a dose-dependent manner that reached significance in 7000 ppm males (34%, $p<0.05$). In females, absolute and relative thymus weight significantly decreased by 20-31% ($p<0.05$-0.001) in all treated groups. Relative Heart weight significantly increased in 7000 ppm males by 12% ($p<0.05$). Relative kidney weight increased significantly in 1500 (12%, $p<.05$) and 7000 ppm (25%, $p<.001$) males. However, relative heart weight changes were not considered significant toxicologically in the absence of a dose response and/or corroborating pathological changes.

The following microscopic changes were observed at an increased incidence in males: diffuse centrilobular hepatocellular hypertrophy at 75 (6/10), 1500 (8/10), and 7000 ppm (8/9) versus controls (0/10); and diffuse paracortical hyperplasia in the submaxillary lymph node at 7000 ppm (5/9 vs 0/10 in controls), testicular unilateral tubular atrophy (3/10), multifocal accumulation of golden-brown pigments in macrophages in the epididymides (4/10) and prostates glands (3/10); and bilateral spermatic granulomas in the epididymides (3/10) at 7000 ppm compared to 0/10 in controls. An increased incidence of thyroid gland follicular hypertrophy in 75 ppm (1/10) and 1500 ppm (3/10) and colloid condensation in 1.25 ppm (1/10), 75 ppm (4/10) and 1500 ppm (6/10) males was observed compared to 0/10 in controls. These effects were considered treatment-related. Also, there was an increased incidence of hyaline droplets accumulation in the corticotubular epithelium of the kidneys in males at 1.25 (4/10) 75(6/10), 1500 (7/10) 7000 ppm (8/9) versus controls (5/10). The increased incidence of multifocal accumulation of hyaline droplets was due to the α2μ-globulin mechanism which is specific to the male rat, therefore, it was not considered to be toxicologically significant.

In females, the following microscopic changes were observed at an increased incidence: multifocal corticotubular basal vacuolation (slight) in the kidneys occurred in a dose-dependent manner 1-6/10 in all treated groups compared to 0/10 in controls; diffuse hypertrophy of the interstitial gland in the ovaries was observed in the 1500 ppm and 7000 ppm groups (3/10) compared to 0/10 in controls. These effects were considered treatment-related. Multifocal accumulation of alveolar macrophages in lungs observed in all treated groups (4-9/10 vs 1/10 in controls) was considered a sporadic finding in the absence of a clear dose response.

The LOAEL is M/F: 4.45/5.59 mg/kg/day (75 ppm), based on neovascularization and opacity of the cornea and increased urinary ketones in both sexes; increased cholesterol, absolute liver weights, and diffuse centrilobular hepatocellular hypertrophy in males; and decreased absolute and relative thymus weights in females. The NOAEL is M/F: 0.07/0.09 mg/kg/day (1.25 ppm).

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

EXECUTIVE SUMMARY: In a 90-day subchronic toxicity study (MRID 466995639), AE 0172747 (94-7-95.5% a.i., batch/lot # PFI 0254) was administered to 10 Rj: WI (IOPS HAN) Wistar rats/sex/dose in the diet at dose levels of 0, 6, 20 or 40 ppm (equivalent to 0, 0.30, 0.98 or 2.20 mg/kg bw/day in males and 0, 0.35, 1.18 or 2.68 mg/kg bw/day in females, respectively) in the diet for at least 90 days. No mortality occurred throughout the course of this study at any dose level. Body weight, body-weight gain, food consumption, hematology and clinical chemistry assessment were unaffected by treatment.

At 6 ppm, no toxicologically significant change was noted.

At 20 ppm, snow flake-like corneal opacity was noted at the ophthalmological examination in the left eye of one male after 3 months of treatment. This male was observed with unilateral keratitis upon microscopic examination. Urinalysis revealed higher ketone levels in both sexes in comparison to controls.

At 40 ppm, clinical signs were noted in a single female and consisted of white areas on the left eye noted at the weekly physical examination on Days 78 and 85. The neurotoxicity assessment revealed no treatment-related effects. At the ophthalmological examination, corneal opacity, neovascularization and edema of the cornea in the left eye of female was confirmed after 3 months of treatment. Urinalysis showed higher ketone levels in both sexes, in association with a mean pH value lowered by 8% in males ($p \leq 0.05$), when compared to the control values. One female was observed with unilateral keratitis at microscopic examination.

The LOAEL is 20 ppm (0.98 mg/kg bw/day in males and 1.18 mg/kg bw/day in females), based on snow flake-like corneal opacity and keratitis of the eyes in males and corneal opacity, neovascularization and edema of the cornea in females. The NOAEL is 6 ppm (0.30 mg/kg bw/day in males and 0.35 mg/kg bw/day in females).

This 90-day subchronic toxicity study in the rat is acceptable/guideline and satisfies the guideline requirement for a 90-day subchronic toxicity study [(OPPTS 870.3100); OECD 408] in rats.

EXECUTIVE SUMMARY: Metabolite AE 1417268 (M5)

In a subchronic oral toxicity study (MRIDs 46695641 and 46695637), AE 1417268 (plant metabolite of AE 0172747; 99% purity; Batch No. NLL 7555-9) was administered to 10 Wistar rats/sex/dose in the diet at dose levels of 0, 200, 1500, or 9000 ppm (equivalent to 0/0, 12.7/15.6, 95.7/115, and 586/718 mg/kg/day in males/females) for 90 days.

No effect was observed on clinical signs of toxicity, body weight, body weight gain, food consumption**,** hematology, clinical chemistry, or urinalysis.

One 9000 ppm male was killed moribund on Day 69, and was found to be suffering from a hemorrhagic syndrome.
At 9000 ppm, increased incidences of slight diffuse acinar degeneration/apoptosis in the pancreas in the males (4/10 treated vs 0/10 controls) and minimal to moderate degeneration in the females (8/10 treated vs 3/10 controls) were observed.

At 9000 ppm, a white area on the right eye of one female was noted from Day 36 onwards. Superficial corneal opacity was observed in one eye in the females (3/10 treated vs 0/10 controls), and was associated with neovascularization of the cornea in 1 of the 3 females and neovascularization of the cornea and edema of the cornea for another of the 3 females. Eye opacity (gross lesion) was present in two females/10 vs 0/10 controls. Increased incidences of slight to moderate unilateral keratitis (2/10 treated vs 0/10 controls) and bilateral keratitis (1/10 treated vs 0/10 controls) were noted in the females. Eye toxicity was considered a critical neurological effect.

Absolute, relative to body, and relative to brain liver weights were increased ($p \leq 0.01$) in the $\geq$1500 ppm males (increase 17-27%). The liver was enlarged in the $\geq$1500 ppm males (8/10 each treated vs 0/10 controls) and had prominent lobulation in the 9000 ppm males (4/10 treated vs 1/10 controls). Increased incidences minimal to slight centrilobular hepatocellular hypertrophy (diffuse) were noted in the $\geq$1500 ppm males (4-5/10 treated vs 0/10). Also, serum triglycerides were increased by 43% in the 9000 ppm females.

The LOAEL is 9000 ppm (equivalent to 586/718 mg/kg/day in males/females), based on acinar degeneration/apoptosis in the pancreas of both sexes, death due to a hemorrhagic syndrome in one male, increased absolute and relative liver weights, enlarged liver with prominent lobulation and hepatocellular hypertrophy in males; and increased serum triglycerides and eye lesions in females. The NOAEL is 1500 ppm (equivalent to 95.7/115 mg/kg/day in males/females).

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

EXECUTIVE SUMMARY : Metabolite AE 0456148 (M6)

In a subchronic oral toxicity study (MRID 46695642), AE 0456148 (a metabolite of AE 0172747; 99.0% purity; Batch No. ABJ1204-PFI) was administered to 10 Wistar rats/sex/dose in the diet at dose levels of 0, 15, 150, 1500, or 15,000 ppm (equivalent to 0/0, 1.19/1.63, 12.34/16.08, 120.19/162.49, and 1203.8/1436.3 mg/kg bw/day in males/females) for at least 94 days.

No adverse, treatment-related effects were observed on mortality, clinical signs, functional observational battery, motor activity, locomotor activity, body weight, food or water consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, or histopathology.

At 15,000 ppm, a decrease in body weight gain during the last week of the study (decr. 71%; $p <= 0.01$) resulting in decreased body weight at Day 91 (decr. 9%; $p <= 0.05$) was observed in females. This decrease in body weights in females corresponded to a decrease in food consumption observed during Week 13 of the study and is considered to be an indirect effect of treatment. Also at 15,000 ppm, mean food consumption was decreased (NS) in females throughout the study. However, this effect only resulted in a minor decrease in body weight during Week 13 of the study; therefore this effect was not considered adverse.

At >= 1500 ppm, an increase in incidence and severity of minimal to moderate hematopoiesis of the spleen was observed in females when compared with controls.

The LOAEL was 1500 ppm (equivalent to 162.49 mg/kg bw/day) in females, based on an increase in the incidence in hematopoiesis of the spleen. The NOAEL is 150 ppm (equivalent to 16.08 mg/kg bw/day) in females. The LOAEL was not determined in males. The NOAEL is 15,000 ppm (equivalent to 1203.8 mg/kg bw/day) in males.

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.

870.3100 90-Day Oral Toxicity - Mouse

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 46695640), AE 0172747 (95.0% w/w a.i.; Batch No. PFI 0195) was administered to 10 C57BL/6J@ Ico mice/sex/dose in the diet at dose levels of 0, 35, 350, 3500, or 7000 ppm (equivalent to 0/0, 5.9/7.3, 64.0/75.6, 631/783, and 1317/1833 mg/kg bw/day in males/females) for 90 days. No treatment-related ophthalmic findings were noted.

A dose-related increased incidence of intense yellow colored urine was noted in 6-10/10 mice in each treated group.

One 7000 ppm male was killed moribund on Day 78. This mouse had reduced motor activity, hunched posture, and was cold to touch. It had a dark intestinal content, which corresponded to marked focal/multifocal ulceration and diffuse transmural hemorrhage in the duodenum observed microscopically. This death was considered related to treatment.

Transient effects on body weight and body-weight gains were observed at 7000 ppm. Overall (Days 1-90) body-weight gains were similar to controls in both sexes. In the males, body-weight gains were decreased by 69% during the first two weeks, while food consumption was only decreased by 9%. However, body-weight gains in the males were generally similar to controls after the first two weeks. In the females, decreased body weights were observed generally each week from Days 15-85. There was no body-weight gain in the females during the first week of treatment; however, the mice consumed 13% more food. Cumulative body-weight gains (Days 1-29) were decreased by 42%; however, after Day 29, the females generally gained weight faster than controls. In the 7000 ppm females, increased food consumption was generally observed weekly from Day 36 until termination. Food consumption was increased dose-dependently in females and was increased by 20% at 7000 ppm. The body weight and body-weight gain changes are minor and are not considered to be adverse effects.

Indications of slight hepatotoxicity were observed at 3500 and 7000 ppm. Absolute, relative to body, and relative to brain liver weights were increased ($p<=0.05$) in the males by 11-36%. Relative to brain liver weights were increased ($p<=0.05$) by 17-28% in the females. The liver was dark in both sexes (2-6/9-10 treated vs 0/10 controls). Increased incidences of slight to mild diffuse centrilobular hepatocellular hypertrophy were observed in both sexes (3-10/9-10 treated vs 0/10 controls).

Slight increased corpora lutea in ovaries was noted in the >=3500 ppm females (8-9/8-10 treated vs 0/10 controls). Proestrus vagina was noted at 7000 ppm (5/10 treated vs 0/10 controls).

The LOAEL is 3500 ppm (631/783 mg/kg/day in males/females), based on decreased uterine weights and increased corpora lutea in the ovary in females; and increased serum alanine aminotransferase activity, liver weights, hepatocellular hypertrophy, dark liver, macroscopic erosive/ulcerative lesions in the stomach and/or dark intestinal content in both sexes. The NOAEL is 350 ppm (64.0/75.6 mg/kg/day in males/females).

This study is classified as **acceptable/non-guideline** and does not satisfy the guideline requirements (OPPTS 870.3100; OECD 408) for a subchronic oral toxicity study in the mouse. The study can not be upgraded due to the absence of hematology data required at the time of study.

870.3150 90-Day Oral Toxicity - Dog

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 46695643), AE 0172747 (94-95.0% w/w, Batch Nos.: PFI 0195 and PFI 0215) was administered to 4 beagle dogs/sex/dose in the diet at doses of 0, 125, or 750 ppm (equivalent to 0/0, 4.5/4.5, and 26.7/28.5 mg/kg/day in males/females) for 90 days. Additionally, a high dose group was fed the test substance in the diet at 4500 ppm (equivalent to 124/111 mg/kg/day in males/females) for 29 days which was then reduced to 2250 ppm from Days 30-90 due to overt signs of toxicity (uncoordinated movements and lack of body-weight gain).

No treatment-related adverse effects were observed on urinalysis or gross pathology at any dose, and no treatment-related effects were observed at 125 or 750 ppm. The following treatment-related effects occurred at 4500/2250 ppm.

One male was killed *in extremis* on Day 38. Clinical signs of toxicity and decreased body-weight gain were observed prior to sacrifice of this animal.

One male (on Days 29-39) and two females (on Days 30-42) had uncoordinated movements. Two males (on Days 41-43) had a wasted appearance, and one of these males continued to have this appearance during the last two weeks of the study. Beginning on Day 34 and lasting up to Day 90, one male and all females displayed one or more of the following signs of toxicity: abnormal placing, posture, hopping, or wheel barrowing. These signs were not observed in the remaining treatment groups.
Body weights in males and females were decreased beginning on Days 19-22 and lasting throughout the study, resulting in decreased overall (Day 1-90) body-weight gains. The decrease in body weights in females corresponded to a decrease in food consumption observed during Weeks 1-5, while being dosed at 4500 ppm. When dosing changed from 4500 ppm to 2250 ppm at Week 5, food consumption remained decreased until Week 9 where values became comparable to or increased over controls for the remainder of the study.

A bilateral corneal opacity was observed in one male during the Weeks 7 and 13 examinations. No other effects were observed on ophthalmoscopy.

The following differences from controls in hematology were observed throughout the study in both sexes: (i) decreased MCH; (ii) increased platelets; (iii) decreased hemoglobin; and (iv) decreased leukocytes and neutrophils. Additionally at this dose, the following differences were observed: (i) increased reticulocytes throughout the study in females; and (ii) decreased mean corpuscular volume (MCV) at Week 13 in males. Changes in erythrocyte morphology observed at Week 7 and/or Week 13 included: slight to severe anisocytosis, anisochromia, and hypochromia and slight to moderate microcytosis. Albumin levels and albumin/globulin ratios were decreased in both sexes at Week 7 and in males at Week 13. Alkaline phosphatase (ALK) activity was increased in females at Week 7, with activity remaining increased to a lesser magnitude on Week 13.

Absolute and relative (to body and brain) liver weights were increased by 17-37% in males and 16-32% in females when compared with controls. Mild diffuse hepatocellular cloudy swelling was observed in all males (3/3), and a slight to mild effect was observed in all females (4/4) compared with 0/4 of the respective control animals. A slight multifocal pigmentation of hepatocytes and Kupffer cells was observed in all males (3/3 vs. 0/4 controls) and 2/4 females (vs. 0/4 controls). Multifocal vacuolation of the adrenal glands was observed in all males (3/3 vs. 0/4 controls).

In the peripheral nerves, an increased number of digestion chambers were noted as follows (vs 0 controls): (i) sciatic nerve of 1/4 female; (ii) radial nerve of 3/3 females; (iii) musculocutaneous nerve of 2/3 males and 1/3 females; and (iv) femoral nerve of 1/3 males and 1/3 females. In the one female with increased number of digestion chambers in the sciatic nerve, a mild atrophy/regeneration of the tibial muscle was also noted. These digestion chambers were a result of focal enlargement of the myelin sheath due to myelin debris, and may account for the neurological effects observed at this dose.

The LOAEL is 4500/2250 ppm (equivalent to 124/111 mg/kg/day M/F), based upon clinical signs of toxicity including neurological effects, decreased body weights and body-weight gains, effects on hematology (including erythrocyte morphology) and clinical chemistry, increased liver weights, and microscopic effects on the liver and peripheral nerves in both sexes; vacuolation of the adrenal glands in males, bilateral corneal opacity in males, and decreased food consumption in females. The NOAEL is 750 ppm (equivalent to 26.7/28.5 mg/kg/day M/F).

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

870.3200 21/28-Day Dermal Toxicity – Rat

EXECUTIVE SUMMARY: In a 28-day dermal toxicity study (MRID 46695644), AE 0172747 (95.4% w/w a.i.; Batch no. PFI0254) was applied to the shaved skin of 10 Wistar rats/sex/dose at dose levels of 0, 250, 500, or 1000 mg/kg bw/day, 6 hours/day for 5 days/week (7 days in Week 4) during a 28-day period.

No treatment-related effects were observed on mortality, clinical signs, neurological toxicity, dermal irritation, body weight, body-weight gain, food consumption, water consumption, hematology, clinical chemistry, glucose levels, organ weights, or gross pathology. No alterations were noted in the skin.

The target organ was the pancreas. Increased incidences of minimal to moderate degenerative changes/increase of apoptotic bodies of the exocrine acinar tissue were noted in the pancreas of all treated groups in both sexes (9-10/10 treated vs 0-2/10 controls). A dose related increase in severity was apparent in the males, but incidence and severity were similar in the 500 and 1000 mg/kg/day females. Degeneration/apoptosis in the pancreas was also noted in a concurrently submitted 28-day dermal toxicity study (MRID 46695645) in the Wistar rat. Additionally in the 1000 mg/kg/day females, increased incidences of minimal to slight ductular proliferation and inflammatory filtrate were observed in the pancreas (3-4/10 treated vs 0/10 controls). There was also increased incidences of minimal to moderate colloid alteration in the thyroid of all treated male (9-10/10 treated vs 3/10 controls) and female (4-6/10 treated vs 0/10 controls) groups and minimal to slight hypertrophic follicular epithelium in the thyroid of the 500 and 1000 mg/kg/day males (6-7/10 treated vs 2/10 controls). In addition, increased incidences of the following lesions were observed (# affected/10 treated vs # affected/10 control): (i) basophilic tubules were noted in the kidneys of all treated male groups (7-9 vs 6), (ii) minimal to slight inflammation in the prostate at 1000 mg/kg/day (3 vs 0); (iii) minimal to slight increased proteinacious material in the Rathke pouch in the pituitary of the 1000 mg/kg/day males (4 vs 1); and (iv) minimal mononuclear infiltrate in the kidneys of the 1000 mg/kg/day males (3 vs 0). These effects were considered treatment related.

The LOAEL is 250 mg/kg/day, based on colloid alterations and hypertrophic follicular epithelium in the thyroid gland; and degenerative changes in the pancreas in both sexes and increased proteinacious material in the Rathke pouch in the pituitary and basophilic tubules in the kidneys of males. The NOAEL was not established.

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.

EXECUTIVE SUMMARY: In a 28-day dermal toxicity study (MRID 46695645), AE 0172747 (94.7% w/w a.i.; Batch no. PFI0254) was applied to the shaved skin of 10 Wistar rats/sex/dose at dose levels of 0, 50, 250, or 1000 mg/kg bw/day, 6 hours/day for 5 days/week (7 days in Week 4) during a 28-day period.

No treatment-related effects were observed on mortality, clinical signs, neurological toxicity, dermal irritation, body weight, body-weight gain, food consumption, water consumption, hematology, clinical chemistry, organ weights, or gross pathology.

The target organ was the pancreas. Increased incidences of minimal to moderate degenerative changes/increase of apoptotic bodies of the exocrine acinar tissue were noted in the pancreas of all treated male groups (6-10/10 treated vs 1/10 controls) and $\geq$250 mg/kg/day females (5-10/10 treated vs 1/10 controls).

The following findings were considered equivocal: minimal to slight condensed cytoplasm in the liver in 1000 mg/kg/day males (5/10 treated vs 2/10 controls) and minimal to moderate proteinaceous plug in the urinary bladder in the 1000 mg/kg/day males (6/10 treated vs 0/10 controls). These findings were not confirmed in a previously conducted 28-day dermal toxicity study (MRID 46695644) in the Wistar rat at doses up to 1000 mg/kg/day.

Minimal to slight colloid alteration in ≥250 mg/kg/day females (2-4/10 treated vs 1/10 controls) and minimal to slight hypertrophic follicular epithelium in the thyroid of the 1000 mg/kg/day females (3 vs 0) were predominantly of minimal severity and an effect was confirmed in the previous dermal toxicity study. Minimal to slight hypertrophic follicular epithelium in the thyroid was noted in the 1000 mg/kg/day males (6/10) compared to concurrent (4/10) and historical (0-5/10 concurrent controls). Minimal to moderate colloid alteration of the thyroid was noted in all treated male groups (8-10 vs 0). Moderate severity was observed in only one 1000 mg/kg/day rat. Erosion/neovascularization and keratitis of the eye were observed in 1000 mg/kg/day males (2/10 vs 0). These findings were considered adverse.

The LOAEL is 50 mg/kg/day for males, based on colloid alterations in the thyroid gland and degenerative changes in the pancreas. The NOAEL was not established. The LOAEL is 250 mg/kg/day for females, based on degenerative changes in the pancreas. The NOAEL is 50 mg/kg/day.

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.3.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study - Rat

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 46695647), AE0172747 (95.0% w/w; Batch# PFI 0195) in 0.5% methylcellulose 400 was administered via gavage at a dose volume of 10 mL/kg to 25 Sprague Dawley rats/dose group at dose levels of 0, 25, 125, or 500 mg/kg/day from gestation days (GD) 6-20. On GD 21, all dams were euthanized, and the uterus was removed via cesarean section and its contents examined. Fetuses were examined for external, visceral, and skeletal malformations, anomalies, and variations.

All dams survived until scheduled termination, and there were no treatment-related macroscopic findings at termination.

Vaginal discharge was observed in one 125 mg/kg/day female on GD 16 and in two 500 mg/kg/day dams (#s 789 and 773) on GD 11 and 16, respectively, compared to 0 controls. Associated anogenital soiling was noted in Dam # 773. Additionally at 500 mg/kg/day, increased salivation was observed in 18/25 dams compared to 0 controls.

Maternal body-weight gains were decreased ($p<=0.05$) by 52-92% at >=25 mg/kg/day during GD 6-8, and continued to be decreased ($p<=0.05$) by 28-32% at >=125 mg/kg/day during GD 8-10. Body-weight gains for the overall (GD 0-21) study were decreased (not significant) by 9% at >=125 mg/kg/day; and these decreases were still evident when corrected for gravid uterine

weight (decr.11-13%). Food consumption was decreased (p<=0.05) by 8-16% in the 125 and 500 mg/kg/day dams during GD 6-12 and remained decreased (decr.11%; p<=0.01) at 500 mg/kg/day during GD 12-14. Because the decrease in body-weight gain in the 25 mg/kg/day group was transient and did not affect overall body-weight gains, it was not considered adverse. Although not adverse to the dams, this initial decrease in weight gain may have contributed to the decreased (decr.3%; p<=0.01) fetal body weights at this dose.

The maternal LOAEL is 125 mg/kg/day based on decreased body-weight gains and food consumption. The maternal NOAEL is 25 mg/kg/day.

There were no abortions, premature deliveries, or complete litter resorptions. Furthermore, there were no effects of treatment on numbers of litters, live fetuses, dead fetuses, resorptions (early or late), or on sex ratio or post-implantation loss. There were no treatment-related external, visceral, or skeletal malformations.

At >=25 mg/kg/day, fetal body weights were dose-dependently decreased (p<=0.01) by 3-16%, and a dose-related increase in the number of runts (fetuses weighing less than 4.0 g) was observed compared to controls. Additionally at these doses, incidences of the following skeletal variations, indicative of altered growth and development, were increased over controls: (i) enlarged (poor ossification) of the anterior and/or posterior fontanelle; (ii) unossified 7th cervical centrum; (iii) incomplete ossification of the 5th and/or 6th sternebrae, hemisternebra of the 5th sternebrae, or bipartite 5th sternebrae; (iv) extra ossification points (unilateral/bilateral) on the 14th thoracic vertebra; (v) incomplete ossification of the thoracic centrum; (vi) unossified 3rd and/or 4th proximal phalanges on the forepaws; (vii) incomplete ossification or unossified 5th metacarpals; (viii) unossified 1st metatarsals; and (ix) less than 9 sacrocaudal vertebrae ossified/9 first sacrocaudal vertebrae.

Additionally at >=125 mg/kg/day, incidences of the following skeletal variations and anomalies were increased over controls: (i) bilateral incomplete ossification of the supraoccipital, interparietal, nasals, frontals, and /or parietals; (ii) unossified 5th and/or 6th sternebrae; (iii) unossified thoracic centrum; and (iv) bipartite and/or dumbbell thoracic centrum and cartilage.

Finally at 500 mg/kg/day, incidences of the following skeletal variations were increased over controls: (i) unossified hyoid centrum; (ii) unossified 7th cervical centrum, cartilage bipartite; (iii) bipartite ossification, incomplete ossification, or unossified 1st, 2nd, and/or 4th sternebrae.

At >=25 mg/kg/day, incidences of short unilateral/bilateral 14th thoracic ribs were increased over controls. Additionally at >=125 mg/kg/day, incidences of bipartite and/or dumbbell thoracic centrum and cartilage were increased over controls. At 500 mg/kg/day, incidences of the following variations were increased over controls: (i) enlarged thymus; (ii) split, bipartite, or branched xiphoid process; (iii) bipartite and/or dumbbell thoracic centrum; and (iv) dumbbell 1st lumbar centrum. Additionally at this dose, enlarged bladder and absent (unilateral) renal papilla were noted in a single fetus.

The developmental LOAEL is 25 mg/kg/day based on increased skeletal variations including delayed ossifications and on decreased growth and development as indicated by

decreased fetal body weights, and an increased number of runts. The developmental NOAEL was not observed.

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

870.3700b Prenatal Developmental Toxicity Study - Rabbit

EXECUTIVE SUMMARY: In a developmental toxicity study (MRIDs 46695703, 46695701, and 46695702), AE0172747 (95.0% w/w; Batch# PFI 0195) in 0.5% methylcellulose 400 was administered via gavage at a dose volume of 4 mL/kg to 25 New Zealand White rabbits/dose group at dose levels of 0, 1, 10, or 100 mg/kg bw/day from gestation days (GD) 6-28. On GD 29, all surviving does were euthanized, and the uterus was removed via cesarean section and its contents examined. Fetuses were examined for external, visceral, and skeletal malformations, anomalies, and variations.

At 100 mg/kg bw/day, between GD 15 and 22, five pregnant females were either found dead or were euthanized *in extremis* or following abortion. Of these five animals, one (# 530) was found dead on GD 15; three (# 529, 526, and 522) were euthanized *in extremis* on GD 16, 17, 22; and another (# 517) aborted and was euthanized on GD 21. Marked reductions in food consumption, body-weight loss (between -0.17 and -0.55 kg), and one or more occasions of few or no feces were observed in all five of these does prior to death. Additionally: Doe # 530 had no urine on one occasion, and Doe # 522, 526, and 529 had red traces on the cage tray prior to necropsy. Necropsy of these animals revealed: dark liquid present in the uterus in Doe # 522 and 529; dark contents in the intestine and pale appearance in Doe #522; and pale liver in Doe # 526.
At 100 mg/kg bw/day, increased incidences of few feces (14/25 treated vs 3/25 controls) and no feces (5/25 treated vs 0/25 controls) were observed. Cumulative body-weight gains during gestation day (GD) 6-14 were decreased ($p \leq 0.05$) at 100 mg/kg bw/day (-0.03 to -0.07 kg) compared to controls (-0.00 to 0.06 kg). The effect on body-weight gain diminished after GD 14, and body-weight gain for the overall (GD 6-29) treatment period at this dose was comparable to controls, whether or not this weight gain was corrected for gravid uterine weight. Absolute and relative (to body weight) food consumption were decreased ($p \leq 0.05$) by 37-38% in the 100 mg/kg bw/day group at the beginning of treatment from GD 6-8. Additionally at 100 mg/kg bw/day, food consumption remained decreased ($p \leq 0.05$) by 23% for GD 8-10 and 10-14. The decreases at 100 mg/kg bw/day corresponded to the significant decreases observed in body-weight gains. After GD 14, food consumption in these groups was comparable to controls.

At 10 mg/kg bw/day, few feces were observed in 6/25 treated does compared to 3/25 controls.
At 10 mg/kg bw/day, one female (# 499) showed a marked reduction in food consumption, body-weight loss of -0.20 kg, and one or more occasions of few or no feces prior to abortion on GD 23.

Absolute and relative (to body weight) food consumption were decreased ($p \leq 0.05$) by 17% in the 10 mg/kg bw/day group at the beginning of treatment from GD 6-8.

At 1 mg/kg bw/day, one female (# 475) was killed *in extremis* on GD 21 following: a marked reduction in food consumption; body-weight loss of -0.35 kg; one or more occasions of few or no feces; and one occasion (GD 19) of no urine.

The maternal LOAEL is 100 mg/kg bw/day based on mortality, clinical signs of toxicity (i.e., few or no feces), abortion and decreased body weight and food consumption. The maternal NOAEL is 10 mg/kg bw/day.

There were no premature deliveries and no complete litter resorptions. Furthermore, there were no effects of treatment on numbers of live fetuses/doe, dead fetuses/doe, resorptions (early or late), resorptions/doe (early or late), or on fetal weights, sex ratio, or post-implantation loss. At 10 and 100 mg/kg/day, incidences of the following skeletal variations and anomalies were increased over controls and indicate decreased or delayed growth and development: (i) enlarged (poor ossification) of the anterior and/or posterior fontanelle; (ii) unossified atlas centrum; (iii) extra ossification site between atlas and axis centrum; (iv) incomplete ossification of the 1st or 2nd sternebra; (v) unilateral/bilateral incomplete ossification of the pubis; (vi) unossified 1st or 2nd sternebra; and (vii) extra sternebral ossification. Additionally at 100 mg/kg/day, the incidence of unossified 6th sternebra was higher than controls.

At 10 and 100 mg/kg/day, incidences of the following skeletal variations were increased over concurrent controls: (i) cartilage of 8th rib (unilateral/bilateral) attached to the sternum; (ii) cartilage of 1st and 2nd rib (unilateral/bilateral) fused; (iii) presence of 27 pre-sacral vertebrae; and (iv) 13 thoracic rib(s) unilateral/bilateral and presence of 27 pre-sacral vertebrae. Additionally at 100 mg/kg/day, (i) unilateral/bilateral 1st ribs short; (ii) cartilage of 1st rib (unilateral/bilateral) not attached to the sternum; and (iii) 14 thoracic ribs (bilateral) or 14 thoracic rib (unilateral) short and/or detached.

Additionally at 100 mg/kg/day, incidences of the following visceral variations were increased over concurrent controls: (i) short innominate arteries; (ii) absent innominate arteries; and (iii) dilated cerebral lateral ventricles (bilateral).

At 100 mg/kg/day, fused kidneys and retroesophageal aortic arch were noted in a single fetus (each) compared to 0 controls. Incidences of all other malformations were unrelated to dose.

The developmental LOAEL is 10 mg/kg bw/day based on decreased or delayed growth and/or development of the skeleton and increased incidences of other skeletal variations and anomalies. The developmental NOAEL is 1 mg/kg bw/day.

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

A.3.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects - Rat

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study (MRID 46695704), AE0172747 (94.0% w/w; Batch# OP2250027) was administered in the diet to 30 Wistar

Hanover (Crl:WI[GLX/BR/HAN]IGS BR) rats/sex/dose at dose levels of 0, 20, 200, or 1500 ppm (equivalent to 0/0, 1.4/1.6, 13.3/15.8, and 100.4/119.3 mg/kg/day). The P generation parents were dosed for 70 days before they were mated to produce the F1 litters. From the F1 weanlings, 30 rats/sex/dose were selected to be parents and were fed the same test diet concentrations as their parents for 70 days prior to mating to produce the F2 litters.

Corneal opacity was observed (vs 0 controls) in all treated groups in both sexes and both generations during all study intervals. With the exception of the pre-mating, mating, and gestation periods in the 20 ppm P generation females, these incidences were significantly ($p \leq 0.01$) increased over controls. The incidence of corneal opacity was generally dose-dependent, and increased in the females during lactation when intake of the test substance approximately doubled. The rate of this increase over the course of the study was similar among the treated groups. These clinical findings were confirmed at termination, with the eyes of both sexes and both generations at ≥20 ppm showing opacity (26.7-96.7%) observed grossly and acute inflammation and neovascularization observed microscopically (26.7-100%) compared to 0 controls. Mean severity of these findings, presented in the study report on a scale of 1 (minimal) to 5 (severe), ranged from 1.1-2.4 but showed no definitive relationship to dose.

During pre-mating, minor decreases in parental body weights were observed in the: (i) 1500 ppm P males beginning on Day 28 through termination; (ii) 200 and 1500 ppm P females from Days 21 through 70; (iii) 200 and 1500 ppm F1 males throughout pre-mating; and (iv) 1500 ppm F1 females during Days 0-14. Body-weight gains for the pre-mating period were decreased in the 1500 ppm P males and in the 200 and 1500 ppm F1 males. Food consumption was decreased in the: (i) 1500 ppm P males from Days 7-21; (ii) P females at 200 ppm from Days 0-7 and 14-21 and at 1500 ppm from Days 0-7 and 14-56; and (iii) F1 males at 200 ppm from Days 56-63 and at 1500 ppm from Days 35-63. During gestation, body weights were decreased in the P dams at 1500 ppm on GD 6 and at 200 and 1500 ppm on GD 13. Food consumption was decreased in the 1500 ppm P dams during GD 6-13. During lactation, body weights in the P dams were decreased at 1500 ppm on LD 4, 7, and 14; however, body-weight gains for the overall (LD 0-21) lactation period were unaffected by treatment. Food consumption was decreased in the P dams at 200 ppm during LD 7-14 and 14-21 and throughout lactation at 1500 ppm. In the 1500 ppm F1 dams, food consumption was decreased during LD 7-14 and 14-21.

Dilated kidneys were noted in the F1 males and females at 20 ppm (3.3-6.9%), 200 ppm (16.7-20.0%), and 1500 ppm (37.9%) compared to controls (0.0-3.3%). The incidence and severity of tubular basophilia (13.8-33.3% treated vs 6.7% controls) and pelvis epithelium hyperplasia (13.8-33.3% treated vs 6.7% controls) in the kidneys was increased at ≥20 ppm in the F1 males and females (3.6-10.0% treated compared to 3.3% controls and 7-56.7% treated vs 3.3% controls, respectively), and the mean severity was slightly higher at 1500 ppm (1.3) compared to controls (1.0). Chronic inflammation of the kidneys was observed at an increased incidence in 1500 ppm F1 males (23.3 % treated vs 0 controls). Also, there was a dose dependent increase in the incidence of pelvic dilatation in F1 males (13.8-53.5%) and females (7-56.7%) relative to controls.

The LOAEL for parental toxicity is 20 ppm (equivalent to 1.4/1.6 mg/kg/day in males/females) based on effects on the eyes, including corneal opacity, acute inflammation, and neovascularization. The NOAEL was not observed.

Treatment-related decreases ($p \leq 0.05$) in pup body weights were observed: in the F1 pups at 200 and 1500 ppm beginning on PND 7 and continuing throughout the reminder of the post-natal period; and in the F2 pups at 200 ppm beginning on PND 21 and at 1500 ppm beginning on PND 14. Body-weight gains in these groups were dose-dependently decreased. Compared to controls, the time until preputial separation was dose-dependently delayed in all treated groups in the F1 and F2 offspring. This effect was considered treatment related. Also, the time to vaginal opening was longer in the 1500 ppm F1 offspring.

Absolute and relative spleen weights were dose-dependently decreased (decr.11-34%; $p \leq 0.05$) in both sexes in the F1 pups at $\geq$20 ppm and in the F2 pups at $\geq$200 ppm. Increased incidences of minimal extramedullary hematopoeisis in the spleen were observed in all treated groups and reached statistical significance ($p \leq 0.05$) at 200 ppm in the F1 female pups (19.2% treated vs 0% controls) and at 1500 ppm in the pups of both sexes and both generations (33.3-82.1% treated vs 0-3.8% controls). This was considered a treatment related effect. Also, absolute brain weights were dose-dependently decreased ($p \leq 0.05$) in both sexes in both generations. In F1 male and female pups, absolute brain weights significantly decreased 3-10% in all treatment groups. In the F2 generation, absolute brain weights significantly decreased 5-9% in males and females at $\geq$200 ppm. Relative brain weights were significantly increased ($p \leq 0.05$) in only F1 males and females by 8-9% at $\geq$200 ppm.

In the F2 juveniles, opacity was macroscopically observed in the eyes of 100% of the treated males and females. Acute inflammation and neovascularization were microscopically observed in the male and female F2 juveniles at 20 ppm (50.0-88.9%) and $\geq$200 ppm (100%) compared to 0 controls. Mean severity of these findings was slightly increased at $\geq$200 ppm (1.9-3.0) compared to 20 ppm (1.0-2.3).

Additionally in the 1500 ppm F2 juvenile males, dilated kidney was noted in 2/2 (100%) animals examined.

The LOAEL for offspring toxicity is 20 ppm (equivalent to 1.4/1.6 mg/kg/day in males/females) based on effects on the eyes, including corneal opacity, acute inflammation, and neovascularization; increased incidences of minimal extramedullary hematopoeisis in the spleen, delayed preputial separation, and decreased absolute brain weight. The NOAEL was not observed.

There were no effects of treatment on any reproductive parameter in either generation, including: the number and duration of estrous cycles; sperm count, motility, and morphology; mating, fertility, and gestation indices; and pre-coital and gestation durations.

The LOAEL for reproductive toxicity was not observed. The NOAEL is 1500 ppm (equivalent to 100.4/119.3 mg/kg/day in males/females).

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.

A.3.4 Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity – Rat

EXECUTIVE SUMMARY: In a combined chronic / carcinogenicity study (MRID 46695707) AE 0172747 (95.0% a.i., batch/lot # PFI 0195) was administered to 60 Rj: WI (IOPS HAN) Wistar rats/sex/dose in the diet at dose levels of 0, 2, 20, 2500 or 5000 ppm (equivalent to 0, 0.10, 1.05, 134 or 280 mg/kg bw/day) for 104 weeks. Additional groups of 10 rats/sex were administered the same dosing regimen, but were terminated at 52 weeks (interim sacrifice). Two groups of 15 rats/sex receiving 0 or 5,000 ppm in the diet for 52 weeks were followed for an additional 13 weeks after treatment ended in the recovery phase of the study.

Excessive toxicity and/or mortality were observed in males in the 2,500 and 5,000 ppm groups. *Therefore, males in the 5,000 ppm group were terminated at Week 6 and males in all the other groups were terminated at Week 43*. Males in the 2 ppm showed a few incidences of corneal opacity, neovascularization of the cornea and snow flake-like corneal opacity after 6 months of treatment. Males and females in the 20 ppm group exhibited corneal opacity, neovascularization of the cornea, snow flake-like corneal opacity, and edema of the cornea (females only). Females in the 20, 2,500 and 5,000 ppm groups exhibited keratitis of the eye. Hair loss, generalized or localized soiled fur and soiled anogenital region were observed in females in the 2,500 and 5,000 ppm groups. At the end of the recovery phase, the only persistent treatment-related clinical signs observed were hair loss in 1/5 animals and white area on one eye in 1/12 animals.

[The data summary presented below addresses only the toxic effects reported for female rats.]

Body weight was slightly decreased by 2 through 6% during the first year of treatment for females in the 2,500 ppm group. Cumulative body-weight gain was decreased by 16% after one week of treatment and by 10% at the end of the first year. By Day 708, body weight was comparable to controls, while cumulative body-weight gain was slightly decreased by 5%. Body weight and cumulative body-weight gain were decreased by 5 and 36% during the first week of treatment for females in the 5,000 ppm group, respectively, when compared to controls. This initial loss was maintained throughout the course of the study leading to a final body-weight reduction on Day 708 of 5% and an overall reduction in cumulative body-weight gain of 7%, compared to controls. Food consumption was decreased by up to 11% during the first six weeks of treatment, but comparable to controls thereafter.

Clinical chemistry revealed an increase in mean total cholesterol concentration (23-59%) on most occasions throughout the study, with increases in triglycerides concentrations at the 5 (87%) and 7 (50%) months and decreases (18%) in mean glucose concentrations for females during the first year of treatment at 5,000 ppm when compared to controls. These changes were reversible after 13 weeks of recovery. Urinalysis revealed increases in ketone levels and decreases in pH values for females in the 5,000 ppm group throughout the study. These changes were reversible after 13 weeks of recovery.

At 2,500 ppm, the mean liver to body weight ratio was increased by 11% when compared to controls. Mean liver weights, liver to body-weight ratios and liver to brain weight ratios were increased in females in the 5,000 ppm group by 19%, 23% and 22%, respectively, when compared to controls. Mean adrenal gland weights were decreased by 34% and 35% in females

in the 2,500 and 5,000 ppm groups, respectively, when compared to controls. Mean adrenal to body-weight ratios were decreased in females in the 20, 2,500, and 5,000 ppm, by 30%, 29% and 29%, respectively, when compared to controls. Mean adrenal to brain weight ratios were decreased in females in the 2,500 and 5,000 ppm groups by 33% and 34%, respectively, when compared to controls. At the end of the recovery period, the mean liver to body-weight ratio was increased in females by 8% when compared to controls.

The incidence of minimal to severe keratitis of the eye was increased at 20, 2,500 and 5,000 ppm (56%, 87% and 83%, respectively) when compared to controls (3%).

Increased incidences of sciatic nerve atrophy were noted at 2,500 and 5,000 ppm (58% and 67%, respectively, versus 28% in controls), and were sometimes associated with a minimal to moderate chronic inflammatory response and/or minimal to marked mineralization of vessels within the nerve. The incidence of chronic inflammation was increased at 5,000 ppm (33% versus 7% in controls), and the incidence of mineralization of the vessels was increased at both 2,500 and 5,000 ppm (37% and 55%, respectively, versus 11% in controls). In the skeletal muscle, the incidence of minimal to moderate atrophy was increased at 5,000 ppm (53%) when compared to controls (31%).

In the liver, the incidence of minimal to marked biliary hyperplasia/fibrosis was increased at 20, 2,500 and 5,000 ppm (67%, 77% and 81%, respectively) when compared to controls (45%). Additionally in the liver, the incidence of minimal to marked sinusoidal dilatation was increased at 2,500 and 5,000 ppm (58% and 64%, respectively) when compared to controls (35%).

In the pancreas, the incidence of minimal to moderate acinar atrophy/fibrosis was increased at 2,500 and 5,000 ppm (42% and 54%, respectively) when compared to controls (25%).

In the adrenal gland, the incidence of minimal to marked cortical atrophy was increased at 5,000 ppm (22%) when compared to controls (3%).

In the lung, the incidence of minimal to slight perivascular cuffing was increased in the 2,500 and 5,000 ppm groups (23% and 34%, respectively) when compared to controls (12%).

The LOAEL is 20 ppm (1.05 mg/kg bw/day) in females, based on keratitis of the eye and biliary hyperplasia/fibrosis. The NOAEL is 2 ppm (0.10 mg/kg bw/day).

At the doses tested, there was no treatment related increase in tumor incidence in female Rj: WI (IOPS HAN) Wistar rats when compared to controls. Dosing was considered adequate in **females only** based on decreased body-weight gain of 14% at 13 weeks, marked biliary hyperplasia/fibrosis, minimal to moderate sciatic nerve atrophy, minimal to moderate atrophy in the skeletal muscle, minimal to moderate acinar atrophy/fibrosis of the pancreas and of minimal to marked cortical atrophy of the adrenal gland at 5,000 ppm. The study did not adequately test for the carcinogenic potential of AE 0172747 in male Rj: WI (IOPS HAN) Wistar rats due to the early termination at 43 (or 6) weeks of all male groups.

This chronic/carcinogenicity study in the rat is unacceptable/guideline and does not satisfy the guideline requirement for a chronic/ carcinogenicity study [(OPPTS 870.4300); OECD 453] in rats. All male groups were terminated early and only very minimal data for males were presented.

EXECUTIVE SUMMARY: In a combined chronic/carcinogenicity study (MRID 46695708) AE 0172747 (95.0% a.i., batch/lot # PFI 0195) was administered to 60 Rj: WI (IOPS HAN) Wistar male rats/dose in the diet at dose levels of 0, 1, 20, 200 or 800 ppm (equivalent to 0, 0.04, 0.79, 8.3 or 31.7 mg/kg bw/day) in the diet for 104 weeks. Additional groups of 10 rats/sex were administered the same dosing regimen, but were terminated at 52 weeks (interim sacrifice). Two groups of 15 male rats receiving 0 or 800 ppm in the diet for 52 weeks were followed for an additional 13 weeks after treatment ended in the recovery phase of the study.

There were no compound related effects on mortality, food consumption or hematology. At 20, 200, and 800 ppm, white area on eyes was noted in most animals. In addition, focal swelling (principally of the hindlimb) occurred at a slightly higher incidence at the three dietary levels (18-24% vs. 9% in the controls), and limited use of limb was increased at 200 ppm (21%), in comparison with the controls (9%). At 800 ppm, hair loss occurred.

Ophthalmological findings revealed corneal opacity, neovascularization and edema of the cornea and snow flake-like corneal opacity were observed at 20, 200, and 800 ppm. After 13 weeks of recovery, corneal opacity, edema of the cornea and snow flake-like corneal opacity were reversible, whereas neovascularization of the cornea persisted in all treated animals in the recovery group (800 ppm).
Body weight and body-weight gain were decreased by 4% ($p \leq 0.01$ or $p \leq 0.05$) during the first year of treatment for animals in the 20 ppm group, compared to controls. However, these parameters were progressively reduced the last six months of treatment, and by Day 708, body weight and body-weight gain were decreased by 11% ($p \leq 0.01$) and 17% ($p \leq 0.01$), respectively, compared to controls. At 200 ppm, body weight and body-weight gain were decreased by 5% and 7% ($p \leq 0.01$ or $p \leq 0.05$), respectively, during the first year of treatment, compared to controls. By Day 708, body weight and body-weight gain were decreased by 15% ($p \leq 0.01$) and 24% ($p \leq 0.01$), respectively, compared to controls. At 800 ppm, by the end of the first year, body weight and body-weight gain were decreased by 6% ($p \leq 0.01$) and 8% ($p \leq 0.01$), respectively, compared to controls. At the end of the study, body weight and body-weight gain were decreased by 7% and 10%, respectively, compared to controls. At the end of the recovery period, body-weight gain body-weight gain were decreased by 37% in the 800 ppm group, compared to controls. At 800 ppm, food consumption was decreased at times by up to 7% ($p \leq 0.01$ or $p \leq 0.05$) during the first five months of the study, but was comparable to controls during the second year of the study.

Total cholesterol concentrations were significantly increased ($p \leq 0.01$) at 200 and 800 ppm (46 and 52%, respectively), compared to controls during the first 18 months of treatment. The increased total cholesterol concentrations observed at 800 ppm during the first 18 months of treatment were still present after 3 months of recovery (43%, $p \leq 0.01$), compared to controls.

Urinalysis revealed increased ketone levels and lower pH values at 20, 200 and 800 ppm throughout the study. Decreased amount of crystals (believed to be linked to the lower pH

values) was also observed. In addition, at 200 and 800 ppm increased protein levels were observed. After 13 weeks of recovery, decreased crystal amount was similar between the 800 ppm group and control group, whereas the increased ketone level, protein level and the lower pH value were not reversible.

Kidney weights were increased at 20, 200, and 800 ppm by 15, 13 and 18% ($p \leq 0.05$), respectively. The kidney to body-weight ratio was increased at 20, 200, and 800 ppm by 24, 31 and 26% ($p \leq 0.01$), respectively. The kidney to brain weight ratio was increased at 20, 200, and 800 ppm by 20, 20 and 23% ($p \leq 0.01$ or $p \leq 0.05$), respectively. At the end of the recovery period, mean kidney weights were higher by between 15 to 25% ($p \leq 0.01$) in animals previously treated at 800 ppm, in comparison to controls.

Gross necropsy revealed a higher incidence of ocular opacity at 20, 200, and 800 ppm. The incidence of minimal to marked keratitis of the eye(s) was significantly increased ($p \leq 0.01$) in males in the 20, 200, and 800 ppm groups (97-98%) when compared to controls (3%). Keratitis included one or more of the following changes in the cornea: acute inflammation, epithelial hyperplasia, keratinization, epithelial vacuolization, erosion and/or ulceration. Generally, the keratitis observed in this study was a multifocal to diffuse chronic active superficial keratitis, involving the corneal epithelium and superficial aspects of the corneal stroma, which did not penetrate the cornea. A slight non-statistically significant elevation (3-5%) of hyperplastic lesions was noted on the cornea of the eye at 200 and 800 ppm, when compared to controls (0%). In addition, a minimal to moderate retinal degeneration, mostly located in the ora serrata area of the retina, was significantly increased ($p \leq 0.05$) in the 800 ppm group (15%) when compared to controls (3%).

In the kidney, a minimal to severe chronic nephropathy was significantly increased ($p \leq 0.01$) in the 20, 200, and 800 ppm group, (87%, 87%, 92% and 83%, respectively) compared to in the control group (63%). Changes within the kidney included one or more of the following changes: tubular cell regeneration, thickened basement membranes (glomerular and tubular), interstitial fibrosis, inflammation, dilated/cystic tubules, protein casts, pigmentation, mineralization, debris, mesangial proliferation, glomerular sclerosis, and hypertrophy/hyperplasia of tubular epithelium. Severity grades moderate or higher generally reflected a kidney with most of the above-mentioned changes, some reflecting end-stage renal disease (probable cause of death).

In the sciatic nerve, minimal to slight nerve fiber degeneration was significantly increased ($p \leq 0.05$) in the 20, 200 and 800 ppm groups (73%, 73% and 75%, respectively), when compared to controls (53%). This change was described as multiple fiber degeneration, loss of stain intensity, decreased density and definition of the nerve fiber and/or demyelination. In addition, sometimes associated with sciatic nerve atrophy was a minimal to moderate chronic inflammatory response and/or minimal to moderate mineralization of the vessels within the nerve. In general, these changes were noted in animals that survived to the terminal sacrifice, indicating a late onset of the exacerbation of this lesion.

In the thyroid gland, the incidence of minimal to marked pigmentation of the cytoplasm of the follicular epithelial cells was significantly increased ($p \leq 0.01$) in the 1, 20, 200, and 800 ppm groups (36%, 66%, 77% and 73%, respectively),when compared to controls (12%). Special stains conducted on two-year males (positive for Schmorl and PAS, minimally positive for

Fontana-Masson and negative for Perls) were compatible with lipofuscin pigments. Minimal to slight colloid alteration of the thyroid gland was significantly ($p \leq 0.05$) increased in the 20, 200 and 800 ppm groups (63%, 62% and 63%, respectively) when compared to controls (55%). Colloid alteration of the thyroid gland was described as an irregular uniformity of the colloid with differences in staining and globule formation. The severity grade for colloid alteration was increased in the 200 and 800 ppm dose groups. Minimal to mark cystic hyperplasia of the thyroid gland was significantly ($p \leq 0.01$) increased in the 200 and 800 ppm groups (13% and 12%, respectively) when compared to controls (0%).

In the pancreas, the incidence of minimal to moderate acinar atrophy/fibrosis was significantly increased ($p \leq 0.01$) in the 200 and 800 ppm groups (63% and 67%, respectively), when compared to controls (35%). Pancreatic acinar atrophy/fibrosis generally is a focal or lobular atrophy (dedifferentiation of acinar cells and an increase in small duct-like structures), sometimes associated with a relative increase in interstitial collagen and a small number of inflammatory cells, but in the 200 and 800 ppm dose groups this lesion was more diffuse in distribution. In the skeletal muscle, the incidence of minimal to moderate atrophy was significantly increased in the 800 ppm group (49%) when compared to controls (32%).

The LOAEL is 20 ppm (0.79 mg/kg bw/day) in males, based on neovascularization and edema of the cornea and snow flake-like corneal opacity, unilateral or bilateral keratitis of the eye, decreased mean body weight and mean body-weight gain, increased total cholesterol, higher ketone level and lower pH values, higher protein levels, increased kidney weight, kidney to body weight and kidney to brain weight ratios, chronic nephropathy and atrophy of the sciatic nerve. The NOAEL is 1 ppm (0.04 mg/kg bw/day).

There was a slight increase in neoplastic lesions; i.e., squamous cell carcinoma of the cornea in the 200 and 800 ppm groups (7% and 3%, respectively), when compared to controls (0%). This change was considered to be a result of the keratitis of the eye. Rats appear to be much more sensitive to tyrosinaemia than humans.

This chronic/carcinogenicity study in the rat is acceptable/guideline and satisfies the guideline requirement for a chronic/ carcinogenicity study [(OPPTS 870.4300); OECD 453] in rats when evaluated together with the associative study most recently completed in females (MRID 46695707).

870.4100b (870.4300b) Chronic Toxicity – Mouse

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 46695706), AE 0172747 (95% w/w a.i.; Batch No. PFI 0195) was administered in the diet to C57BL/6 J@ Ico mice (50/sex/dose) at doses of 0, 30, 300, 1000, or 3000 ppm (equivalent to 0/0, 4/5, 43/54, 146/179, and 440/552 mg/kg/day in males/females) for up to 78 weeks. Additionally, 10 mice/sex/dose were treated similarly for up to 52 weeks.

No treatment-related effect was observed on mortality or ophthalmoscopic examination.

At 30 ppm (the lowest dose tested), there was evidence of toxicity in the gallbladder and liver in both sexes. The toxicity became more severe at higher doses. In all treatment groups at 12 months, incidences (n=10) of the following lesions were increased in the gallbladder and liver: (i) minimal to moderate gallstones in males and females (2-5 treated vs 1 control); (ii) minimal to marked gallstones in females (2-7 treated vs 0 controls); and (iii) minimal to moderate centrilobular to panlobular hepatocellular hypertrophy (diffuse) in females (5-10 treated vs 0 controls).

In all treatment groups at 18 months, gallbladder stones were observed in mice at necropsy in both sexes (18-36/50 treated vs 1/50 controls). Incidences of the following microscopic lesions were increased in all treatment groups in the gallbladder (# affected/50 treated vs # affected/50 controls, except n=49 in male controls and 1000 ppm females): (i) minimal to marked gallstones in both sexes (6-26 vs 0-1; $p<=0.001$); (ii) minimal to marked eosinophilic cytoplasmic alteration (focal/multifocal) in females (9-28 vs 2; $p<=0.05$); and (iii) minimal to moderate subepithelial mixed cell infiltrate (focal/multifocal) in females (15-29 vs 11; not statistically significant). Hepatotoxicity was indicated in all treatment groups by increased ($p<=0.01$) relative to body liver weights in both sexes (incr 6-26%); increased incidences of minimal to moderate centrilobular to panlobular hepatocellular hypertrophy (diffuse) in females (12-47/49-50 vs 0/50; $p<=0.001$); and macroscopic white foci in males (4-6/50 treated vs 1/50 control). An increased incidence of papillary mineralization was also observed in the kidneys of females at 18 months. Slight anemia was observed in all treated female groups at 18 months, as evidenced by decreases in hemoglobin concentration, hematocrit, and erythrocyte count.

At 300 ppm and above at 18 months, incidences of the following lesions were increased in the liver: minimal to moderate centrilobular to panlobular hepatocellular hypertrophy (diffuse) in the males; and minimal to slight hepatocellular degeneration (focal/multifocal) in females. Minimal to marked eosinophilic cytoplasmic alteration (focal/multifocal) in male gallbladders was considered equivocally treatment-related because the incidence and/or severity were not clearly related to dose.

At 1000 ppm and above, intense yellow colored urine was noted in males and females. This finding was first observed at the end of the third month of treatment at 3000 ppm and the fifth month at 1000 ppm. Once noted, this finding continued to be observed throughout treatment. Decreased food consumption in females was often observed beginning at Day 22. Food consumptions during the first 4-week period and the following 12-week period were reduced.

At 1000 ppm and above at 18 months, the incidences of the following lesions were increased in males: (i) minimal to marked epithelial hyperplasia (multifocal/diffuse) in the gallbladder; (ii) minimal to marked focal tubular degeneration (bilateral) in the testes; and (iii) minimal to slight interstitial cell hyperplasia (focal/multifocal) in testes. Increased incidences of dilatation of uterine horns were noted grossly at ≥1000 ppm.

At 3000 ppm, decreased body weights were observed sporadically in females throughout the treatment period and contributed to decreased bodyweight gain (Days 92-344) and overall (Days 1-540) body-weight gain. After 18 months in the males, absolute and relative to body testicular weights were decreased. Increased incidences of the following gross lesions were noted: red foci

in the male liver, prominent lobulation in the female liver, and renal pelvic dilatation in the females.

At 3000 ppm at 18 months, incidences of the following microscopic lesions were increased in the liver: (i) minimal to slight hepatocellular degeneration (focal/multifocal) in the males; (ii) minimal to slight hepatocellular vacuolation (diffuse) in the males; (iii) increased number of mitoses in the females; and (iv) minimal to moderate eosinophilic focus(i) of altered hepatocytes (focal/multifocal) in the females. Additionally, an increased incidence of minimal to moderate interstitial mixed cell infiltrate (focal/multifocal) in the liver in males was considered equivocal because only minimal severity was observed at 3000 ppm and the incidence and severity were not clearly related to dose. Minimal to marked horn dilatation (diffuse) in the uterus at 3000 ppm was considered treatment-related.

The LOAEL is 30 ppm (equivalent to 4/5 mg/kg/day in males/females), based on gallstones, eosinophilic cytoplasmic alteration, subepithelial mixed cell infiltrate, and dilatation in/of the gallbladder; hepatocellular vacuolation, hepatocellular hypertrophy, and increased liver weight in males and females; and papillary mineralization of the kidney and changes in hematological parameters indicative of anemia in females. The NOAEL was not established.

At the doses tested, there was not a treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on toxicity noted in the gallbladder, liver, and testes, decreased body weight and body-weight gain, and decreased food consumption.

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

870.4100b Chronic Toxicity - Dog

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 46695705), AE 0172747 (95.4% w/w, Batch #: PFI 0254) was administered to 4 beagle dogs/sex/dose in the diet for 52 weeks at doses of 0, 75, 300, or 1200 ppm (equivalent to 0/0, 2.5/2.5, 9.0/10.2, and 37.8/41.6 mg/kg bw/day in males/females).

No treatment-related adverse effects were observed on mortality, body weights, body-weight gains, food consumption, ophthalmoscopic examination, urinalysis, or clinical chemistry at any dose. Increased incidence of urinary ketone levels were observed in all treated groups throughout the study. This effect would seem reasonable considering that the test substance is a herbicide of the triketone family.

At 1200 ppm, one male displayed disturbance in locomotion between Days 112 and 287, had soft or liquid feces throughout the study, and had a general wasted appearance during Days 78-321, even though this animal ate its entire daily food ration.

The following differences from controls were observed throughout the study in both sexes at 1200 ppm: (i) increased platelets (incr. 51-95%); (ii) decreased mean corpuscular hemoglobin (MCH) (decr. 8-18%); and (iii) decreased mean corpuscular volume (MCV) (decr. 6-17%). Additionally, erythrocytes were increased (incr. 21%) in the females at 12-13 months. One male and all females displayed some changes in erythrocyte morphology including: slight to severe anisocytosis, microcytosis, anisochromia, and hypochromia; poikilocytosis; slight to moderate basophilic stippling; and target cells.
In the 1200 ppm males, an increased number of digestion chambers of the sciatic nerve were observed. Minimal to slight increased number of digestion chambers located unilaterally/bilaterally was observed at: 75 ppm (1), 300 ppm (1), and 1200 ppm (2). In the females, this finding was only noted in 1/4 females each at 75 and 300 ppm. Apparently, these digestion chambers were a result of focal enlargement of the myelin sheath due to myelin debris and may account for the neurological effect (disturbances in locomotion) observed in one of the 1200 ppm males. In the subchronic dog study (MRID 46695643), reviewed concurrently with this study, an increased number of digestion chambers of the sciatic nerve were observed in the 4500/2250 ppm treatment group.

The LOAEL is 75 ppm (equivalent to 2.5 mg/kg bw/day) in males, based upon the increased number of digestion chambers of the sciatic nerve. The NOAEL was not determined in males. The LOAEL is 1200 ppm (equivalent to 41.6 mg/kg bw/day) in females, based on decreases in MCH and MCV, increased platelet counts, changes in erythrocyte morphology and pigmentation of the thyroid gland. The NOAEL is 300 ppm (equivalent to 10.2 mg/kg bw/day) in females.

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.3.5 Carcinogenicity

870.4200a Carcinogenicity Study – rat

EXECUTIVE SUMMARY: In a combined chronic / carcinogenicity study (MRID 46695707) AE 0172747 (95.0% a.i., batch/lot # PFI 0195) was administered to 60 Rj: WI (IOPS HAN) Wistar rats/sex/dose in the diet at dose levels of 0, 2, 20, 1250 or 2,500 ppm (equivalent to 0, 0.10, 1.05, 134 or 280 mg/kg bw/day) for 104 weeks. Additional groups of 10 rats/sex were administered the same dosing regimen, but were terminated at 52 weeks (interim sacrifice). Two groups of 15 rats/sex receiving 0 or 5,000 ppm in the diet for 52 weeks were followed for an additional 13 weeks after treatment ended in the recovery phase of the study.

Excessive toxicity and/or mortality were observed in males in the 2,500 and 5,000 ppm groups. *Therefore, males in the 5,000 ppm group were terminated at Week 6 and males in all the other groups were terminated at Week 43*. Males in the 2 ppm showed a few incidences of corneal opacity, neovascularization of the cornea and snow flake-like corneal opacity after 6 months of treatment. Males and females in the 20 ppm group exhibited corneal opacity, neovascularization of the cornea, snow flake-like corneal opacity, and edema of the cornea (females only). Females in the 20, 2,500 and 5,000 ppm groups exhibited keratitis of the eye. Hair loss, generalized or localized soiled fur and soiled anogenital region were observed in females in the 2,500 and 5,000

ppm groups. At the end of the recovery phase, the only persistent treatment-related clinical signs observed were hair loss in 1/5 animals and white area on one eye in 1/12 animals.

[The data summary presented below addresses only the toxic effects reported for female rats.]

Body weight was slightly decreased by 2 through 6% during the first year of treatment for females in the 2,500 ppm group. Cumulative body weight gain was decreased by 16% after one week of treatment and by 10% at the end of the first year. By Day 708, body weight was comparable to controls, while cumulative body weight gain was slightly decreased by 5%. Body weight and cumulative body weight gain were decreased by 5 and 36% during the first week of treatment for females in the 5,000 ppm group, respectively, when compared to controls. This initial loss was maintained throughout the course of the study leading to a final body weight reduction on Day 708 of 5% and an overall reduction in cumulative body weight gain of 7%, compared to controls. Food consumption was decreased by up to 11% during the first six weeks of treatment, but comparable to controls thereafter.

Clinical chemistry revealed an increase in mean total cholesterol concentration (23-59%) on most occasions throughout the study, with increases in triglycerides concentrations at the 5 (87%) and 7 (50%) months and decreases (18%) in mean glucose concentrations for females during the first year of treatment at 5,000 ppm when compared to controls. These changes were reversible after 13 weeks of recovery. Urinalysis revealed increases in ketone levels and decreases in pH values for females in the 5,000 ppm group throughout the study. These changes were reversible after 13 weeks of recovery.

At 2,500 ppm, the mean liver to body weight ratio was increased by 11% when compared to controls. Mean liver weights, liver to body weight ratios and liver to brain weight ratios were increased in females in the 5,000 ppm group by 19%, 23% and 22%, respectively, when compared to controls. Mean adrenal gland weights were decreased by 34% and 35% in females in the 2,500 and 5,000 ppm groups, respectively, when compared to controls. Mean adrenal to body weight ratios were decreased in females in the 20, 2,500, and 5,000 ppm, by 30%, 29% and 29%, respectively, when compared to controls. Mean adrenal to brain weight ratios were decreased in females in the 2,500 and 5,000 ppm groups by 33% and 34%, respectively, when compared to controls. At the end of the recovery period, the mean liver to body weight ratio was increased in females by 8% when compared to controls.

The incidence of minimal to severe keratitis of the eye was increased at 20, 2,500 and 5,000 ppm (56%, 87% and 83%, respectively) when compared to controls (3%).

Increased incidences of sciatic nerve atrophy were noted at 2,500 and 5,000 ppm (58% and 67%, respectively, versus 28% in controls), and were sometimes associated with a minimal to moderate chronic inflammatory response and/or minimal to marked mineralization of vessels within the nerve. The incidence of chronic inflammation was increased at 5,000 ppm (33% versus 7% in controls), and the incidence of mineralization of the vessels was increased at both 2,500 and 5,000 ppm (37% and 55%, respectively, versus 11% in controls). In the skeletal muscle, the incidence of minimal to moderate atrophy was increased at 5,000 ppm (53%) when compared to controls (31%).

In the liver, the incidence of minimal to marked biliary hyperplasia/fibrosis was increased at 20, 2,500 and 5,000 ppm (67%, 77% and 81%, respectively) when compared to controls (45%). Additionally in the liver, the incidence of minimal to marked sinusoidal dilatation was increased at 2,500 and 5,000 ppm (58% and 64%, respectively) when compared to controls (35%).

In the pancreas, the incidence of minimal to moderate acinar atrophy/fibrosis was increased at 2,500 and 5,000 ppm (42% and 54%, respectively) when compared to controls (25%).

In the adrenal gland, the incidence of minimal to marked cortical atrophy was increased at 5,000 ppm (22%) when compared to controls (3%).

In the lung, the incidence of minimal to slight perivascular cuffing was increased in the 2,500 and 5,000 ppm groups (23% and 34%, respectively) when compared to controls (12%).

The LOAEL is 20 ppm (105 mg/kg bw/day) in females, based on keratitis of the eye and biliary hyperplasia/fibrosis. The NOAEL is 2 ppm (0.10 mg/kg bw/day).

At the doses tested, there was no treatment related increase in tumor incidence in female Rj: WI (IOPS HAN) Wistar rats when compared to controls. Dosing was considered adequate in **females only** based on decreased body weight gain of 14% at 13 weeks, marked biliary hyperplasia/fibrosis, minimal to moderate sciatic nerve atrophy, minimal to moderate atrophy in the skeletal muscle, minimal to moderate acinar atrophy/fibrosis of the pancreas and of minimal to marked cortical atrophy of the adrenal gland at 5,000 ppm. The study did not adequately test for the carcinogenic potential of AE 0172747 in male Rj: WI (IOPS HAN) Wistar rats due to the early termination at 43 (or 6) weeks of all male groups.

This chronic/carcinogenicity study in the rat is unacceptable/guideline and does not satisfy the guideline requirement for a chronic/ carcinogenicity study [(OPPTS 870.4300); OECD 453] in rats. All male groups were terminated early and only very minimal data for males were presented.

EXECUTIVE SUMMARY: In a combined chronic/carcinogenicity study (MRID 46695708) AE 0172747 (95.0% a.i., batch/lot # PFI 0195) was administered to 60 Rj: WI (IOPS HAN) Wistar male rats/dose in the diet at dose levels of 0, 1, 20, 200 or 800 ppm (equivalent to 0, 0.04, 0.79, 8.3 or 31.7 mg/kg bw/day) in the diet for 104 weeks. Additional groups of 10 rats/sex were administered the same dosing regimen, but were terminated at 52 weeks (interim sacrifice). Two groups of 15 male rats receiving 0 or 800 ppm in the diet for 52 weeks were followed for an additional 13 weeks after treatment ended in the recovery phase of the study.

There were no compound related effects on mortality, food consumption or hematology. At 20, 200, and 800 ppm, white area on eyes was noted in most animals. In addition, focal swelling (principally of the hindlimb) occurred at a slightly higher incidence at the three dietary levels (18-24% vs. 9% in the controls), and limited use of limb was increased at 200 ppm (21%), in comparison with the controls (9%). At 800 ppm, hair loss occurred.

Ophthalmological findings revealed corneal opacity, neovascularization and edema of the cornea and snow flake-like corneal opacity were observed at 20, 200, and 800 ppm. After 13 weeks of recovery, corneal opacity, edema of the cornea and snow flake-like corneal opacity were reversible, whereas neovascularization of the cornea persisted in all treated animals in the recovery group (800 ppm).
Body weight and body weight gain were decreased by 4% ($p \leq 0.01$ or $p \leq 0.05$) during the first year of treatment for animals in the 20 ppm group, compared to controls. However, these parameters were progressively reduced the last six months of treatment, and by Day 708, body weight and body weight gain were decreased by 11% ($p \leq 0.01$) and 17% ($p \leq 0.01$), respectively, compared to controls. At 200 ppm, body weight and body weight gain were decreased by 5% and 7% ($p \leq 0.01$ or $p \leq 0.05$), respectively, during the first year of treatment, compared to controls. By Day 708, body weight and body weight gain were decreased by 15% ($p \leq 0.01$) and 24% ($p \leq 0.01$), respectively, compared to controls. At 800 ppm, by the end of the first year, body weight and body weight gain were decreased by 6% ($p \leq 0.01$) and 8% ($p \leq 0.01$), respectively, compared to controls. At the end of the study, body weight and body weight gain were decreased by 7% and 10%, respectively, compared to controls. At the end of the recovery period, body weight gain body weight gain were decreased by 37% in the 800 ppm group, compared to controls. At 800 ppm, food consumption was decreased at times by up to 7% ($p \leq 0.01$ or $p \leq 0.05$) during the first five months of the study, but was comparable to controls during the second year of the study.

Total cholesterol concentrations were significantly increased ($p \leq 0.01$) at 200 and 800 ppm (46 and 52%, respectively), compared to controls during the first 18 months of treatment. The increased total cholesterol concentrations observed at 800 ppm during the first 18 months of treatment were still present after 3 months of recovery (43%, $p \leq 0.01$), compared to controls.

Urinalysis revealed increased ketone levels and lower pH values at 20, 200 and 800 ppm throughout the study. Decreased amount of crystals (believed to be linked to the lower pH values) was also observed. In addition, at 200 and 800 ppm increased protein levels were observed. After 13 weeks of recovery, decreased crystal amount was similar between the 800 ppm group and control group, whereas the increased ketone level, protein level and the lower pH value were not reversible.

Kidney weights were increased at 20, 200, and 800 ppm by 15, 13 and 18% ($p \leq 0.05$), respectively. The kidney to body weight ratio was increased at 20, 200, and 800 ppm by 24, 31 and 26% ($p \leq 0.01$), respectively. The kidney to brain weight ratio was increased at 20, 200, and 800 ppm by 20, 20 and 23% ($p \leq 0.01$ or $p \leq 0.05$), respectively. At the end of the recovery period, mean kidney weights were higher by between 15 to 25% ($p \leq 0.01$) in animals previously treated at 800 ppm, in comparison to controls.

Gross necropsy revealed a higher incidence of ocular opacity at 20, 200, and 800 ppm. The incidence of minimal to marked keratitis of the eye(s) was significantly increased ($p \leq 0.01$) in males in the 20, 200, and 800 ppm groups (97-98%) when compared to controls (3%). Keratitis included one or more of the following changes in the cornea: acute inflammation, epithelial hyperplasia, keratinization, epithelial vacuolization, erosion and/or ulceration. Generally, the keratitis observed in this study was a multifocal to diffuse chronic active superficial keratitis, involving the corneal epithelium and superficial aspects of the corneal stroma, which did not

penetrate the cornea. A slight non-statistically significant elevation (3-5%) of hyperplastic lesions was noted on the cornea of the eye at 200 and 800 ppm, when compared to controls (0%). In addition, a minimal to moderate retinal degeneration, mostly located in the ora serrata area of the retina, was significantly increased ($p \leq 0.05$) in the 800 ppm group (15%) when compared to controls (3%).

In the kidney, a minimal to severe chronic nephropathy was significantly increased ($p \leq 0.01$) in the 20, 200, and 800 ppm group, (87%, 87%, 92% and 83%, respectively) compared to in the control group (63%). Changes within the kidney included one or more of the following changes: tubular cell regeneration, thickened basement membranes (glomerular and tubular), interstitial fibrosis, inflammation, dilated/cystic tubules, protein casts, pigmentation, mineralization, debris, mesangial proliferation, glomerular sclerosis, and hypertrophy/hyperplasia of tubular epithelium. Severity grades moderate or higher generally reflected a kidney with most of the above-mentioned changes, some reflecting end-stage renal disease (probable cause of death).

In the sciatic nerve, minimal to slight nerve fiber degeneration was significantly increased ($p \leq 0.05$) in the 20, 200 and 800 ppm groups (73%, 73% and 75%, respectively), when compared to controls (53%). This change was described as multiple fiber degeneration, loss of stain intensity, decreased density and definition of the nerve fiber and/or demyelination. In addition, sometimes associated with sciatic nerve atrophy was a minimal to moderate chronic inflammatory response and/or minimal to moderate mineralization of the vessels within the nerve. In general, these changes were noted in animals that survived to the terminal sacrifice, indicating a late onset of the exacerbation of this lesion.

In the thyroid gland, the incidence of minimal to marked pigmentation of the cytoplasm of the follicular epithelial cells was significantly increased ($p \leq 0.01$) in the 1, 20, 200, and 800 ppm groups (36%, 66%, 77% and 73%, respectively),when compared to controls (12%). Special stains conducted on two-year males (positive for Schmorl and PAS, minimally positive for Fontana-Masson and negative for Perls) were compatible with lipofuscin pigments. Minimal to slight colloid alteration of the thyroid gland was significantly ($p \leq 0.05$) increased in the 20, 200 and 800 ppm groups (63%, 62% and 63%, respectively) when compared to controls (55%). Colloid alteration of the thyroid gland was described as an irregular uniformity of the colloid with differences in staining and globule formation. The severity grade for colloid alteration was increased in the 200 and 800 ppm dose groups. Minimal to mark cystic hyperplasia of the thyroid gland was significantly ($p \leq 0.01$) increased in the 200 and 800 ppm groups (13% and 12%, respectively) when compared to controls (0%).

In the pancreas, the incidence of minimal to moderate acinar atrophy/fibrosis was significantly increased ($p \leq 0.01$) in the 200 and 800 ppm groups (63% and 67%, respectively), when compared to controls (35%). Pancreatic acinar atrophy/fibrosis generally is a focal or lobular atrophy (dedifferentiation of acinar cells and an increase in small duct-like structures), sometimes associated with a relative increase in interstitial collagen and a small number of inflammatory cells, but in the 200 and 800 ppm dose groups this lesion was more diffuse in distribution. In the skeletal muscle, the incidence of minimal to moderate atrophy was significantly increased in the 800 ppm group (49%) when compared to controls (32%).

The LOAEL is 20 ppm (0.79 mg/kg bw/day) in males, based on neovascularization and edema of the cornea and snow flake-like corneal opacity, unilateral or bilateral keratitis of the eye, decreased mean body weight and mean body weight gain, increased total cholesterol, higher ketone level and lower pH values, higher protein levels, increased kidney weight, kidney to body weight and kidney to brain weight ratios, chronic nephropathy and atrophy of the sciatic nerve. The NOAEL is 1 ppm (0.04 mg/kg bw/day).

There was a slight increase in neoplastic lesions; i.e., squamous cell carcinoma of the cornea in the 200 and 800 ppm groups (7% and 3%, respectively), when compared to controls (0%). This change was considered to be a result of the keratitis of the eye. Rats appear to be much more sensitive to tyrosinaemia than humans.

This chronic/carcinogenicity study in the rat is acceptable/guideline and satisfies the guideline requirement for a chronic/ carcinogenicity study [(OPPTS 870.4300); OECD 453] in rats when evaluated together with the associative study most recently completed in females (MRID 46695707).

870.4200b Carcinogenicity (feeding) - Mouse

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 46695706), AE 0172747 (95% w/w a.i.; Batch No. PFI 0195) was administered in the diet to C57BL/6 J@ Ico mice (50/sex/dose) at doses of 0, 30, 300, 1000, or 3000 ppm (equivalent to 0/0, 4/5, 43/54, 146/179, and 440/552 mg/kg/day in males/females) for up to 78 weeks. Additionally, 10 mice/sex/dose were treated similarly for up to 52 weeks.

No treatment-related effect was observed on mortality or ophthalmoscopic examination.

At 30 ppm (the lowest dose tested), there was evidence of toxicity in the gallbladder and liver in both sexes. The toxicity became more severe at higher doses. In all treatment groups at 12 months, incidences (n=10) of the following lesions were increased in the gallbladder and liver: (i) minimal to moderate gallstones in males and females (2-5 treated vs 1 control); (ii) minimal to marked gallstones in females (2-7 treated vs 0 controls); and (iii) minimal to moderate centrilobular to panlobular hepatocellular hypertrophy (diffuse) in females (5-10 treated vs 0 controls).

In all treatment groups at 18 months, gallbladder stones were observed in mice at necropsy in both sexes (18-36/50 treated vs 1/50 controls). Incidences of the following microscopic lesions were increased in all treatment groups in the gallbladder (# affected/50 treated vs # affected/50 controls, except n=49 in male controls and 1000 ppm females): (i) minimal to marked gallstones in both sexes (6-26 vs 0-1; $p<=0.001$); (ii) minimal to marked eosinophilic cytoplasmic alteration (focal/multifocal) in females (9-28 vs 2; $p<=0.05$); and (iii) minimal to moderate subepithelial mixed cell infiltrate (focal/multifocal) in females (15-29 vs 11; not statistically significant). Hepatotoxicity was indicated in all treatment groups by increased ($p<=0.01$) relative to body liver weights in both sexes (incr 6-26%); increased incidences of minimal to moderate centrilobular to panlobular hepatocellular hypertrophy (diffuse) in females (12-47/49-50 vs 0/50; $p<=0.001$); and macroscopic white foci in males (4-6/50 treated vs 1/50 control). An increased incidence of papillary mineralization was also observed in the kidneys of females at 18 months. Slight anemia was observed in all treated female groups at 18 months, as evidenced by decreases in hemoglobin concentration, hematocrit, and erythrocyte count.

At 300 ppm and above at 18 months, incidences of the following lesions were increased in the liver: minimal to moderate centrilobular to panlobular hepatocellular hypertrophy (diffuse) in the males; and minimal to slight hepatocellular degeneration (focal/multifocal) in females. Minimal to marked eosinophilic cytoplasmic alteration (focal/multifocal) in male gallbladders was considered equivocally treatment-related because the incidence and/or severity were not clearly related to dose.

At 1000 ppm and above, intense yellow colored urine was noted in males and females. This finding was first observed at the end of the third month of treatment at 3000 ppm and the fifth month at 1000 ppm. Once noted, this finding continued to be observed throughout treatment. Decreased food consumption in females was often observed beginning at Day 22. Food consumptions during the first 4-week period and the following 12-week period were reduced.

At 1000 ppm and above at 18 months, the incidences of the following lesions were increased in males: (i) minimal to marked epithelial hyperplasia (multifocal/diffuse) in the gallbladder; (ii) minimal to marked focal tubular degeneration (bilateral) in the testes; and (iii) minimal to slight interstitial cell hyperplasia (focal/multifocal) in testes. Increased incidences of dilatation of uterine horns were noted grossly at $\geq$1000 ppm.

At 3000 ppm, decreased body weights were observed sporadically in females throughout the treatment period and contributed to decreased bodyweight gain (Days 92-344) and overall (Days 1-540) body weight gain. After 18 months in the males, absolute and relative to body testicular weights were decreased. Increased incidences of the following gross lesions were noted: red foci in the male liver, prominent lobulation in the female liver, and renal pelvic dilatation in the females.

At 3000 ppm at 18 months, incidences of the following microscopic lesions were increased in the liver: (i) minimal to slight hepatocellular degeneration (focal/multifocal) in the males; (ii) minimal to slight hepatocellular vacuolation (diffuse) in the males; (iii) increased number of mitoses in the females; and (iv) minimal to moderate eosinophilic focus(i) of altered hepatocytes (focal/multifocal) in the females. Additionally, an increased incidence of minimal to moderate interstitial mixed cell infiltrate (focal/multifocal) in the liver in males was considered equivocal

because only minimal severity was observed at 3000 ppm and the incidence and severity were not clearly related to dose. Minimal to marked horn dilatation (diffuse) in the uterus at 3000 ppm was considered treatment-related.

The LOAEL is 30 ppm (equivalent to 4/5 mg/kg/day in males/females), based on gallstones, eosinophilic cytoplasmic alteration, subepithelial mixed cell infiltrate, and dilatation in/of the gallbladder; hepatocellular vacuolation, hepatocellular hypertrophy, and increased liver weight in males and females; and papillary mineralization of the kidney and changes in hematological parameters indicative of anemia in females. The NOAEL was not established.

At the doses tested, there was not a treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on toxicity noted in the gallbladder, liver, and testes, decreased body weight and body weight gain, and decreased food consumption.

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

A.3.6 Mutagenicity

Gene Mutation

870.5100, *In vitro* Bacterial Gene Mutation MRID 46695709 Acceptable/guideline	0, 5, 15, 50, 150, 500, 1500 and 5000 ug/plate in the presence and absence of mammalian metabolic activation in the range-finding assay (standard plate test) and concentrations of 0, 50, 150, 500, 1500 and 5000 ug/plate in the presence and absence of mammalian metabolic activation in the second assay (pre-incubation test). Negative for inducing gene mutations in *S. typhimurium* strains TA 1535, TA1537, TA1538, TA98 and TA100 up to 5000 µg/plate (limit concentration) in the absence and presence of metabolic activation.
Metabolites of Tembotrione	
870.5100, *In vitro* Bacterial Gene Mutation MRID 46695710 Acceptable/guideline	AE0456148 0, 16, 50, 158, 500, 1581 and 5000 µg/plate in the presence and absence of mammalian metabolic activation. Negative for inducing gene mutations in *S. typhimurium* strains TA 1535, TA1537, TA1538, TA98 and TA100 tested up to 5000 µg/plate (limit concentration) in the absence and presence of metabolic activation
870.5100, *In vitro* Bacterial Gene Mutation MRID 46695711 Acceptable/guideline	AE1417268 0, 16, 50, 158, 500, 1581 and 5000 µg/plate in the presence and absence of mammalian metabolic activation. Negative for inducing gene mutations in S. typhimurium strains TA 1535, TA1537, TA1538, TA98 and TA100 tested up to 5000 µg/plate (limit concentration) in the absence and presence of metabolic activation.
870.5100, *In vitro* Bacterial Gene Mutation MRID 46695712 Acceptable/guideline	AE1392936 0, 16, 50, 158, 500, 1581 and 5000 ug/plate in the presence and absence of mammalian metabolic activation. Negative for inducing gene mutations in S. typhimurium strains TA 1535, TA1537, TA1538, TA98 and TA100 tested up to 5000 µg/plate (limit concentration) in the absence and presence of metabolic activation.

Cytogenetics

870.5300, *In Vitro* Mammalian Cells in Culture Gene Mutation assay in Chinese Hamster V79 Cells (HPRT Locus Assay); MRID 46695713 Acceptable/guideline	0, 250, 500, 1000, 1400, 1500 and 1600 µg/mL, with and without metabolic activation. Negative for inducing gene mutations in *Chinese hamster V79 cells* in the absence and presence of metabolic activation tested up to cytotoxicity, 1600 ug/mL.
870.5375, *In vitro* Mammalian Cytogenetics Chromosomal Aberration Assay in Human Lymphocytes MRID 46695717 Unacceptable/Guideline	In the first assay, 0, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5 and 10 mM (equivalent to 0, 35.26, 70.53, 136.65, 278, 551, 1102, 2204 and 4408 ug/mL) with and without metabolic activation (S9). In a second assay, 0, 1.25, 2.5, 5, 7.5 and 10 mM (equivalent to 0, 551, 1102, 2204, 3306 and 4408 ug/mL) with and without metabolic activation. Equivocal because structural aberrations and polyploidy were observed in the absence of excessive cytotoxicity at 3306 ug/mL with metabolic activation. In the first test, up to the limit concentration (4408 ug/mL); no increases were seen; therefore, clastogenicity and polyploidy were not confirmed.
Metabolites of Tembotrione	
870.5300, *In Vitro* Mammalian Cells in Culture Gene Mutation assay in Chinese Hamster V79 Cells (HPRT Locus Assay); MRID 46695714 Acceptable/guideline	AE0456148 0, 55, 110, 220, 440, 880, 1760 and 3520 µg/mL with and without metabolic activation. Negative for inducing gene mutations in Chinese hamster V79 cells tested up to 3520 ug/mL (limit concentration) in the absence and presence of metabolic activation.
870.5300, *In Vitro* Mammalian Cells in Culture Gene Mutation assay in Mouse Lymphoma L5178Y Cells (MLA) (TK Locus Assay); MRID 46695715 Acceptable/guideline	AE1417268 0, 302, 614, 1075, 1844, 2534, and 3115 ug/mL for experiment 1 and 0, 235, 499, 1036, 1670, 2534; and 3023 ug/mL for experiment 2. Positive for inducing weak increases in the mutant colonies over background following 24 hours of exposure in the absence of S9 at high concentrations (2534 and 3023 ug/mL). There was no repeat testing for confirmation.
870.5300, *In Vitro* Mammalian Cells in Culture Gene Mutation assay in Chinese Hamster V79 Cells (HPRT Locus Assay); MRID 46695716 Acceptable/guideline	AE1392936 0, 45, 90, 180, 360, 720, and 1440 µg/mL with and without metabolic activation. Negative for inducing gene mutations in Chinese hamster V79 cells in the absence and presence of metabolic activation tested up to its limit of solubility, 1440 ug/mL.
870.5375, *In vitro* Mammalian Cytogenetics Chromosomal Aberration Assay in Human Lymphocytes MRID 46695718 acceptable/Guideline	AE0456148 0, 900, 1800 or 3600 µg/mL for four and 18 hours with and without metabolic activation (S9-mix). Negative for inducing chromosome structural aberrations and polyploidy in Chinese hamster V79 cells tested up to 3600 ug/mL (limit of solubility) in the absence and presence of metabolic activation.
870.5375, *In vitro* Mammalian Cytogenetics Chromosomal Aberration Assay in Human Lymphocytes MRID 46695719 acceptable/Guideline	AE1417268 0, 10, 50, 100, 250, 500, 1000, 2000, 2500, 3000, 3500, 4000 and 4724 ug/mL for three hours with and without metabolic activation Negative for inducing structural aberrations or polyploidy tested up to cytotoxic concentrations, 4724 ug/mL.

870.5375, *In vitro* Mammalian Cytogenetics Chromosomal Aberration Assay in Chinese Hamster V79 Cells MRID 46695720 acceptable/Guideline	AE1392936 0, 350, 700, and 1400 ug/mL for 4 hours with and without metabolic activation. Negative for inducing chromosome structural aberrations or polyploidy up to cytotoxic concentrations up to the solubility limit.

Other Genotoxicity

870.5395, *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus assay in mice MRID 46695721 Acceptable/guideline	500, 1000 and 2000 mg/kg body weight Negative for the increase in frequency of micronucleated immature erythrocytes in mouse bone marrow tested up to 2000 mg/kg (limit dose).
870.5550, Unscheduled DNA Synthesis in Primary Rat Hepatocytes/Mammalian Cell Cultures MRID 46695722 Acceptable/Guideline	1,000 or 2,000 mg/kg body Negative for inducing unscheduled DNA synthesis in Wistar rat primary hepatocytes tested up to 2000 mg/kg (limit dose).

A.3.7 Neurotoxicity

870.6100 Delayed Neurotoxicity Study - Hen

870.6200 Acute Neurotoxicity Screening Battery

EXECUTIVE SUMMARY: In an acute neurotoxicity study (MRID 46695723), groups of non-fasted, young-adult Wistar rats (12/sex/dose) were given a single oral (gavage; 10 mL/kg) dose of AE 0172747 (94% a.i., Batch No. PFI 0215) in aqueous 0.5% methyl cellulose/0.4% Tween 80 at doses of 0, 200, 500 or 2000 mg/kg (limit dose) and observed for 14 days. A functional observational battery (FOB) and motor activity testing were performed on all animals during pre-exposure, Day 0 (at 3 hours post-dosing, the estimated time-of-peak effect), and Days 7 and 14. At study termination, 6 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. The brain and peripheral nervous system tissues collected from the perfused animals in the control and 2000 mg/kg groups were subjected to histopathological evaluation. Positive control data were not provided; however, data previously reviewed by the Agency have been included in this DER.

No compound-related effects on mortality, body weight, body-weight gain, brain weight, gross pathology, or neuropathology were observed at any dose in either sex.

At 200 mg/kg and above, the following treatment-related effect was noted: FOB effect on Day 0, decreased arousal in the open-field in the males (2-7).

At 500 mg/kg and above, the following treatment-related effects were noted: (i) increased incidence (# affected/12 vs. 0/12 controls) of urine stain at 500 mg/kg (2 females) and 2000 mg/kg (8 of each sex), and red nasal stain at 500 mg/kg (1 of each sex) and 2000 mg/kg (4 males); (ii) FOB effects on Day 0 at 500 mg/kg included, decreased ($p<=0.05$) body temperature

(°C) in the females (37.4 treated vs. 38.1 controls); and (iii) on Day 0, decreased (p<=0.05) total session motor activity in the males (decr 41-70%) and females (decr 27-66%) and total session locomotor activity in the males (decr 42-71%) and females (decr 29-76%).

Additional FOB effects on Day 0 noted at 2000 mg/kg included: (i) decreased arousal in the open-field in the females (7/12 treated vs. 0 controls); (ii) decreased number of rears in the males (0.6 treated vs. 2.2 controls) and females (2.3 treated vs. 6.6 controls, p<=0.05); (iii) decreased (p<=0.05) body temperature (°C) in the males (36.8 treated vs. 37.2 controls) and females (36.7 treated vs. 38.1 controls); and (iv) decreased (p<=0.05) approach response (no reaction) in the males (6/12 treated vs. 0 controls).

All clinical signs of toxicity were initially observed on Days 0-3 and were resolved by Day 8, and all FOB parameters and motor activity were similar to controls on Days 7 and 14.

The LOAEL is 200 mg/kg in males based on FOB effects, decreased arousal in the open-field on Day 0. The NOAEL in males was not identified. The LOAEL is 500 mg/kg in females based on urine staining, red nasal discharge, and on FOB effects decreased body temperature on Day 0, and decreased motor and locomotor activity on Day 0. The NOAEL in females is 200 mg/kg.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (870.6200; OECD 424) for an acute neurotoxicity study in rats.

870.6200 Subchronic Neurotoxicity Screening Battery

EXECUTIVE SUMMARY: In a subchronic neurotoxicity study (MRID 46695724), AE 0172747 (94% a.i., Batch No. PFI 0215) was administered in the diet to 12 young-adult Wistar rats/sex/group at dose levels of 0, 20, 250, or 2500 ppm (equivalent to 0/0, 1.33/1.75, 16.4/21.0, and 160/224 mg/kg bw/day [M/F], respectively) for 13 weeks. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in 12 rats/sex/group at pre-dosing and Weeks 2, 4, 8, and 13. At study termination, 6 rats/sex/group were anesthetized and perfused *in situ* for neuropathological examination. The tissues from the perfused animals in the control and 2500 ppm groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Positive control data were not provided; however, data previously reviewed by the Agency have been included in this DER.

No compound-related effects were observed in mortality, clinical signs of toxicity, ophthalmoscopic effects, FOB, motor activity, brain weights, or gross or neuropathology.

At 2500 ppm, slight decreases (3-8%; not statistically significant) in body weight were noted in both sexes throughout the study, and overall (Days 0-91) body-weight gain (calculated by the reviewers) was decreased by 18-19% in the both sexes compared to controls.

No treatment-related effects were observed at 250 ppm or lower in either sex.

No neurological effects were observed at any dose in either sex.

The LOAEL is 2500 ppm (equivalent to 160/224 mg/kg bw/day [M/F]) based on decreased body weight and body-weight gain in both sexes. The NOAEL is 250 ppm (equivalent to 16.4/21.0 mg/kg bw/day [M/F]).

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

870.6300 Developmental Neurotoxicity Study

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRID 46695725) technical grade AE 0172747 (94% a.i., Batch #s PFI 0215 and OP2250027) was administered to approximately 30 mated female Wistar rats per dose in the diet at nominal dose levels (gestation) of 0, 10, 200, or 1500 ppm from gestation day (GD) 6 through lactation day (LD) 21. Doses were adjusted during lactation to achieve a more consistent dosage throughout exposure. The mean daily intake during gestation and lactation was 0, 0.8, 16.3, and 118 mg/kg/day. Dams were allowed to deliver naturally and were killed on LD 21, following weaning of their respective litters. Any females that were found to be sperm positive and/or with a vaginal plug, but did not deliver, were sacrificed on GD 24; eight treated dams were examined for pregnancy status. On postnatal day (PND) 4, litters were standardized to 8 pups/litter; the remaining offspring and dams were sacrificed and discarded without further examinations. Subsequently, 1 pup/litter/group (at least 10 pups/sex/dose when available) was allocated to subsets for FOB, motor activity, acoustic startle response, learning and memory evaluation, and neuropathological examination.

No treatment-related effects were observed on mortality or reproductive parameters or at necropsy in dams. At ≥16.3 mg/kg/day, corneal opacity was observed during lactation in dams both upon clinical examination and during the FOB. Body weight in dams was decreased by 5-7% during gestation and by 3-5% during lactation at ≥16.3 mg/kg/day. Overall body-weight gain in dams was decreased by 13-17% during gestation at ≥16.3 mg/kg/day. Overall body-weight gain during lactation was similar to controls at all doses. During gestation, no treatment-related differences in food consumption were observed. During lactation, food consumption in dams was decreased by 8-12% for part (≥16.3 mg/kg/day) or all (118 mg/kg/day) of the pre-weaning period.

The maternal LOAEL is 16.3 mg/kg/day, based on corneal opacity during lactation. The maternal NOAEL is 0.8 mg/kg/day.

In pups, no compound-related effects were observed on litter parameters (including litter size), vaginal patency, motor or locomotor activity, and learning and memory assessments. In addition, no clinical signs of toxicity were observed during pre-weaning at any dose. During post-weaning, increased incidences of corneal opacity were observed in pups at ≥16.3 mg/kg/day at the time of clinical observations and during the FOB. Offspring pre-weaning body weights were decreased by 7-14% at ≥16.3 mg/kg/day for most days of lactation. Body-weight gains were also decreased by 8-32% at ≥16.3 mg/kg/day throughout most pre-weaning intervals. Offspring post-weaning body weights remained decreased by 5-16% in both sexes throughout the study at ≥16.3 mg/kg/day. Decreases (5-6%) in post-weaning body weight in the 0.8 mg/kg/day males were also considered treatment-related since they were observed many weeks

after treatment was discontinued and therefore appeared to be delayed-onset effects. Preputial separation was delayed by 2.1 days in the 118 mg/kg/day males.

On PND 60, overall acoustic startle peak amplitude was decreased in males by 40-50% at ≥16.3 mg/kg/day. In addition, in males on PND 60, the interval peak amplitude values were decreased by 40-50% during most or all blocks at ≥16.3 mg/kg/day. At 0.8 mg/kg/day, mean peak amplitude was decreased by 38% ($p<0.05$) during block 2 only. PND 21 absolute brain weights were decreased in males by 6-9% at ≥16.3 mg/kg/day and in females by 6% at 118 mg/kg/day; terminal body weight was also decreased in both sexes. PND 75 absolute brain weights were decreased in both sexes by 6-7% at 118 mg/kg/day either with (males) or without (females) corresponding reductions in terminal body weights. Changes were observed in several morphometric parameters in adult animals at ≥0.8 mg/kg/day; however, statistical analysis of brain morphometry data for PND 21 and 70 males and females was inappropriate. Measurements at each dose level were compared separately to those in controls (i.e., 2-group comparisons) using individual t-tests. More appropriate is the use of Dunnett's test (as used for brain weights) for group comparisons against a single control.

The offspring LOAEL is 0.8 mg/kg/day, based on decreased post-weaning body weight (males), decreased acoustic startle response on PND 60 (males), and brain morphometric changes on PND 75 (males and females). The offspring NOAEL was not determined.

This study is classified **Acceptable/non-guideline** and may be used for regulatory purposes. It does not, however, satisfy the guideline requirement for a developmental neurotoxicity study in rats [OPPTS 870.6300, §83-6; OECD 426 (draft)] due to the pending review of the positive control data.

A.3.8 Metabolism

870.7485 Metabolism - Rat

EXECUTIVE SUMMARY: In a series of metabolism studies (MRIDs 46695726, 46695727, 46695728, and 46695729), [phenyl-U-^{14}C]-AE 0172747 (Batch # Z 31053-4; radiochemical purity 99.5%) or [cyclohexyl-UL-^{14}C]-AE 0172747 (Batch #s BECH 1517 or BECH 1523; radiochemical purity >98%) in PEG 200 was administered by oral gavage to groups of four Wistar rats/sex/dose at doses of 5 or 1000 mg/kg. The concentration time-courses of radioactivity in blood and plasma were calculated, the concentrations of radioactivity in tissues and excreta were determined, and metabolites were identified and quantified in the urine and feces.

The test compound was absorbed rapidly, as radioactivity was detected in the blood and plasma of all animals at the first time point measured (30 min post-dosing) for both radiolabeled forms. Males had higher mean blood and plasma maximum concentrations (C_{max}) than females. Also, males displayed higher AUC values than females in both blood and plasma at both doses. In both sexes, the AUC for both blood and plasma indicated a disproportionally higher mean systemic exposure at 1000 mg/kg than at 5 mg/kg (>200-fold) that was apparently due to a saturation of the initial elimination/biotransformation processes, resulting in a slower initial

elimination phase. Other blood and plasma parameters were generally similar across doses and radiolabeled forms.

In the 5 mg/kg animals dosed with either radiolabeled form, the liver and kidneys contained the highest mean levels of radioactivity. No other tissue exceeded 0.12% of the administered dose. In the 1000 mg/kg animals dosed with [phenyl-U-^{14}C]-AE 0172747, the skin/fur and carcass contained the highest mean levels of radioactivity. No other tissue exceeded 0.06% of the administered dose.

In the 5 mg/kg [phenyl-U-^{14}C] males, the highest concentrations of radioactivity were detected in the, liver, kidneys, skin, and carcass. In the 5 mg/kg [phenyl-U-^{14}C] females and [cyclohexyl-UL-^{14}C] males and females, the highest concentrations of radioactivity were detected in the liver, kidneys, skin, and carcass. In the 1000 mg/kg [phenyl-U-^{14}C] males and females, the highest concentrations of radioactivity were detected in the skin, liver, kidneys, stomach (and contents), and carcass and there was no evidence of bioaccumulation.

Total recoveries ranged from 96.3-102.7% of the administered doses, with no differences observed between dose levels or position of the radiolabel. Substantial sex differences were observed in the routes of excretion. At 5 mg/kg, the majority of the radioactivity was recovered in the feces of the males, while in the females, the majority of the radioactivity was recovered in the urine. At this dose, the majority of the radioactivity in the urine was recovered during the first 6 h, while the majority of radioactivity in the feces was recovered during the first 24 h.

Tissues and cage wash each accounted for <5.1%. Sex differences in the routes of excretion were also observed in the 1000 mg/kg group. In the males, approximately equal proportions of radioactivity were recovered in the feces and urine, while in the females, the majority of the radioactivity was recovered in the urine. At this dose, the majority of the radioactivity in the urine was recovered during the first 24 h, while the majority of radioactivity in the feces was recovered during the first 48 h. Tissues and cage wash each accounted for <10.1%.

The test compound was extensively metabolized. The majority of radioactivity in urine and fecal extract samples was present as parent and up to eleven metabolites. Metabolic profiles were qualitatively similar for both radiolabeled forms; however, profiles for the high and low doses were dissimilar, and major differences were noted between sexes. The major route of metabolism was found to be hydroxylation (oxidative pathway) of the cyclohexyl ring of the molecule. In excreta, parent and identified compounds accounted for 68.1-93.2% of the administered dose, while unidentified metabolites accounted for 2.5-13.8% of the administered dose. The total administered dose accounted for in the excreta was 82.3-104.9%.

Parent compound accounted for 1.9-59.9% of the total radioactivity eliminated, and was found in greatest quantity in the urine of the females (44.1-59.4%). Low dose males eliminated small amounts of parent (1.9-3.0%), while high dose males eliminated moderate amounts (33.8%). The metabolite found in the greatest quantity at both doses was 4-hydroxy-AE 0172747, with low dose males eliminating more than low dose females. High dose males and females eliminated approximately equal amounts. The only other metabolite found at >5% of the administered dose was 5-hydroxy-AE 0172747. Males excreted greater quantities than females.

This metabolism study in the rat is classified **acceptable/guideline** and satisfies the guideline requirement for a Tier 1 metabolism study [OPPTS 870.7485, OECD 417] in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided.

870.7600 Dermal Absorption - Rat

EXECUTIVE SUMMARY: In an *in vivo* dermal penetration study (MRID 46695730), [phenyl-UL-^{14}C]-AE 0172747 (>98% radiochemical purity; batch # BECH 0857) in a suspension concentrate formulation containing 420 g/L AE 0172747 and 210 g/L Isoxadifen-ethyl was applied to four male Wistar (Rj:WI[IOPS HAN]) rats/group on 2 x 6 cm^2 skin areas at dose levels of 0, 6.6, 66, or 660 µg/cm^2. Exposure times were 0.5, 1, 2, 4, 10, and 24 h for each dose. At the end of each exposure period, the skin was swabbed, and urine, feces, treated skin, cardiac blood, kidneys, liver, brain, spleen, and residual carcass were collected and analyzed for radioactivity.

Recovery of the applied dose was 90.8-98.7% of the administered dose. The distribution profile of radioactivity was qualitatively similar between the dose groups. The majority of the administered dose was recovered from the skin swabs, accounting for 76-93% of the administered doses. A total of 76-94% of the applied doses was not absorbed. A general trend of increasing dermal absorption with increasing time was observed, and the amount of radioactivity found in the treated skin generally increased with decreasing dose level. Estimates of dermal absorption were based on the sum of the treated skin + the total directly absorbed (urine + feces + cage wash + carcass + brain + spleen + liver + kidneys + blood + non-treated skin + surrounding skin). Dermal absorption was 8.3-14.9% (low), 4.8-12.8% (intermediate), and 1.7-4.8% (high) of the applied doses. The amount of dermal absorption was not proportional to dose.

All treatments (dose levels applied) were for exposure periods for up to 24 h. The most conservative value for risk assessment is a dermal-absorption of 15% observed at the low dose (6.6 µg/cm^2) at 4 h after application. This value should be considered to protect commercial applicators.

This study is **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.7600; OECD none) for a dermal penetration study in rats.

A.3.9 Special/Other Studies

Effects on Blood Coagulation Parameters - rats; Non-guideline

EXECUTIVE SUMMARY: The purpose of this non-guideline study (MRID 46695731) was to investigate the potential effect of AE 0172747 with and without co-administration of vitamin K1 on blood coagulation in rats. Vitamin K1 is essential for the production of Prothrombin and Factors VII, IX, and X by the liver. In this study, AE 0172747 (95.4% a.i.; Batch # PFI 0254) in 0.5% aqueous methylcellulose was administered daily via oral gavage at a dose volume of 10 mL/kg to groups of eight male Wistar (Rj:WI(IOPS HAN) rats for three consecutive days. One

group was dosed with the test compound at 1000 mg/kg, while a second group was dosed at 1000 mg/kg and also was given daily 10 mg/kg doses of vitamin K1 by subcutaneous injection. A third group received vehicle only via daily gavage. On Day 4, the rats were killed and plasma fibrinogen, prothrombin time, activated partial thromboplastin time, and specific coagulation factor times of the extrinsic (Factors II, V, VII, and X) and intrinsic (Factors VIII, IX, XI, and XII) pathways were measured.

Systemic effects:

No effects of treatment were observed on mortality.

On Day 2, tilting head was observed in 2/8 rats in the 1000 mg/kg AE 0172747 group, and in 1/8 rats in the 1000 mg/kg AE 0172747 + vitamin K1 group. Additionally in the vitamin K1 group, another animal presented with piloerection and hunched posture on Day 2, and reduced motor activity, increased salivation, soiling around the mouth, and hunched posture on Day 3. Body-weight losses of 3 and 5 g were noted during treatment (Days 1-3) in the 1000 mg/kg AE 0172747 group and vitamin K1 group, respectively, while control rats gained 5 g during the same period. Food consumption was decreased by 26-42% in all treated rats during treatment. In the 1000 mg/kg AE 0172747 group, single or multiple red foci were observed in the following organs (# affected/8 treated) compared to 0 controls: stomach (6); lungs (3); testes (2); epididymides (2); prostate (1); and thymus (1). Additionally in this group, unilateral or bilateral dark red epididymides were noted in 5 animals. These changes were considered to be treatment-related hemorrhagic foci. These findings were not observed in the vitamin K1 group.

Coagulation effects:

The following parameters were increased ($p<=0.01$) in the 1000 mg/kg AE 0172747 treated group: (i) prothrombin time (incr. 971%); (ii) Factor II (incr. 322%); (iii) Factor VII (incr. 110%); (iv) Factor X (incr. 256%); (v) activated partial thromboplastin time (incr. 319%); and (vi) Factor IX (incr. 46%). These parameters were comparable to controls in the vitamin K1 group. These data indicate that the alterations in clotting parameters were mediated by effects on vitamin K1 clotting factors.

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

Non-guideline; Blood Tyrosine Levels – Rabbit

EXECUTIVE SUMMARY: This non-guideline study (MRID 46695732) was performed to evaluate the effects of AE 0172747 on blood tyrosine levels in pregnant rabbits following administration by gavage from GD 6-28. AE 0172747 has been shown to inhibit 4-hydroxyphenylpyruvate dioxygenase (HPPDase). HPPDase is involved in L-tyrosine catabolism, and inhibition of this enzyme leads to an increase in systemic L-tyrosine concentrations. In this study, AE 0172747 (95.0% a.i.; Batch # PFI 0195) in aqueous 0.5% methylcellulose was administered daily via oral gavage at a dose volume of 4 mL/kg to groups of 6 presumed pregnant New Zealand White (KBL [NZW]) rabbits/dose at dose levels of 0 or 10 mg/kg bw/day on gestation days (GD) 6-28. Clinical observations, body weights, and food consumption were recorded at regular intervals during treatment. Blood samples were taken

from each animal on GD 4, 10, 15, 22, and 29, and the levels of tyrosine were determined. All surviving does were killed on GD 29 for examination of their uterine contents.

Maternal toxicity: No treatment-related effects were observed on mortality, clinical signs of toxicity, body weights, body-weight gains, food consumption, or gross pathology.

Pre-treatment (GD 4) L-tyrosine levels were similar between the treated and control groups. Control group tyrosine levels also remained relatively constant throughout the study (GD 4-29). Animals treated with AE 0172747 displayed marked increases in blood tyrosine levels at all time points examined (39.33-98.93 mg/L) compared to controls (10.00-15.32 mg/L), and the changes in blood tyrosine levels relative to GD 4 were significantly ($p \leq 0.01$) higher than controls for all intervals measured during treatment.

Developmental toxicity: No effects of treatment were observed on numbers of litters, live fetuses, or complete litter resorptions.

This study in the rabbit is classified **acceptable/non-guideline**.

Inhibition of 4-Hydroxyphenylpyruvate Dioxygenase in Rats and *In Vitro*; Non-guideline

EXECUTIVE SUMMARY: In two non-guideline studies (MRIDs 46695733 and 46695734), the potential of AE 0172747 and three of its metabolites (AE 1417268, AE 0456148, and AE 1392936) to inhibit 4-hydroxyphenylpyruvate dioxygenase (HPPDase) *in vivo* in the rat was examined, and the levels of tyrosine and 4-hydroxyphenyl lactic acid (4-HPLA) in suspensions of immobilized hepatocytes from rat, dog, rabbit, mouse and human livers following exposure to AE 0172747 *in vitro* were measured. In the *in vivo* studies, AE 1417268 (Batch # 2003BRP003-284), AE 0456148 (Batch # OD05/01), AE 1392936 (Batch # LSMI 1-2-34), or AE 0172747 (Batch # PFI 0195) in PEG 400 was administered once via oral gavage at a dose volume of 5 mL/kg to groups of three male Wistar (OFA) rats at a dose level of 10 mg/kg. Plasma tyrosine concentrations were measured prior to dosing, and at 2, 4, 8, 24, 48, and 72 h post-dosing. The purpose of these studies was to evaluate the potential inhibition of HPPDase by AE 1417268, AE 0456148, and AE 1392936, and compare the results to those obtained with the parent compound. HPPDase is involved in L-tyrosine catabolism, and inhibition of this enzyme leads to an increase in systemic L-tyrosine concentrations. In the *in vitro* studies, AE 0172747 (94.7% a.i.; Batch # PFI 0254) was dissolved in dimethylsulfoxide (DMSO). Cytotoxicity assays were then performed on rat and mouse hepatocytes using 30, 60, or 120 µM AE 0172747 in a final concentration of 1% DMSO in the culture medium. Next, the test substance was added to cultures of immobilized rat, dog, rabbit, mouse, and human hepatocytes (Liverbeads™) to a final concentration of 120 µM in a final concentration of 1% DMSO in the culture medium, and incubated for 0, 2, or 4 h at 37ºC. The concentrations of tyrosine and 4-HPLA in the Liverbeads™ were then determined. The purpose of these studies was to rank the different species according to their ability to produce 4-HPLA. When HPPDase is inhibited, 4-HPLA is produced by an alternative pathway and helps limit systemic tyrosine increases.

***In vivo* studies (MRID 46695733):** AE 0172747 had a strong effect on plasma tyrosine levels, causing an approximately 20-fold increase at 24 h post-dosing. AE 1417286 caused a smaller 5-fold increase in plasma tyrosine levels that peaked at 8 h post-dosing. AE 0456148 and AE

1392936 had no effect on plasma tyrosine levels and were similar to the PEG 400-treated controls.

***In vitro* studies (MRID 46695734)**

Rat and mouse hepatocytes exposed to AE 0172747 showed no evidence of cytotoxicity at the highest concentration tested (120 µM). Therefore, 120 µM AE 0172747 was selected to inhibit HPPDase activity in the Liverbead™ assays. Mouse Liverbeads™ incubated for up to 4 hours decreased tyrosine levels compared to the levels at 0 h in both basal (↓22-34%) and L-tyrosine supplemented (↓9-22%) media. At 4 h, L-tyrosine levels in both basal and L-tyrosine supplemented media with AE 0172747 added were increased ($p<=0.05$) compared to basal and L-tyrosine supplemented media. In all other species (rat, dog, rabbit, and human), L-tyrosine levels were unchanged at all time points. 4-HPLA was not detected in basal medium at any time point in any species except the mouse. Mouse Liverbeads™ produced very low levels of 4-HPLA (0.10-0.12 µg/mg protein) at all time points that did not increase with incubation time. In basal medium with AE 0172747, 4-HPLA was detected at 2 and 4 h in human (0.20-0.38 µg/mg protein; $p<=0.05$) and mouse (0.42-0.65 µg/mg protein, $p<=0.05$) Liverbeads™, and the levels increased with time. 4-HPLA was not detected in rat, dog, or rabbit Liverbeads™ incubated in basal medium with AE 0172747. Similarly, 4-HPLA was not detected in L-tyrosine supplemented medium at any time point in any species except the mouse. Mouse Liverbeads™ produced low levels of 4-HPLA (0.12-0.27 µg/mg protein) at all time points that increased with incubation time. In L-tyrosine supplemented medium with AE 0172747, 4-HPLA was detected at 2 and 4 h in rabbit (0.19-0.32 µg/mg protein), human (0.40-0.84 µg/mg protein), and mouse (0.94-1.40 µg/mg protein) Liverbeads™, and the levels increased with time. 4-HPLA was also detected at 4 h in rat (0.18 µg/mg protein) and dog (0.15 µg/mg protein) Liverbeads™. Therefore, the ranking of species by their ability to produce 4-HPLA after inhibition of HPPDase is (from most to least produced): mouse, human, rabbit, rat, and dog.

In summary, AE 1417268 has an inhibitory effect on HPPDase activity *in vivo*, but much lower than that observed with AE 0172747, while AE 0456148 and AE 1392936 had no inhibitory effect on HPPDase activity. Human and mouse hepatocytes produced more 4-HPLA *in vitro* than rabbit, dog, or rat hepatocytes under all experimental conditions. Thus, human and mouse hepatocytes were able to use an alternative pathway for tyrosine catabolism when HPPDase was inhibited. Rabbit, dog, and rat were much less efficient under both normal and extreme conditions.

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

Tyrosinemia Tissue Effects – Rat; Nonguideline

EXECUTIVE SUMMARY: In a subchronic toxicity study (MRID 47044502), two groups of five male and five female Wistar rats (Groups 1 and 3) were fed basal diet while two groups of five male and five female Wistar rats (Groups 2 and 4) were fed diets supplemented with 20,000 ppm (2%) L-tyrosine (Lot No. 114K0375, purity 98.9%) for 28 days. (The tyrosine supplementation was approximately three to five times the normal dietary intake.) Rats in Groups 3 and 4 received 10 µg/kg bw/day 2-(2-nitro-4-trifluoromethyl-benzoyl)-1,3-cyclohexanedione (NTBC), an inhibitor of 4-hydroxyphenylpyruvate dioxygenase, daily by gavage. The study was done to

determine the effects of increased plasma tyrosine concentration to the eye, kidney, liver, pancreas, and thyroid of rats

No toxicologically significant effects on body weight or food intake were noted. All male and 1/5 female rats in Group 4 (2% dietary tyrosine + 10 µg/kg bw/day NTBC by gavage) developed white areas on the eye beginning on Day 24 through the end of the study. In addition, the eyes of 4/5 Group 4 male rats were half-closed beginning on Day 22 through the remainder of the study.

The average plasma tyrosine concentration of Group 4 male and female rats increased with time from approximately three to five fold on Day 2 to a 24-fold increase in males and 18-fold increase in females by Day 21. Treatment with 10 µg/kg bw/day NTBC alone had little effect on plasma tyrosine in male and female rats until Day 29/30 when it was increased 3-fold and 5.8-fold in males and females, respectively. After an overnight fast, plasma tyrosine was increased in NTBC-treated rats 18-fold in males and 27-fold in females. Treatment with 2% dietary tyrosine alone induced a < 5-fold increase of plasma tyrosine in male and female rats that decreased with fasting.

There were no effects on the absolute or relative liver, brain, kidney, or thyroid weights of tyrosine-, NTBC, or tyrosine/NTBC-treated rats. Macroscopically, minimal to slight bilateral ocular opacity was observed in all male and 1/5 female rats treated with tyrosine/NTBC and microscopically, treatment-related effects were found in the eye, pancreas, and thyroid. Bilateral keratitis was observed in the eyes of all males and one female and diffuse interstitial mixed cell inflammation was noted in the pancreas of two males and one female rat treated with tyrosine/ NTBC. The pancreatic changes were associated with an increased incidence of focal/multifocal acinar degeneration and apoptosis. Minimal to slight thyroid colloid alteration was noted in 3/5 Group 4 male rats. No treatment-related effects, to the eye, pancreas, or thyroid, were noted in rats treated only with tyrosine or NTBC.

This study demonstrated a prolonged threshold tyrosine concentration exists in rats, above which macroscopic and/or microscopic effects occur to the eye, pancreas, and thyroid. These effects occurred when rats were fed diets containing three to five times the normal dietary intake of tyrosine while one of the tyrosine catabolizing enzymes was inhibited.

This subchronic study in the rat is Acceptable/Nonguideline. The relevance of the study to the chemical tembotrione was not explained.

Prenatal Developmental Toxicity Study - Rat

EXECUTIVE SUMMARY: In a non-guideline developmental toxicity study (MRID 47044503), L-tyrosine (>99% a.i., Batch nos. 111K0888 and 078H06822) was administered in feed at dietary concentrations of 0 or 20,000 ppm (equivalent to 0 or 1404-1461 mg/kg bw/day) on gestation days (GD) 6-21, and NTBC (99.7% a.i., batch #MKH13222-3-2) was administered by gavage in demineralized water at dose levels of 0 or 10 ug/kg bw/day on GD 6-20. Four groups of 23 mated female Sprague-Dawley [Crl:CD(SD)] rats were fed/dosed as follows: basal diet/demineralized water (controls); treated diet/demineralized water; basal diet/NTBC; and treated diet/NTBC. On GD 21, blood was drawn for plasma tyrosine measurement, and dams were sacrificed and necropsied. All live fetuses were weighed, sexed, and examined externally;

approximately one-half were subjected to skeletal evaluation, and visceral evaluations were not done. The objective of the study was to evaluate the developmental effects of an increased blood tyrosine level produced by the co-administration of increased dietary L-tyrosine and NTBC, an inhibitor of 4-hydroxyphenyl–pyruvate dioxygenase, a tyrosine catabolizing enzyme.

One female in the NTBC-only group was sacrificed on GD 13, following weight loss (21 g during GD 10-12), reduced motor activity and head tilt (both GD 12-13); no abnormal findings were noted at necropsy and a definitive relationship to treatment could not be established. Maternal toxicity was evident in the L-tyrosine/NTBC group as an increased incidence of corneal opacity at gross necropsy (4/23 dams vs. 0/23 controls). One animal in the NTBC-only group had treatment-related ocular effects noted during physical examination (a small right eye on GD 7-21 and a white area on the right eye on GD 14-21). There were no treatment-related effects on body weight, food consumption, or liver weight. On GD 21, mean plasma tyrosine concentrations of the control, L-tyrosine-only, NTBC– only, and combined L-tyrosine/NTBC groups were 46.04, 216.4, 388.6, and 2888 nmol/mL, respectively; thus, the mean plasma tyrosine levels of the L-tyrosine-only, NTBC-only, and L-tyrosine plus NTBC groups were increased 4.7-fold, 8.4-fold, and 62.7-fold, respectively, relative to controls.

Mean fetal weight was decreased in both sexes in the group treated with combined L-tyrosine/NTBC (-7%, $p<0.01$). There were no treatment-related effects on live litter size or postimplantation loss, including early/late resorptions or dead fetuses, or on fetal sex ratio. The litter incidence of unossified 7th cervical centrum was increased in all treated groups (control: 1/23, L-tyrosine: 6/22, NTBC: 6/20, L-tyrosine+NTBC: 19/23). In the L-tyrosine/NTBC-combined group, there was an increased litter incidence of extra ossification point(s) of the 14th thoracic vertebrae (11/23 vs. 2/23 controls), along with slightly increased litter incidences of unossified or incompletely ossified 3rd and/or 4th proximal phalanges of the forepaw, 5th metacarpal, 1st metatarsal, 5th sternebra, and the first 9 sacrocaudal vertebrae; these differences are consistent with delayed fetal ossification.

This study demonstrates that co-administration of dietary L-tyrosine at 20,000 (1461 mg/kg bw/day) on GD 6-21 with oral NTBC at 10 ug/kg bw/day on GD 6-20 results in altered fetal growth in Sprague-Dawley rats.

This developmental toxicity study in the rat is classified **Acceptable/Non-guideline**. The relevance of the study to the chemical tembotrione was not explained.

Tyrosinemia Tissue Effects – Rat; Nonguideline

EXECUTIVE SUMMARY: In a subchronic toxicity study (MRID 47044504), two groups of 10 male and 10 female Wistar rats (Groups 1 and 3) were fed basal diet while two groups of 10 male and 10 female Wistar rats (Groups 2 and 4) were fed diets supplemented with 20,000 ppm (2%) L-tyrosine (Lot/batch No. 078H06822 and 123K0376; purity >99%) for 28 days. (Tyrosine supplementation was approximately three to five times the normal dietary intake.) Rats in Groups 3 and 4 received 10 µg/kg bw/day 2-(2-nitro-4-trifluoromethyl-benzoyl)-1,3-cyclohexanedione (NTBC), an inhibitor of 4-hydroxyphenylpyruvate dioxygenase, daily by gavage. The study was done to determine the effects of increased plasma tyrosine to the eye, kidney, liver, pancreas, and thyroid of rats.

One Group 3 female rat died during the study, but its death was unrelated to treatment. No treatment-related effects were noted on body weight, body weight gain, or food consumption. Nine of ten male and 3/10 female rats in Group 4 (2% tyrosine + 10 µg/kg bw/day NTBC) developed white areas on the eye between Days 23-26 on one or more occasions. Following opthalmoscopic examination prior to sacrifice, 9/10 male rats in Group 4 had developed corneal edema and all male and 3/10 female rats had developed "snow flake" corneal opacities. In addition, three Group 4 male rats had developed congestive iritis. None of the male and female rats in Group 2 (2% tyrosine) or Group 3 (10 µg/kg bw/day NTBC) developed ocular abnormalities.

The average plasma tyrosine concentration of Group 3 and Group 4 male and female rats was markedly increased 18-23 fold on the day of sacrifice, while plasma tyrosine was unaffected by treatment in Group 2 rats.

Although the liver to body weight ratio of male and female rats in Group 4 was statistically increased, no histological correlates were found. No other treatment-related effects were noted on organ weight. Microscopic treatment-related effects were found in the pancreas, thyroid, and eyes of Group 4 rats. The incidences of focal/multifocal acinar atrophy/ fibrosis and/or acinar degeneration/apoptosis, as well as the incidence of focal/multifocal or diffuse inflammation were increased in the pancreas of Group 4 male and female rats. In the thyroid, an increased incidence of colloid alteration was found in male, but not female rats of Group 4 rats. In the eye, the incidence of unilateral and bilateral keratitis was markedly increased in male rats while minimal keratitis was found in 1/10 Group 4 female rats. No treatment-related effects were noted in male or female Group 2 and Group 3 rats.

This study suggests that male rats are more sensitive to treatment with 2% tyrosine + 10 µg/kg bw/day NTBC than female rats and that the eye and thyroid are target organs for toxicity.

This subchronic study in the rat is **Acceptable/Nonguideline**. The relevance of the study to the chemical tembotrione was not explained.

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Appendix B: Metabolism Assessment

B.1 Metabolism Guidance and Considerations

Table B.2. Tabular Summary of Metabolites and Degradates

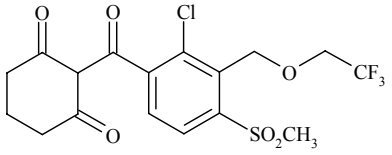
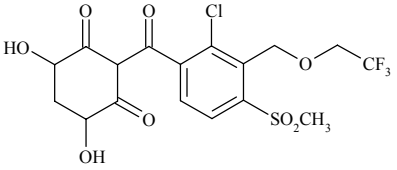
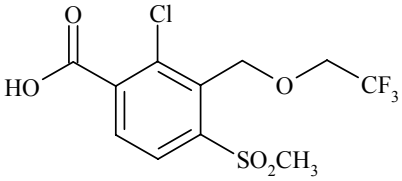
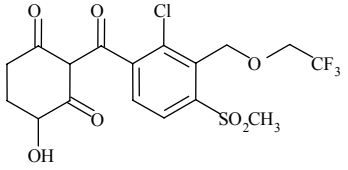
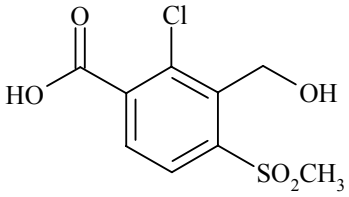
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM)[1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
Tembotrione (2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione)	Corn	-	-	
	Rotational Crops	-	-	
	Ruminant	Kidney, Liver		
	Poultry	Tissues, Eggs		
	Rat	Excreta		
	Water	yes		
M5 (2-[2-Chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione)	Corn		Forage, Stover, Grain	
	Rotational Crops			
	Ruminant	-	-	
	Poultry	-	-	
	Rat	-	-	
	Water	-	-	
M6 (2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy) methyl]benzoic acid)	Corn	Forage, Stover, Grain		
	Rotational Crops	Swiss chard, Turnip tops & roots; Wheat forage, hay, straw, & grain		
	Ruminant	-	-	
	Poultry	-	-	
	Rat		Excreta	
	Water	maximum 96%		
M10 2-[2-Chloro-4-(methylsulfonyl)-3-[((2,2,2-trifluoroethoxy)methyl]benzoyl]-4-hydroxy-1,3-cyclohexanedione	Corn	Immature Plants		
	Rotational Crops	-	-	
	Ruminant	-	-	
	Poultry	-	-	
	Rat	Excreta		
	Water	-	-	

Table B.2.	**Tabular Summary of Metabolites and Degradates**			
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM)[1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
M2 (2-Chloro-3-hydroxymethyl-4-mesyl-benzoic acid)	Corn	Forage, Stover	Grain	
	Rotational Crops	Wheat forage, hay, straw, & grain	Turnip roots	
	Ruminant	-		
	Poultry	-	-	
	Rat	-	-	
	Water	maximum 17%		

Corn (phenyl-label), 46695530; 0.181 lb ai/A; 1.1X rate; growth stage BBCH 12-14; 84 days (forage); and maturity, 124 days (stover and grain).
Cow (PH label); 46695532; 8.01 ppm; 6.8X MTDB; 7 days; 23 hour PSI
Hen (PH label); 46695534; 11.33 ppm; 470X MTDB; 14 days; 24 hour PSI
Rotational Crops; 46695612; Swiss chard, turnips, and spring wheat; 1.2X, applied to bare soil;90-day PBI
Rat Metabolism; 5 or 1000 mg gavage dose; Wistar, 168-hour depuration.

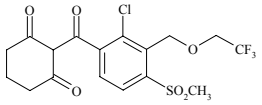
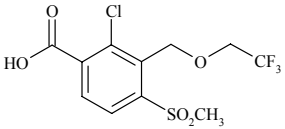
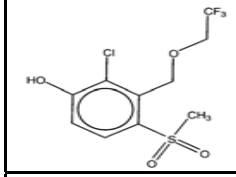
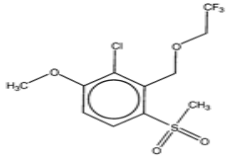
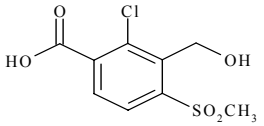
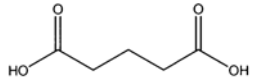
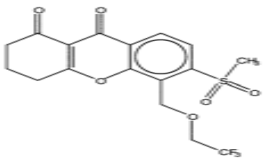
Table B.3. Environmental Fate Summary for Tembotrione.							
Degradate Name	**% Applied Dose or $T_{1/2}$**						
	Aerobic Soil Metabolism	**Anaerobic Soil Metabolism**	**Field Dissipation**	**Aerobic Aquatic Metabolism**	**Anaerobic Aquatic Metabolism**	**Photolysis**	**Hydrolysis**
Parent 	$T_{1/2}$ = 10.5 days	$T_{1/2}$ = 257 days	$T_{1/2}$ = 5.9 days (CA)	$T_{1/2}$ = 62.4 days	$T_{1/2}$ = 448 days	Aqueous: stable	stable @ pH 5, 7, and 9 at 25 ºC for 30 days
	$T_{1/2}$ = 72-131 days (NC)					Soil: $T_{1/2}$ = 29-32 d	
AE 0456148 (M6) 	72.4% @ 14 days	41.6% @ 120 days	maximum of 36.1% (CA)	95.2% @ 141 days	maximum of 2.4%		
	maximum of 25.8% days (NC)					Soil: 22.0% @ 9 days	
AE 0968400 	14.4% @ 35 days			maximum 4.4%			
	maximum 6.1% (NC)						
AE 1124336 	maximum 2.6%						
	maximum 0.8% (NC)						
AE 1392936 (M2) 							
	maximum of 17.1% (NC)						
AE 1392936 (glutaric acid) 						Aqueous: 6.8% @ 10 days	
						Soil: 13.8% @ 3 day	
AE 0941989						Soil: 17.9% @ 1 day; 15.3% @ 3 days	

Table B.3. Environmental Fate Summary for Tembotrione.							
Degradate Name 	**% Applied Dose or $T_{1/2}$**						
	Aerobic Soil Metabolism	**Anaerobic Soil Metabolism**	**Field Dissipation**	**Aerobic Aquatic Metabolism**	**Anaerobic Aquatic Metabolism**	**Photolysis**	**Hydrolysis**
Study MRID No.	46695414 46695416	46695420	46695425	46695422	46695423	Aqueous: 46695411 Soil: 46695412, 46695413	46695410

Appendix C: Tolerance Reassessment Summary and Table

Table C.1. Tolerance Summary for Tembotrione.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Corn Commodities			
Field Corn, grain	0.01	0.02	*Corn, field, grain*
Field Corn, forage	0.6	0.60	*Corn, field, forage*
Field Corn, stover	0.7	0.45	*Corn, field, stover*
Sweet Corn, K + CWHR	0.03	0.04	*Corn, sweet, kernel plus cob with husks removed*
Sweet Corn, forage	1.0	1.0	*Corn, sweet, forage*
Sweet Corn, stover	1.5	1.2	*Corn, sweet, stover*
Popcorn, grain	0.01	0.02	*Corn, pop, grain*
Popcorn, stover	0.20	0.35	*Corn, pop, stover*
Livestock Commodities			
Cattle Liver	0.5	0.40	*Cattle, liver*
Cattle Kidney	0.07	0.07	*Cattle, meat byproducts, except liver*
Goat Liver	0.5	0.40	*Goat, liver*
Goat Kidney	0.07	0.07	*Goat, meat byproducts, except liver*
Hog Liver	0.5	Not required	Based on the TCs for livestock tissues and relatively low dietary burdens for swine of 0.024 ppm for tembotrione and 0.006 ppm for metabolite M5, tolerances for hogs are not needed.
Hog Kidney	0.07	Not required	
Sheep Kidney	0.07	0.07	*Sheep, meat byproducts, except liver*
Sheep, meat by products	0.5	0.40	*Sheep, liver*
Horse Kidney	0.07	0.07	*Horse, meat byproducts, except liver*
Horse, meat by products	0.5	0.40	*Horse, liver*
Additional Livestock Commodity Tolerance That Needs to be Established			
Poultry, liver	None	0.07	