Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note REG2005-02

Mesotrione

Callisto 480SC Herbicide

The active ingredient Mesotrione Technical Herbicide, the associated manufacturing-use product Mesotrione Wet Paste Herbicide and the associated end-use product (EP) Callisto 480SC Herbicide containing mesotrione (guarantee 480 g/L) for the control of specific annual broadleaf weeds in field corn, production seed corn and sweet corn have been granted temporary registration under the Pest Control Products Regulations.

This Regulatory Note provides a summary of data reviewed and the rationale for the regulatory decision for these products.

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has carried out an assessment of available information for the following products in accordance the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value of these products:

i) Mesotrione Technical Herbicide for use as a technical grade active ingredient (TGAI);
ii) Mesotrione Wet Paste Herbicide for use as a manufacturing concentrate; and
iii) Callisto 480SC Herbicide as a herbicide for pre-emergence use in field, seed and sweet corn as well as early postemergence use in field corn for control of specific annual broadleaf weeds.

The Agency has concluded that the uses have merit and value consistent with the Pest Control Products Regulations and do not entail an unacceptable risk of harm.

The Agency has determined that Mesotrione Technical Herbicide and Callisto 480SC Herbicide are eligible for temporary registration, subject to the provision of required data and label amendments. Mesotrione Wet Paste Herbicide is being granted a temporary registration until the terms and conditions of temporary registration are met for Mesotrione Technical Herbicide and Callisto 480SC Herbicide. There are no outstanding data requirements for Mesotrione Wet Paste Herbicide; however, registration of this product is contingent upon the fulfilment of outstanding data gaps for Mesotrione Technical Herbicide and Callisto 480SC Herbicide.

Syngenta will carry out additional toxicology, metabolism and value studies as a condition of temporary registration. Following the review of this information, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

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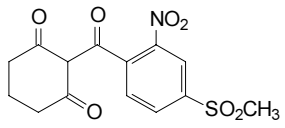
1.0 The Active Substances, its Properties and Uses

1.1 Identity of the Active Substance and Impurities (OECD 2.1.1)

Identification of the Technical Grade Active Ingredient

Active substance		Mesotrione
Function		Herbicide
Chemical name		
1.	International Union of Pure and Applied Chemistry	2-(4-mesyl-2-nitrobenzoyl)cyclohexane-1,3-dione
2.	Chemical Abstracts Service (CAS)	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
CAS number		104206-82-8
Molecular formula		$C_{14}H_{13}NO_7S$
Molecular weight		339.32
Structural formula		
Nominal purity of active		96.8% (nominal) (Limits: 93.9–99.7%)
Identity of relevant impurities of toxicological, environmental or other significance		The technical grade mesotrione does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances

1.2 Physical and Chemical Properties (OECD 2.1.2)

Table 1.2.1 Technical Product: Mesotrione Technical Herbicide

Property	Result	Comment
Colour and physical state	Light tan or sand opaques solid	
Odour	Slight odour, sweet	
Melting point or range	148.7–152.5°C with decomposition	
Boiling point or range	Not applicable.	
Density	1.46 g/mL at 20°C	
Vapour pressure	$< 5.7 \times 10^{-6}$ Pa at 20°C	Not volatile from water.
Henry's Law constant	$1/H = 1.9 \times 10^{10}$ $K = 1.27 \times 10^{-12}$ atm m^3/mole	Non-volatile from water and moist soil surface.
Ultraviolet (UV)–visible spectrum	λ(max) = 256 nm (in methanol) Not expected to absorb UV at $\lambda > 350$ nm.	Minimal phototransformation is expected in the natural environment.
Solubility in water at 20°C	**pH** — **Solubility (mg/L)** unbuffered — 160 4.8 — 2200 6.9 — 15 000 9 — 22 000	Very soluble in water. One of the indicators of high potential to leach.
Solubility in organic solvents	**Solvent** — **Solubility (mg/L)** methanol — 3.7×10^3 ethyl acetate — 1.7×10^3 toluene — 2.7×10^3 1,2-dichloroethane — 8.9×10^4 acetonitrile — 10.4×10^4 xylenes — 1.4×10^3 heptane — $< 0.3 \times 10^3$ acetone — 8.1×10^4	

Property	Result	Comment
n-octanol–water partition coefficient (K_{ow}) at 25°C	**pH** / **log K_{ow}** unbuffered / 0.11 5 / -1.0767 7 / < -1 9 / < -1	Low potential for bioaccumulation.
Dissociation constant (pK_a) at 25°C	pKa = 3.12 at 20°C	
Stability (temperature, metal)	Stable for 14 days at 54°C and is expected to be stable to sunlight, metal and metal ions.	

Table 1.2.2 Mesotrione Wet Paste and Callisto 480SC Herbicide

Property	Results	
	Mesotrione Wet Paste	**Callisto 480SC Herbicide**
Colour	Brown	Light brown
Odour	Odourless at 25°C	Weak, aromatic
Physical state	Solid at 25°C	Opaque liquid
Formulation type	Wet paste	Suspension Concentrate (SC)
Guarantee	79% (nominal) (limits: 74–84%)	480 g/L (limits: 466–494 g/L)
Formulants	Product does not contain any United States Environmental Protection Agency (USEPA) Inert List 1 or 2 formulants.	
Container material and description	Drums made of HDPE and bags made with a blend of polypropylene and polyethylene	Metal / HDPE plastic 1L, 10L, 12L, 55L, 110L, 150L and bulk.
Specific gravity	0.438 g/mL at 20°C	1.19 g/mL at 20°C
pH	3–5 (1% dispersion in water)	2.3–2.4 (neat solution) 3.3–3.4 (1% aqueous solution)
Oxidizing or reducing action	Product does not contain any oxidizing or reducing agents.	
Storage stability	The data provided in the storage stability study show that the product is stable for at least one year in their respective commercial packagings.	
Explodability	Product is not potentially explosive.	

1.3 Details of Uses and Further Information (OECD 2.1.3)

Mesotrione belongs to the triketone class of herbicides that inhibit the enzyme 4-hydroxyphenyl-pyruvate-dioxygenase (4-HPPD), an essential enzyme in the synthesis of carotenoids. Susceptible plants that do not rapidly detoxify the herbicide become chlorotic. This is followed by tissue necrosis and plant death. Mesotrione herbicide is formulated as a suspension in 1 EP, Callisto 480SC Herbicide, containing 480 g/L of active ingredient (a.i.).

Callisto 480 SC Herbicide is a selective herbicide for use in Eastern Canada in field, seed and sweet corn grown under conventional tillage systems at an application rate of 140 g a.i./ha to control lamb's-quarters, redroot pigweed, velvetleaf and wild mustard as well as to suppress common ragweed. In field corn, Callisto 480SC Herbicide is for use at either the pre-emergence or early postemergence (up to the crop and weed 2-leaf stage) timings; it is not for use in fields planted to hybrids with corn heat unit (CHU) ratings of 2500 or less, or those situated in geographic regions of 2500 or less average seasonal CHUs. In seed and sweet corn, Callisto 480SC Herbicide may only be applied at the pre-emergence timing. In field corn only, Callisto 480SC Herbicide may be applied in a tank mixture with Dual II Magnum (s-metolachlor), Primextra II Magnum (s-metolachlor and atrazine), or a combination of Dual II Magnum plus atrazine (as Aatrex Nine-O or Aatrex Liquid 480) at either the pre-emergence and early postemergence timings for broader spectrum weed control, including annual grasses. Callisto 480SC Herbicide may be applied a maximum of once per year by ground equipment only in a volume of 200 L water/ha.

Corn (field, silage, seed, sweet) may be planted as a salvage crop following application (in the case of crop failure). Winter wheat may be planted 4 months after application, and spring wheat may be planted 10 months after application.

2.0 Methods of Analysis (OECD 4)

2.1 Analytical Methods for Analysis of the Active Substance as Manufactured (OECD IIA4.2.1)

A reversed phase high performance liquid chromatography with fluorescence detection (HPLC/UV) method was provided for the determination of the active, mesotrione, in the technical product. Based on the validation data and the chromatograms provided, the method was assessed to be sufficiently specific, precise and accurate.

Table 2.1.1 Analytical Methods for Analysis of the Active Substance as Manufactured

Product	Analyte	Method Type	Linearity Range	Recovery (%) (n)	RSD (%) (n)	LOQ (%)	Method
Mesotrione Technical Herbicide	Mesotrione	HPLC/UV at 280 nm	0.5–1.6 mg/mL	Not required	0.6 (6)	Not required	Accepted
Mesotrione Technical Herbicide	Major impurities	HPLC/UV at 270 nm	0.04–2.0%	92–105 (3)	0.6 – <10 (6)	0.04	Accepted

2.2 Analytical Methods for Formulation Analysis (OECD IIIA5.2.1)

A reversed phase HPLC/UV method was provided for the determination of mesotrione present in Mesotrione Technical Wet Paste and in Callisto 480SC Herbicide. Based on the validation data and the chromatograms of the standard solution, formulation blank and formulation, the method was assessed to be specific, precise and accurate for use as an enforcement analytical method.

Table 2.2.1 Analytical Methods for Formulation Analysis

Product	Analyte	Method Type	Linearity Range	Recovery (%)	RSD (%)	Method
Mesotrione Technical Wet Paste	Mesotrione	HPLC/UV at 280 nm	0.02–0.07 mg/ml	83.8 (n = 6)	0.4	Accepted
Callisto 480SC Herbicide	Mesotrione	HPLC/UV at 280 nm	1.1–3.5 mg/mL	99.3–100.6	0.4	Accepted

2.3 Analytical Methods for Residue Analysis

2.3.1 Methods for Environmental Residue Analysis

Appendix I, Table 1 presents a summary table of methods for environmental residue analysis.

2.3.1.1 Analytical Methodology (parent compound and transformation products)—Soil (OECD IIA 4.4)

One liquid chromatographic method was submitted for the determination of residues of the parent compound, mesotrione, and its major transformation products, methylsulfonyl-2-nitrobenzoic acid (MNBA) and 2-amino-4-methylsulfonylbenzoic acid (AMBA), in

soil. Based on the validation data and the chromatograms provided, the methods were assessed to be sufficiently sensitive, precise, accurate and specific for the determination.

2.3.1.2 Analytical Methodology (parent compound and transformation products)—Sediment (OECD IIA 4.6)

The applicant has requested to extend the soil method to the sediment given that the metabolism studies show no new transformation products in sediment. As the aqueous extraction solvent is used for soil, it is expected to comparable extraction efficiencies for aqueous sediment, the request was accepted.

2.3.1.3 Analytical Methodology (parent compound and transformation products)—Water (OECD IIA 4.5)

One chromatographic method was provided for the determination of the parent compound in water. Based on the validation data and chromatograms provided, the method was assessed to be sufficiently sensitive, precise, accurate and specific for the determination.

2.3.1.4 Analytical Methodology (parent compound and transformation products)—Biota (OECD IIA 4.8)

In lieu of specific analytical methods for plant and animal matrices, the applicant provided a method for the determination of the residues of the parent compound and its metabolites, MNBA and AMBA, in corn silage and a method for the determination of the residues of the parent compound in ground beef. Based on the validation data provided, they were acceptable and were extended to the residue method for plant and animal matrices.

2.3.2 Multiresidue Methods for Residue Analysis

The behaviour of mesotrione through the multiresidue methods was evaluated using multiresidue protocols A through F of the United States Food and Drug Administration's (USFDA) *Pesticide Analytical Manual*, Volume 1, Third Edition (January 1994). Mesotrione was not evaluated through Protocols A and B because it does not possess an N-methylcarbamate structure (Protocol A), or a carboxylic acid or phenolic group (Protocol B). The results from Protocol C (gas chromatographic screening) indicated that mesotrione chromatographed poorly on DB-1, DB-17 and DB-225 megabore columns, had marginal response with an electron capture detector and had no response with nitrogen-phosphorous or flame-photometric detectors in sulfur mode. Furthermore, mesotrione was not recovered from Florisil with methylene chloride eluant or two mixed ether eluants during Protocol D (Florisil cleanup procedures) evaluation. Finally, mesotrione was not evaluated through protocols E (for non-fatty food) or F (for fatty food) because it was not recoverable from Florisil at a level above 30% in Protocol D. The multiresidue methods were shown to be unsuitable for the analysis of mesotrione. Therefore, the multiresidue methods are not applicable for enforcement purposes.

2.3.3 Methods for Residue Analysis of Plants and Plant Products

The residue of concern (ROC) for enforcement and risk assessment purposes was defined as mesotrione. Four analytical methods for the analysis of residues of both mesotrione and the metabolite MNBA in plant matrices were proposed. Although the ROC has been defined as mesotrione only, the applicant included MNBA when the methods were developed since, in the corn metabolism studies, MNBA was greater than 10% total radioactive residues (TRRs) in corn forage treated as a preplant application. It should be noted that for methods TMR 0643B and TMR 0882B, the UV detector response linearity was not demonstrated over the concentration range of interest. For future expansion of use, the applicant will have to provide the data to confirm the detector linearity of methods TMR 0643B and TMR 0882B.

Method TMR 0689B, a common moiety method for the analysis of the combined residues of mesotrione and the metabolite MNBA as isopropyl-MNBA in corn matrices, was used for data-gathering purposes. Briefly, residues were extracted with acetonitrile:water and partitioned into methylene chloride. Total MNBA residues (MNBA residues + mesotrione residues oxidized to MNBA) were extracted with ethyl acetate. Derivatization of the total MNBA residues was performed by heating the mixture with 2-iodopropane and potassium carbonate forming the isopropyl ester of MNBA. The quantitation of isopropyl-MNBA (combined residues of the parent compound, mesotrione, and MNBA) was achieved by gas chromatography using mass-selective detection (GC/MSD). Ion 246 m/z was used for detection and quantitation. The LOQ of Method TMR 0689B was reported as 0.01 ppm. The method was found to give excellent recoveries within the range of 70–120% for the analysis of all corn matrices. The coefficients of variation measured with respect to recoveries following spiking at 0.01 ppm (LOQ) and 0.10 ppm indicated the method has satisfactory repeatability. No independent laboratory validation (ILV) was performed. Method TMR 0689B is considered acceptable as a data-gathering method in corn matrices.

Methods TMR 0643B and TMR 0882B (a modified version of TMR 0643B), common moiety methods for the analysis of mesotrione and the metabolite MNBA, separately, in corn matrices, were used for data-gathering purposes. In contrast to Method TMR 0689B, the common moiety (AMBA conversion product) was formed as a result of postcolumn derivatization of individual fractions, enabling the quantitation of each analyte separately. Briefly, residues were extracted with acetonitrile:water and partitioned into ethyl acetate. The organic phases were collected, combined and concentrated under a stream of nitrogen. The residues were purified on a silica solid phase extraction (SPE) column. In Method TMR 0882B, the acetonitrile was evaporated, resulting in the elimination of the ethyl acetate partitioning and of the SPE cleanup steps. In both methods, the extracts were further cleaned up by reversed-phase HPLC. MNBA and mesotrione fractions were collected separately. Each fraction was evaporated to dryness. The first fraction collected contained MNBA residues that were reduced to AMBA. The second fraction collected contained mesotrione residues that were oxidized to MNBA. The MNBA formed from the oxidation of mesotrione was then further reduced to AMBA. Each fraction was

submitted to a postconversion cleanup step using a Bond Elut LRC C_{18} SPE column and each was quantitated for AMBA conversion product using reversed-phase HPLC (Phenomenex Prodigy C_{18} column) with fluorescence detector (HPLC/UV).

For Method TRM 0643B, the LOQ and limit of detection (LOD) in corn matrices were reported as 0.01 ppm and 0.002 ppm, respectively, for each analyte. Procedural recoveries were generally within the range of 70–120% except for mesotrione recoveries in corn fodder at the 0.10 ppm spiking level, which averaged to 67%. However, concurrent recoveries for mesotrione in corn fodder taken from field trials were within the acceptable range of 70–120% indicating acceptable accuracy and precision of the method. The coefficients of variation measured with respect to recoveries following spiking at 0.01 ppm (LOQ) and 0.10 ppm indicated the method has satisfactory repeatability. An interference study has been conducted for Method TMR 0643B and no interferences were observed (against 77 pesticides). Radiovalidation was performed, and the results showed adequate extraction efficiency of the aged bioincurred residues of mesotrione and the metabolite MNBA in corn matrices. The ILV did validate Method TMR 0643B for residues of mesotrione and MNBA in corn matrices, indicating good reproducibility. Method TMR 0643B is considered acceptable as a data-gathering method in corn matrices.

For Method TMR 0882B, the LOQ was reported as 0.01 ppm for each analyte. The LODs were reported as 0.004 ppm for mesotrione and as 0.002 ppm for MNBA in corn matrices. The method was found to give excellent recoveries within the range of 70–120% for the analysis of all corn matrices. The coefficients of variation measured with respect to recoveries following spiking at 0.01 ppm (LOQ) and 0.10 ppm indicated the method has satisfactory repeatability. The ILV did validate Method TMR 0882B for residues of mesotrione and MNBA in corn matrices, indicating good reproducibility. Method TMR 0882B is considered acceptable as a data-gathering method in corn matrices.

Method RAM 366/01, used for data-gathering and proposed as the enforcement method, determined residues of mesotrione and the metabolite MNBA separately in plant matrices. Briefly, residues were extracted with acetonitrile:ultra-pure water in the presence of sodium chloride, and the extract was diluted with 2.5% formic acid in water. The analytes were concentrated using an OASIS HLB SPE cartridge. To elute mesotrione and MNBA from the cartridge, a solution of methanol:formic acid was used. The eluate was evaporated to dryness under a stream of dry air and finally reconstituted in ultra-pure water and methanol. Quantification was achieved by high performance liquid chromatography with triple quadrupole mass spectrometric detection (HPLC/MS/MS). The mass spectrometer was monitoring for mass transition 244.0 → 142.0 for the metabolite MNBA and for mass transition 338.0 → 290.7 for mesotrione. The LOQ of the method was reported as 0.01 ppm for each analyte. The LOD was reported as 0.003 ppm for each analyte. The recoveries for mesotrione and MNBA residues in corn matrices were within 70–120% with acceptable coefficient of variation indicating adequate accuracy and precision in the range of spiking levels of 0.01 to 10 ppm for each analyte

and good reproducibility. An ILV was conducted to verify the reliability of Method RAM 366/01 for the determination of mesotrione and MNBA residues in corn matrices. The values obtained indicated that Method RAM 366/01 was reliable. The linearity of the detector was demonstrated within the range of 0.0008 to 0.12 µg/mL. Method RAM 366/01 is considered valid and can be used as the enforcement method in plant matrices.

2.3.4 Methods for Residue Analysis of Food of Animal Origin

For animal matrices, the ROC for enforcement and risk assessment purposes was defined as mesotrione. The petitioner has proposed two analytical methodologies for the analysis of mesotrione residues in animal matrices. During the validation of Method TMR 0739B ADD in beef liver, mesotrione residues were found to be unstable during the extraction procedure, with procedural recoveries ranging from 45% to 64% when extraction was delayed for an hour after the blending of the spiked samples (Time 1 hour). When extraction started immediately after spiking, the procedural recoveries ranged from 66% to 81% (Time 0). This instability was probably not enzymatic since cooling or even boiling the liver sample before the procedure in order to denaturate the enzymes did not improve the recoveries. The proposed enforcement method, Method TMR 0914B, used the same extraction procedure. Procedural recoveries in beef liver at Time 0 ranged from 69% to 84%. It should be noted that the applicant did not provide recoveries at Time 1 hour. Both analytical methods are considered unacceptable for the analysis of mesotrione residues in liver samples.

Method TMR 0914B has been proposed as the enforcement method in animal matrices. Briefly, mesotrione residues were extracted from milk and egg matrices with acetone and from animal tissues with acetone:water. An aliquot of the extract was diluted with acidified water and partitioned into methylene chloride. Mesotrione was oxidized to MNBA by heating the mixture in the presence of hydrogen peroxide. The resulting MNBA was then reduced to AMBA by heating and using a solution of stannous chloride ($SnCl_2$) in hydrochloric acid (HCl). Quantitation of AMBA conversion products was achieved by reversed-phase HPLC/UV. The LOQ was reported as 0.01 ppm.

Mean procedural recoveries for Method TMR 0914B for mesotrione were within the range of 70–120% for milk, eggs and ground beef. Mesotrione residues were found to be unstable in beef liver; procedural recoveries in beef liver ranged from 69% to 84% when extraction started immediately after spiking (Time 0). The coefficients of variation measured with respect to recoveries following spiking between 0.01 ppm and 1.00 ppm indicate the method has satisfactory repeatability. The method was successfully validated using ground beef and milk (it should be noted that liver was not used) by an independent laboratory, indicating good reproducibility. Method TMR 0914B is considered conditionally acceptable as an enforcement method in all animal matrices except liver pending the submission of the raw data illustrating the UV detector linearity over the concentration range of interest and the radiovalidation of the method using animal matrices (including the liver). Furthermore, a reliable and validated analytical method for

the analysis of mesotrione residues in liver samples is required, in which degradation of mesotrione residues is not observed.

Briefly, Method TMR 0739B ADD involved extracting milk and egg matrices with acetone and animal tissues with acetone:water. After centrifugation, an aliquot of the extract was taken, diluted with water (or 10% sodium sulfate for milk), acidified and partitioned into methylene chloride. Mesotrione was oxidized to MNBA by heating the mixture with Jones Reagent (concentrated sulfuric acid added to water, followed by addition of chromium (VI) oxide). The resulting MNBA residues were extracted into ethyl acetate in the presence of sodium sulfate and, by heating the mixture with 2-iodopropane and potassium carbonate for one hour, the isopropyl ester of MNBA was formed. The quantitation of isopropyl-MNBA (conversion product of parent mesotrione) was achieved by GC/MSD. Ion 246 m/z was used for detection and quantitation. The LOQ was reported as 0.01 ppm.

Mean procedural recoveries for Method TMR 0739B ADD for mesotrione were within the range of 70–120% for milk, eggs and ground beef. Mesotrione residues were found to be unstable in beef liver during the extraction procedure, with procedural recoveries ranging from 45% to 64% when extraction was delayed for an hour after the blending of the spiked samples (Time 1 hour). When extraction started immediately after spiking, the procedural recoveries ranged from 66% to 81% (Time 0). The coefficients of variation measured with respect to recoveries following spiking between 0.01 ppm and 0.10 ppm indicated the method has satisfactory repeatability. The method was successfully validated in ground beef and milk (it should be noted that liver was not used) by an independent laboratory, indicating good reproducibility. Method TMR 0739B ADD is considered acceptable as a data-gathering method in all animal matrices except liver.

3.0 Impact on Human and Animal Health (OECD 2.3)

3.1 Integrated Toxicological Summary

A detailed review of the toxicology database available for the new herbicide, mesotrione, has been completed. A summary is presented in Appendix II, Table 1. Data submitted were complete and well presented; they included the full battery of studies currently required for registration purposes. The submitted studies were conducted in conformance with currently acceptable international testing protocols. The sponsor also submitted extensive data in support of the proposed mechanism of action for mesotrione.

Following oral dosing in mice, radiolabelled mesotrione was rapidly absorbed, distributed and excreted, with ~79% (single low dose) and ~92% (single high dose) of the administered dose (AD) being eliminated within 72 hours postdosing. The urine was the principle route of excretion, accounting for 40.6% to 62.9% of the AD for males and 58.6% to 69.8% of the AD for females. Fecal elimination for males accounted for 27.3% to 37.7% of the AD and for females accounted for 20.9% to 24.5% of the AD. Tissue distribution and bioaccumulation accounted for ~14.0% (single low dose) and ~0.4%

(single high dose) of the AD. The highest tissue concentration of radioactivity was present in the liver, accounting for ~13.0% (single low dose) and ~0.20% (single high dose) of the AD. The major radioactive component excreted was mesotrione, i.e., 49% to 70% of the AD in males and 65% to 78% of the AD in females. Minor identified metabolites were hydroxy mesotrione, MNBA and AMBA, accounting for 2 to 6% of the AD. The minor unidentified metabolites accounted for 1 to 8% of the AD and were considered to possibly be the result of metabolism of mesotrione by the intestinal microflora. There were no significant differences in the metabolic profile between sexes or dose level. The first metabolic pathway involves hydroxylation of the cyclohexane ring on the parent compound to form hydroxy mesotrione. The second pathway involves an aromatic nitro reduction of the parent compound, forming an aromatic amide intermediate, which is then cleaved at the cyclohexane ring, resulting in AMBA as a metabolite. The final pathway involves cleaving the C=O bridge from the cyclohexane (MNBA as the intermediate) followed by aromatic nitro reduction to form AMBA.

In the rat, radiolabelled mesotrione was rapidly absorbed, distributed and excreted, with ~80% to 92% (oral dosing) and ~97% (intravenous dose) of the AD being eliminated within 72 hours postdosing. Urine was the major route of elimination, accounting for ~55% to 67% (oral dosing) and ~80% (intravenous dose) of the AD. Fecal elimination accounted for ~23% to 30% (oral dosing) and ~2% to 7% (intravenous dose) of the AD. Smaller amounts of mesotrione were eliminated via the bile, accounting for up to 11% of the AD in males and up to 3% of the AD in females. Mesotrione was eliminated largely unchanged in bile. Feces from the cannulated rats contained only small amounts of unchanged mesotrione, indicating that mesotrione was metabolized by the gut microflora. Radioactivity remaining in the carcass and tissues 72 hours postdosing ranged from 5% to 12% of the AD for the orally dosed animals and ~10% of the AD after intravenous administration. The highest tissue concentrations were present in the liver and kidneys. There were no significant sex-related differences in excretion pattern or tissue distribution of radioactivity. The major portion of the AD was excreted as unchanged Mesotrione in urine, i.e., ~90% of the urinary radioactivity, or 47% to 59% of the AD. Fifteen minor metabolites were isolated in the excreta, 4 of which were identified, i.e., 4-hydroxy-mesotrione, MNBA, AMBA and 5-hydroxy-mesotrione. Each was present at $\leq$ 5% of the AD. Mesotrione undergoes a limited metabolism, represented by hydroxylation in either the 4- or 5- position on the dione ring. The polarity of the Mesotrione molecule enables excretion directly via urine, which was shown to be the major route of excretion of the absorbed dose. A lesser proportion of the absorbed doses was also eliminated via the bile, in both sexes. Small amounts of aromatic ring cleavage products, resulting from metabolism of mesotrione by the intestinal flora, appeared to have been absorbed and eliminated in the urine.

Rats were orally dosed with radiolabelled MNBA. Twelve hours postdosing, 44% of the AD was present in the gastrointestinal tract (GIT) contents and 16% of the dose was present in urine. Residual carcass and feces accounted for 2% and 27% of the AD. Total recovery of radioactivity was 91%. The major metabolite of MNBA was AMBA, which accounted for 58% of urinary radioactivity and 100% of radioactivity present in the

solvent extract of the GIT contents. MNBA was almost quantitatively reduced to AMBA in the gastrointestinal tract. MNBA was present in quantity in urine only at the 6-hour time point; at the 12-hour time point AMBA was the major radioactive component present in the urine and the gastrointestinal tract contents. MNBA and AMBA were not well absorbed within the first 12 hours postdosing.

Acute dosing revealed that technical mesotrione was of low toxicity by the oral, dermal and inhalation routes in rats. It was slightly irritating to the skin of rabbits and minimally irritating when instilled into the eyes; it was not a dermal sensitizer in guinea pigs (maximization method). The Callisto 480SC Herbicide formulation, containing 40.0% mesotrione, was of low toxicity by the oral, dermal and inhalation routes. It was mildly irritating to the skin, minimally irritating when instilled into the eyes and was determined to be a dermal sensitizer (Buehler method).

Short-term (21 days) repeated dermal dosing in rabbits with technical mesotrione did not result in any adverse treatment-related systemic effects up to and including the highest dose level tested of 1000 mg/kg bw/day (limit dose). The only dermal finding was slight erythema noted at doses of 500 mg/kg bw/day and higher.

In mice, short-term (3 months) exposure to technical mesotrione via the oral route resulted in decreased body-weight gains for males only at the highest dose level tested of 1396.6 mg/kg bw/day. Slightly lower dose levels (i.e., 1222.5 and 1212.4 mg/kg bw/day) in parallel 3 month studies did not result in toxicologically significant body weight changes. There were no other treatment-related findings. After long-term (52 weeks and 80 weeks) exposure the only treatment-related findings were decreased body-weight gain and decreased food efficiency for males only at the highest dose levels tested of 1114.0 mg/kg bw/day (52 weeks) and 897.7 mg/kg bw/day (80 weeks).

In dogs, short-term exposure for 6 weeks did not elicit any adverse, treatment-related effects up to and including the high dose level of 1000 mg/kg bw/day. The only findings observed after treatment for 3 months were decreased body-weight gain and mesothelial proliferation of the atrium of the heart, both observed in males only at the high dose of 1000 mg/kg bw/day. The target organ for dogs after exposure for one year was the eye. Findings were keratitis and lenticular/corneal opacities noted at the high dose of 600 mg/kg bw/day, with a corresponding increase in plasma tyrosine and urine phenolic acid concentrations. Increases in plasma tyrosine and urine phenolic acids were noted at lower doses, but were not considered adverse in the absence of any corresponding treatment-related effects. Body-weight gain was lower for females in the 600 mg/kg bw/day group. In addition, 1 female in the 600 mg/kg bw/day group was diagnosed with lymphocytolysis. This finding is rarely seen in dogs; therefore, it was considered to be treatment related. There were no other toxicologically relevant findings.

The target organ for rats after short-term (3 months) and long-term (105 weeks) exposure was the eye, manifest as corneal opacity/vascularization and keratitis. These ocular effects were observed at dose levels $\geq$ 0.63/14.48 mg/kg bw/day (short-term exposure) and

≥ 0.48/7.68 mg/kg bw/day (long-term exposure). Ocular effects were not observed after exposure for 28 days. Special studies indicated that the ocular lesions were associated with an increase in plasma tyrosine and urine phenolic acid concentrations. The only other findings after short-term exposure were decreased body-weight gain and an increased incidence of renal tubular hyaline droplet formation, males only, noted at the high dose of 1110.9 mg/kg bw/day. Hyaline droplet formation was apparent after exposure for 28 days in both sexes at doses ≥ 131.4/133.3 mg/kg bw/day (lowest dose tested). After long-term exposure, body-weight gain was decreased for males only at doses of 0.48 mg/kg bw/day and higher, there was an increased incidence of thyroid cysts at 6.48/7.68 mg/kg bw/day and higher, and hepatocyte vacuolation was observed at 0.48/7.68 mg/kg bw/day and higher. In addition, a number of age-related changes were noted at a higher frequency than seen in the control groups, but most fell within the historical control range of values. These findings were considered to possibly reflect a secondary effect of treatment, but were not considered to be toxicologically significant.

There was no evidence of carcinogenic potential of mesotrione in mice up to the highest dose level tested of 897.7/1102.9 mg/kg bw/day. For rats, the only oncogenic finding was an increased incidence of benign thyroid follicular cell adenomas (i.e., 6.3% vs control range of 0–3.9%) seen in females at the high dose of 189.5 mg/kg bw/day. However, there was no increase in the incidence of thyroid follicular cell carcinomas in either sex. In addition, mesotrione was not considered to be genotoxic based on the weight of evidence obtained from the results of in vitro and in vivo mutagenicity assays. It was therefore concluded that there is no concern for carcinogenic potential in the thyroid gland. In special biochemical studies conducted in mice and rats, mesotrione was not hepatotoxic and did not induce hepatomegaly nor peroxisome proliferation. In addition, only minimal induction of CYP enzymes was noted, indicating that mesotrione was unlikely to be hepatocarcinogenic.

In the mouse, mesotrione did not affect reproductive performance at any dose level tested. Parental findings were noted at the high dose level of 1471.9/1439.1 mg/kg bw/day, manifest as opaque/cloudy eyes with cataractous change and a corresponding increase in plasma tyrosine levels. The same eye lesions were observed at lower dose levels in the offspring, i.e., ≥ 311.8/301.6 mg/kg bw/day, along with lower body weight/body-weight gain, indicating increased quantitative susceptibility of the young.

In rats, mesotrione resulted in decreased litter size, decreased pup survival to day 22, decreased percentage of pups born live and increased whole litter loss at the high dose level of 278.1/297.2 mg/kg bw/day. Eye lesions were observed in parental animals at dose levels of 1.1 mg/kg bw/day and higher, and in offspring at dose levels of 0.3 mg/kg bw/day and higher, manifest as cloudy/opaque eyes, corneal vascularization and keratitis, with a corresponding increase in plasma tyrosine levels. For parent animals, plasma tyrosine levels were also increased at 0.3 mg/kg bw/day, but this was not considered adverse in the absence of any other corresponding treatment-related findings. Since eye lesions were observed in the offspring at lower dose levels than noted for parents, it is apparent that there is increased quantitative susceptibility of rat pups following exposure

to mesotrione. An increased incidence of bilateral hydronephrosis was noted for parents in the F_1 and F_2 continuous treatment and recovery groups and for offspring in the F_{1A}, F_{2A} and F_{3A} continuous treatment litters at doses of 1.6 mg/kg bw/day and higher. Since the F_0 generation parents were unaffected, it is apparent that in utero exposure is required for the development of bilateral hydronephrosis, indicating increased qualitative susceptibility of rat pups following exposure to mesotrione.

A special rat reproduction study was conducted in which test animals were dosed with tyrosine alone, mesotrione alone or a combination of mesotrione and tyrosine. Results indicated a possible causal relationship between tyrosine and reduced litter size, increased perinatal mortality and hydronephrosis. However, treatment with tyrosine alone did not result in reduced litter size, increased perinatal mortality or bilateral renal pelvic dilatation, and there was no dose-response relationship associated with the degree of the tyrosinaemia and the observed findings. In addition, a specific mechanism of action was not proposed as to how increased plasma tyrosine levels could induce the noted findings. It was therefore concluded it was inadequately demonstrated that the tyrosinemia associated with mesotrione administration directly caused reduced litter size, increased perinatal mortality and hydronephrosis.

Mesotrione was not teratogenic to rat, rabbit or mouse fetuses at dose levels up to and including 1000 mg/kg bw/day (rats), 500 mg/kg bw/day (rabbits) and 600 mg/kg bw/day (mice). For mice, there were no treatment-related maternal or developmental effects noted at any dose level tested.

For rats, maternal toxicity was noted at dose levels of 100 mg/kg bw/day and higher, manifest as lower body-weight gain during the dosing period. Toxicologically significant developmental findings were noted at doses $\geq$ 100 mg/kg bw/day and included an increased incidence of minor skeletal anomalies (unossified cervical centra 3 to 7 and extra 14^{th} ribs) and skeletal variants (unossified centrum 2 and odontoid). Lower fetal body weight was noted at 1000 mg/kg bw/day.

For rabbits, maternal findings were a slight increase in abortions noted at $\geq$ 250 mg/kg bw/day and decreased body-weight gain during the dosing period at 500 mg/kg bw/day. Developmental findings were an increased incidence of skeletal variants (partially ossified odontoid, 27 presacral vertebrae and extra 13^{th} ribs of normal length) at doses $\geq$ 100 mg/kg bw/day. However, these transient delays in ossification were not considered to be adverse, toxicologically significant findings in terms of postnatal development.

A special rabbit developmental study was conducted in which test animals were dosed with tyrosine alone, mesotrione alone or a combination of mesotrione and tyrosine. Results indicated a possible causal relationship between tyrosine and specific fetal ossification changes. However, treatment with tyrosine alone did not elicit the observed findings, nor was a specific mechanism of action proposed as to how increased plasma tyrosine levels could induce the noted findings. It was therefore not conclusively

demonstrated that the tyrosinemia associated with mesotrione directly caused the specific fetal ossification changes.

There was no evidence for increased susceptibility of mouse or rabbit fetuses following in utero exposure to mesotrione. However, it was evident in the rat reproduction study that in utero exposure was required for the development of bilateral hydronephrosis, indicating increased quantitative susceptibility of rat fetuses.

Mesotrione showed no evidence of neurotoxicity in rats by either acute or subchronic exposure up to and including the highest dose levels tested of 2000 mg/kg bw and 402.8/466.6 mg/kg bw/day, respectively.

The primary effect of systemic exposure to mesotrione in mammals is inhibition of the enzyme HPPD, which is important in the metabolism of the amino acid, tyrosine. Prolonged inhibition of this enzyme results in an increase in plasma tyrosine levels (tyrosinaemia). Excess tyrosine in the blood is metabolized to phenolic acids and excreted in the urine. Following inhibition of HPPD, the maximal extent of the tyrosinaemia is controlled by another catabolic enzyme, tyrosine aminotransferase (TAT). The toxic response to mesotrione is proposed to be dependent on the severity of the tyrosinaemia. The species differences in the toxic response to mesotrione are the result of different steady-state tyrosine levels, maintained by the differential activities of TAT. Higher TAT activity results in lower steady-state plasma tyrosine levels, and lower TAT activity results in higher steady-state plasma tyrosine levels. TAT has relatively low activity in the rat, resulting in a severe tyrosinaemia at low mesotrione levels; the effect is more pronounced in male rats. In contrast, TAT activity is much greater in the mouse, i.e., 3–4 times the activity seen in rats, leading to relatively minor increases in plasma tyrosine levels, with no significant toxic effects. The activity of TAT in humans has been shown to be similar to the values for mice, i.e., below levels that cause the systemic toxicity seen in rats. Hepatic TAT activity is 1.7 ± 0.2 nmol HPPA/min/mg protein for the male rat, 3.3 ± 0.5 nmol HPPA/min/mg protein for the female rat, 7.8 ± 1.5 nmol HPPA/min/mg protein for the male mouse, 10.5 ± 1.9 nmol HPPA/min/mg protein for the female mouse and 7.17 ± 1.17 nmol HPPA/min/mg protein for male and female humans. The maximal steady-state concentration of tyrosine is ~3000–3500 nmol/mL in male rats, ~1500–1800 nmol/mL in female rats, ~800 nmol/mL in male and female mice and ~800 nmol/mL in male and female humans. There is evidence of some adaptation to the primary biochemical changes. Plasma tyrosine levels as high as 3500 nmol/mL were found after the first week of continual treatment in male rats. By the end of 13weeks, plasma tyrosine steady-state concentrations had reduced to ~2500 nmol/mL.

A direct correlation has been shown between tyrosinaemia and ocular toxicity. Published literature indicates that tyrosine accumulates in the anterior aqueous humor, and tyrosine crystals are then deposited in the cornea. It has adequately been demonstrated that the threshold plasma tyrosine concentration for ocular effects in all species is ~1000 nmol/mL, which must be exceeded for a prolonged period of time before ocular lesions develop. In rats, ocular lesions developed at dose levels ≥ 0.48 mg/kg bw/day and

≥ 7.8 mg/kg bw/day for males and females, respectively, after tyrosine concentrations had been maintained above the threshold for ~10 weeks. On removal of mesotrione from test diets fed to rats, the tyrosinaemia was reversed and the corneal lesions were resolved within a few weeks. In dogs, plasma tyrosine levels were above threshold for corneal opacities/keratitis at 600 mg/kg bw/day. Corneal lesions were first observed between 13 and 26 weeks on treatment. In female mice dosed at 1436.4 mg/kg bw/day, plasma tyrosine concentrations were above the threshold for ocular toxicity, i.e., 1251 nmol/mL, during the first week of a 3-month feeding study. However, threshold levels were not maintained long enough for ocular lesions to develop, i.e., plasma tyrosine had returned to steady-state levels (800 nmol/mL) by the fourth week, the next time point measured. A similar increase in plasma tyrosine was not seen in males dosed at 1222.5 mg/kg bw/day. In the mouse reproduction study, ocular lesions, manifest as opaque/cloudy eyes with cataractous change, were observed at the high dose of 1471.9/1439.1 mg/kg bw/day in parents and offspring, and at the mid-dose of 311.8/301.6 mg/kg bw/day in the offspring only. The eye lesions seen in mice were not consistent with the corneal lesions normally associated with tyrosinaemia. It is therefore uncertain whether the ocular lesions were directly caused by exposure to mesotrione or were caused by the tyrosinaemia associated with mesotrione administration. Plasma tyrosine concentrations, measured only at study termination, revealed values of ~1023 nmol/mL for parents at the high dose, and values of ~820 nmol/mL and ~1350 nmol/mL for offspring at the mid- and high-dose levels, respectively. These values are slightly higher than the normal threshold plasma tyrosine levels for mice and are above the threshold for ocular lesions at the high dose level. These data indicate that the ocular lesions could possibly be related to the tyrosinaemia. It also appears that slightly higher steady-state plasma tyrosine levels may be attainable during reproduction in parental animals and offspring. However, since plasma tyrosine concentrations were only measured at one time-point, definitive conclusions cannot be made.

To summarize, special studies have adequately demonstrated that the tyrosinaemia associated with mesotrione directly caused corneal lesions when the plasma tyrosine concentrations exceeded ~1000 nmol/mL. It was therefore concluded that the findings and effect levels for eye lesions established in mice are considered to be more relevant than rats for the human risk assessment, since TAT activity and the resulting plasma tyrosine concentrations are similar between mice and humans. However, special reproduction and developmental studies did not adequately demonstrate a direct causal relationship between the tyrosinaemia resulting from mesotrione administration and decreased litter size, decreased pup survival, bilateral hydronephrosis and fetal ossification changes. Therefore, human risk assessment for reproductive and developmental findings should not be restricted to findings observed in mice; rather, data generated from all reproduction and developmental studies, regardless of species, should be considered.

Two metabolites of mesotrione, MNBA and AMBA, were subjected to additional testing. A metabolite characterization study with MNBA indicated that the major metabolite of MNBA was AMBA. MNBA is almost quantitatively reduced to AMBA in the

gastrointestinal tract. MNBA was present in quantity in the urine only at 6 hours; AMBA was the major component in the urine at 12 hours. MNBA and AMBA were not well absorbed within the first 12 hours postdosing. MNBA was of low acute toxicity by the oral and dermal routes, and was not considered to be genotoxic. Short-term (28 days and 3 months) exposure to MNBA via the oral route in rats did not result in any adverse, treatment-related effects up to and including the high dose levels of 1000 mg/kg bw/day and 231.0/263.7 mg/kg bw/day, respectively.

AMBA was shown to be of low acute toxicity by the oral route and was not considered to be genotoxic. Special studies conducted with both MNBA an AMBA indicated that neither metabolite would likely interfere significantly with tyrosine catabolism in vivo. Based on the submitted data, it was demonstrated that the metabolites MNBA and AMBA are less toxic than the parent compound.

3.2 Toxicological Endpoint for Assessment of Risk Following Long-term Dietary Exposure—Acceptable Daily Intake (OECD 2.3.2)

The proposed no observed adverse effect level (NOAEL) for determination of the acceptable daily intake (ADI) was 2.5 ppm, equal to 0.3/0.3 mg/kg bw/day, established in the rat reproduction study, based on bilateral hydronephrosis (parents and pups), observed at dose levels ≥ 1.1 mg/kg bw day.

Eye lesions seen in rats were not considered for human risk assessment since the mouse was considered to be a more appropriate model for eye lesions. In the mouse, eye lesions were only observed in the mouse reproduction study. Findings were observed at the high dose level of 1471.9/1439.1 mg/kg bw/day for parents and at dose levels of ≥ 311.8/297.2 mg/kg bw/day for offspring.

It was not conclusively demonstrated that non-ocular effects were the direct result of increased plasma tyrosine levels, rather than a direct effect of exposure to mesotrione. Therefore, human risk assessment for reproductive and developmental findings were not restricted to findings observed in mice; rather, data generated from all reproduction and developmental studies were considered.

For the calculation of the ADI for all populations, it is proposed that an additional factor of 3 be added to the standard uncertainty factor of 100 (10× for interspecies differences and 10× for intraspecies differences) due to increased qualitative and quantitative susceptibility of rat pups (bilateral hydronephrosis) and increased quantitative susceptibility of mouse pups (eye lesions). The ADI recommended is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UF}} = \frac{0.3 \text{ mg/kg bw/day}}{300} = 0.001 \text{ mg/kg bw/day of mesotrione}$$

3.3 Toxicological Endpoint for Assessment of Risk Following Acute Dietary Exposure—Acute Reference Dose (OECD 2.3.3)

No acute endpoints of concern were identified. As such, an acute reference dose (ARfD) is not required.

3.4 Toxicological Endpoint for Assessment of Occupational, Residential and Bystander Risks

During application of the product, there is a potential for short-term exposure to farmers who mix, load and apply over a period of not more than 7 consecutive days and to custom applicators who mix, load and apply over a period of not more than 30 consecutive days. There is a potential for short-term exposure to the following workers post application:

- scouters who re-enter sweet corn several hours per day intermittently throughout the season,
- re-entry workers who detassel corn for seed production, which is performed for approximately three weeks in July and August for eight hours per day, seven days per week; and
- workers who hand-harvest sweet corn for several weeks at the end of the growing season.

The principal route of exposure is dermal.

For short-term occupational exposures via the dermal route, the rat three-generation dietary study with a NOAEL of 0.3 mg/kg bw/day was considered the most appropriate toxicity endpoint of concern. The NOAEL was based on bilateral hydronephrosis in F_1 and F_2 adults, and in F_{1A}, F_{2A} and F_{3A} continuous treatment litters. A target margin of exposure (MOE) of 300 was considered appropriate for this toxicological endpoint based on an extra safety factor of 3 (indication of increased sensitivity of young) applied to the safety factor of 100 (for interspecies and intraspecies differences).

Dermal Absorption

A dermal absorption value of 1% was used for deriving systemic exposure estimates from dermal exposure estimates based on an in vivo dermal absorption study in the rat. Callisto 480 SC Herbicide was applied dermally to male rats at 4.8 mg/cm^2 (formulation concentrate) and a 1/952 spray-strength dilution, 4.8 µg/cm^2. Groups of 4 animals were sacrificed after 10 hours, 24 hours, 72 hours and 120 hours for each dose level. The skin was washed at 10 hours and prior to sacrifice. For the 72-hour and 120-hour groups, an interim skin wash was performed after 48 hours. At termination for all animals, the test site was tape-stripped after washing to remove the *stratum corneum*. Total absorbed dose was calculated from the sum of excreted residues (urine, feces, cage wash, bandage), absorbed residues (GIT and contents, carcass) and skin residues (tape-strips and application site skin). There were no major limitations to the study design. Total recovery of the applied dose (mass balance) was acceptable and ranged from 99.48% to 102.03% for the high dose group, and 99.16% to 101.01% for the low dose group.

The dermal absorption study indicates that mesotrione in the Callisto 480 SC Herbicide formulation is poorly absorbed through rat skin. In the high dose group (4.8 mg/cm^2), the majority of applied radioactivity was removed in the skin washes and protective cover and ranged from 99.3% to 101.8% of the applied dose throughout this study. Little to no radioactivity was absorbed systemically or found in tape-strips or in the skin at the test site. A maximum total absorption (excretion + residues + skin + tape-strips) of 0.56% of the applied dose occurred at 10 hours.

In the low dose group (4.8 µg/cm^2), the majority of applied radioactivity was removed in the skin washes and protective cover and ranged from 82–85% of the applied dose throughout the study. The systemically absorbed fraction (urine, feces, cage wash, bandage, GIT and contents, carcass) increased gradually from 0.2% of the applied dose at 10 hours to a maximum of 1.4% of the applied dose after 120 hours. The amounts in the skin at the test site decreased gradually from 0.73% of the applied dose at 10 hours to 0.16% of the applied dose at 120 hours. Similarly, the amounts in the tape-strips decreased from 16.9% of the applied dose at 10 hours to 12.4% of the applied dose at 120 hours (there was an additional wash at 48 hours that removed 2.2–2.5% of the applied dose). Results for blood and plasma were expressed only in terms of µg equivalents of mesotrione per gram and were not reported separately in terms of percentage of applied dose. However, the results from the µg equivalents per gram showed that all of the results were < LOD.

Since the study duration was not long enough to adequately determine the fate of skin-bound residues, the excretion data in the low dose group were analysed to predict the maximum potential excreted according to the exponential saturation model (Thongsinthusak, T., et al. 1999):

$$RECOV = MAX \times [1-EXP(-RATE \times (TIME-LAG))]$$

where RECOV (Y) = the cumulative percentage of the dose recovered in excreta (urine, feces, cage wash)
MAX (A) = the maximum excretion of administered dose at asymptote
TIME (X) = the time after administration of the dose
RATE (B) = the first-order rate constant for excretion
LAG (C) = the estimated time from the administration to the initial excretion

Since most fecal and cage wash values were below LOD at all time points and ½ LOD was used in calculations and included for all time points, the percentage total excreted estimates are considered conservative. The model is considered appropriate to this data set; excretion was rapid, exhibiting an initial increase followed by a slowing rate of elimination over time and minimal accumulation in the tissue compartment.

The study authors reported probable oral exposure for 1 animal sacrificed at 72 hours and for 3 animals sacrificed at 120 hours as indicated by loosened and gnawed o-rings. These animals showed an unusually high amount of fecal radioactivity relative to the urine

(3–16 times higher than amounts excreted in urine). Other absorption studies by the oral and intravenous routes show the majority of the absorbed dose is excreted in the urine and only minimal amounts excreted in feces (via the bile). Therefore, it is highly unlikely that in the dermal study, the animals with high fecal amounts of radioactivity were a result of dermal absorption; rather, ingestion of bits of the o-ring may have occurred in these animals and these data were removed from the data set.

The total amounts of radioactivity excreted in the urine, feces and cage wash at 10, 24, 48, 72, 96 and 120 hours were plotted and analysed by nonlinear regression (Systat®). A robust correlation was obtained for the maximum excretion of 0.115% (r^2 = 0.996; 95% CI = 0.062–0.168); where 95% of the maximum would occur by 7 days and 99% of the maximum would occur by 11 days. Therefore, only a minimal additional amount of excretion is predicted to occur after 120 hr and the amount of radioactivity found in the tape-strips at 120 hours (12%) is not anticipated to further contribute to the total amount absorbed.

Total dermal absorption was determined to be 0.58%, by summing the maximum potential excreted taken from the curve at asymptote plus the amounts in the terminal cage wash, bandages, GIT + contents and carcass at the 24 hour time point (highest of all time points). Considering the study and analytical limitations, a dermal absorption value of 1% was used for deriving systemic exposure estimates from dermal exposure estimates.

3.5 Impact on Human or Animal Health Arising from Exposure to the Active Substance or to Impurities Contained in it

3.5.1 Occupational Exposure and Risk

3.5.1.1 Handler Exposure and Risk

Occupational exposure estimates were determined for farmers and custom operators applying Callisto 480SC Herbicide (480 g/L), a suspension concentrate, on corn by groundboom equipment based on data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. The PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates. With a few exceptions, the PHED estimates meet the criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides. M/L subsets for liquids (open or closed transfer; single layer, gloves) and APPL subsets for groundboom application (open cab, single layer, no gloves) were based on high confidence PHED runs with adequate numbers of replicates and A and B grade data. All inhalation subsets were from A and B grade data. For addition of coveralls to the M/L and APPL subsets, a 75% protection factor was assumed for body deposition data from the single layer subsets. Central tendency estimates are presented on the basis of measures of “best-fit” from summing the measure of central tendency for each body part that is most appropriate to

the distribution of data for that body part (i.e., arithmetic mean if normal distribution, geometric mean if lognormal distribution, median if any other distribution). The PHED data do not provide exposure estimates for clean-up/repair activities nor quantify the variability of exposure estimates.

Unit exposure estimates normalized to µg a.i./kg ai handled were based on total dermal and inhalation deposition and are presented in Appendix III, Table 2. Scenario-specific exposure estimates are presented in Table 3.5.1.1.2. Total daily exposure was estimated for application by farmer or custom operators handling of 11.2 kg a.i./day (80 ha/d × 140 g a.i./ha) or 19.6 kg a.i./day (140 ha/day × 140 g a.i./ha), respectively, of mesotrione from application to corn by groundboom and assumed proposed personal protective equipment (PPE), open cabs and 70 kg body weight. Systemic exposure was determined by using a 1% dermal absorption factor.

The primary route of exposure was dermal. For all scenarios, inhalation unit exposure accounted for 1–5% of the total unit deposition (µg a.i./kg a.i. handled). Mixing/loading contributed 61% of the total unit exposure.

For the proposed scenario of farmers wearing a single layer of protection and gloves during open mixing/loading and using an open cab, the total exposure (dermal + inhalation) was estimated to be 13.87 µg/kg bw/day (deposited) or 0.54 µg/kg bw/day (systemic).

For the proposed scenario of custom operators wearing a single layer of protection and gloves during open mixing/loading and applying with an open cab, total exposure (dermal + inhalation) was estimated to be 24.27 µg/kg bw/day (deposited) or 0.95 µg/kg bw/day (systemic).

For farmers and custom operators, the addition of cotton coveralls reduced total deposition by 35% and systemic exposure by 8%. For short-term exposure, MOEs were determined for the toxicity endpoint from the rat reproduction study (NOAEL 0.3 mg/kg bw/d) and a target MOE of 300 (Appendix III, Table 3). With the proposed PPE, acceptable MOEs were determined for farmers (556) and custom operators (316).

3.5.1.2 Postapplication Exposure and Risk

In the absence of chemical-specific data, a Tier I exposure estimate was performed using default assumptions of dislodgeable residues of 20% of the rate of application and 10% dissipation of residue per day. The exposure estimates were refined using a dermal absorption factor of 1%.

Exposure estimates were determined for several re-entry scenarios after one application at the beginning of the growing season including:

i) scouters who re-enter fields daily for several hours per day intermittently throughout the season when foliage development is minimal (immediately after application; 0 days dissipation) and when foliage development is full (mid-season; 35 days dissipation);

ii) workers who detassel corn for seed production for approximately 3 weeks from mid-July to August for 8 hours per day, 7 days per week (50 days dissipation); and

iii) workers who hand-harvest sweet corn for 8 hours per day for several weeks at the end of the growing season (100 days after planting; 85 days dissipation).

Re-entry exposure estimates were based on the following equation and assumptions:

dermal exposure (µg/kg bw/d) = DFR × TC × T × DA / bw

where DFR =	dislodgeable foliar residue (ug/cm^2); 20% of application rate = 0.28 ug/cm^2; 10% dissipation/day		
TC =	transfer coefficient (cm^2/hr)	= hand-harvesting (17,000 cm^2/hr)	
		= detasseling (17,000 cm^2/hr)	
		= scouting (400 cm^2/hr min foliage; 1000 cm^2/hr full foliage)	
T =	time for activity (hr)	= hand-harvesting	8 hr
		= detasseling	8 hr
		= scouting	3 hr
DA =	percent dermal absorption	= 1%	
bw =	body weight (kg)	= 70 kg	

The maximum daily exposure estimates for re-entry activities are presented in Appendix III, Table 4. MOEs were determined for the toxicity endpoint from the rat reproduction study (NOAEL 0.3 mg/kg bw/day) and a target MOE of 300. Target MOEs were achieved for all re-entry activities.

3.5.2 Residential Exposure and Risk

There are no proposed residential uses. Therefore, a residential exposure assessment was not required.

3.5.3 Bystander Exposure and Risk

Bystander exposure is anticipated to be significantly less than occupational exposure. Therefore, a bystander risk assessment was not required.

3.5.4 Residues Relevant to Consumer Safety—Aggregate Exposure and Risk Assessment

There are no proposed residential uses. Therefore, an aggregate risk assessment was not required.

4.0 Residues

4.1 Residue Summary

Nature of the Residue in Plants
Mesotrione (radiolabelled in the phenyl or the cyclohexanedione rings) was applied either to soil as preplant incorporated at a rate of 280–307 g a.i./ha (~ 2× the proposed maximum seasonal rate) or by foliar treatment to corn plants as a postemergent application (28 days after planting [DAP]) at a rate of 161–164 g a.i./ha (~1×). In an additional corn metabolism study, corn plants were treated with [^{14}C-phenyl] mesotrione as a pre-emergent application to soil at 302 g a.i./ha followed by a foliar postemergent application at 179 g a.i./ha (31 DAP), for a total rate of 481 g a.i./ha (~3.4×). No parent compound or other predominant metabolite were found in corn grain. In the cyclohexanedione radiolabelled study, the major source of radioactive residues came from the incorporation of ^{14}C into biomolecules which differed significantly from the phenyl radiolabelled study where there was no incorporation observed.

The proposed metabolic pathway was proceeded by two metabolic pathways. In the first route that represented the major pathway, mesotrione was cleaved releasing the cyclohexanedione ring (which was further broken down and reincorporated in biomolecules) and the MNBA metabolite (which was further reduced to AMBA that, in turn, could be further conjugated to form numerous other metabolites). In the second route, the cyclohexanedione ring of mesotrione was hydroxylated to form 4-OH mesotrione and conjugated to a glucose molecule to give 4-OGlc mesotrione. The ROC may be defined as mesotrione. The metabolism of mesotrione in corn plants is well understood.

Confined Accumulation in Rotational Crops
The confined crop rotation trial studies were conducted by applying mesotrione (radiolabelled in the phenyl or the cyclohexanedione rings) to sandy loam soil at a rate of 308 g a.i./ha (~ 2× the proposed maximum seasonal rate for the 30 DAT interval) or 462 g a.i./ha (~3× for the 120 DAT and the 300 DAT intervals). Wheat and soybeans were planted in the aged soil at 30 DAT. Wheat, soybeans, endives and radishes were planted at 120 DAT and 300 DAT intervals.

In the phenyl radiolabelled study, MNBA was the predominant metabolite identified in all matrices, except for the 120 and 300 DAT wheat grain and the 300 DAT radish root and top. AMBA (free and conjugated) was also a major metabolite in all the 30 DAT soya and wheat matrices, except wheat grain. In the cyclohexanedione radiolabelled study, none of the identified metabolites accounted for more than 0.01 ppm. Most of the radioactivity

was incorporated into biomolecules, which is consistent with the results observed in the corn metabolism study. The maximum ^{14}C-residues occurred at the 30-day plantback interval for both radiolabels. The magnitude of the residues in the rotational crops from the confined crop rotation studies triggered a need for a field accumulation study.

Field Accumulation in Rotational Crops

During the field crop rotation study, 2 plots were treated with mesotrione formulated as a suspension concentrate and one plot served as control (Plot 1). Plot 2 received only one preplant incorporated application at a rate of 340 g a.i./ha (~2.4×) and Plot 3 received 2 applications for a total application rate of 560 g a.i./ha (4×) with a crop oil concentrate adjuvant (1%). On the day of the first application, field corn was planted in all plots. Prior to planting secondary crops at the three plantback intervals, the primary crop (field corn) was destroyed after being harvested. Radishes, soybeans, endives, wheat, millet and sorghum were planted at a number of time intervals posttreatment (30 DAT; 74–100 DAT and 300 DAT). All raw agricultural commodities were collected at normal harvest. Residues of mesotrione and MNBA were less than the LOQ (<0.01 ppm) for all the samples (soybean forage, hay and seed; endive leaves; radish roots and tops; millet forage, hay, grain and straw; wheat forage, hay, grain and straw; sorghum) from the 2 first intervals (30 DAT and 74–100 DAT). A plantback interval of 30 days for all crops will be required on the label.

Nature of the Residue in Animals

In the lactating cow metabolism studies, mesotrione (radiolabelled in the phenyl or the cyclohexanedione rings) and the major plant metabolite, AMBA (radiolabelled in the phenyl ring), were administered individually to separate lactating Friesian cows at dose levels of 12 mg/kg feed/day ([^{14}C-phenyl] mesotrione), 10 mg/kg feed/day ([^{14}C-cyclohexanedione] mesotrione) and 12 mg/kg feed/day ([^{14}C-phenyl] AMBA) for 7 consecutive days. The doses were administered orally twice daily after milking.

Urinary and faecal excretion were the predominant routes of elimination. In the phenyl radiolabelled study, no unmetabolized parent was found in the excreta and the major metabolite observed was identified as AMBA. The remainder of the ^{14}C-residues in excreta consisted of an array of minor unknown metabolites demonstrating that extensive metabolism occurred. The parent compound was found to be the predominant residue in liver and kidney and AMBA was also a major metabolite in kidney. In the cyclohexanedione radiolabelled study, no unmetabolized parent or predominant metabolites were identified in the excreta. Mesotrione was extensively metabolized producing a number of minor metabolites. Mesotrione was the predominant residue in liver and kidney. The predominant metabolite in milk was ^{14}C-lactose.

In the laying hen metabolism studies, mesotrione (radiolabelled in the phenyl or the cyclohexanedione rings) was administered to 10 Lohmann Brown laying hens at dose levels of 1.6 mg/day via oral dosing capsules (equivalent to a 10 ppm feeding level) for 10 consecutive days.

Urinary and faecal excretion were the predominant routes of elimination. The parent compound, mesotrione, was found to be the predominant residue in all of the poultry edible tissues demonstrating that minimal metabolism occurred. No other metabolites were identified in any of the edible tissues, except for ^{14}C-palmitic/oleic/stearic acid in egg yolk.

The proposed metabolic pathway proceeded via cleavage between the two rings of mesotrione. The released cyclohexanedione ring was further broken down to carbon units, which were available for incorporation into natural components such as sugars and proteins. The nitro group of the released phenyl ring of mesotrione was reduced to an amino group forming the metabolite AMBA. The ROC may be defined as mesotrione.

Each individual animal metabolism study is acceptable. However, the metabolism of ^{14}C-mesotrione in ruminants and poultry are qualitatively and quantitatively different. When compared to the rat and mouse metabolism studies, the hen metabolism was found to be similar with minimal metabolism of mesotrione being observed in contrast to the cow metabolism where mesotrione was extensively metabolized. Accordingly, the requirements for a swine metabolism study are triggered, as per Regulatory Directive DIR98-02, *Residue Chemistry Guidelines*.

Methods for Residue Analysis of Plants and Plant Products
Four analytical methods (TMR 0643B [HPLC/UV], TMR 0882B [HPLC/UV], TMR 0689B [GC/MSD], RAM 366/01[LC/MS/MS]) were proposed for data gathering and/or enforcement purposes. The method LOQ was reported as 0.01 ppm. These methods were found to give acceptable recoveries for the analysis of corn matrices. The ILV did support the reliability and reproducibility of methods TMR 0643B, TMR 0882B and RAM 366/01 for the determination of the mesotrione in corn matrices. Method TMR 0643B has been adequately radiovalidated. Multiresidue methods Protocols A through F were shown by the applicant to be unsuitable for the analysis of mesotrione.

Methods for Residue Analysis of Food of Animal Origin
Two analytical methods (TMR 0914B [HPLC/UV] and TMR 0739B ADD [GC/MSD]) were proposed for data-gathering and/or enforcement purposes. The method LOQ was reported as 0.01 ppm. These methods were found to give acceptable recoveries for the analysis of poultry and beef matrices (except in liver). The ILV did support the reliability and reproducibility of methods TMR 0914B and TMR 0739B ADD for the determination of the mesotrione in poultry and beef matrices (except liver).

Storage Stability Data—Plant/Animals
The data presented in the freezer storage stability study indicated that residues of mesotrione and the metabolite MNBA were stable at $< -18 \pm 5^{o}$C for 42 months in corn grain, corn forage and corn fodder; 44 months in radish roots; and 40 months in soybean seed. Samples of corn, radish and soybean were spiked with standard solutions of either mesotrione in methanol or MNBA (metabolite) in methanol, at a level of 0.1 ppm.

No freezer storage stability data in animal matrices were submitted. Since there is no expectation of finite residues of mesotrione in animal matrices following feeding of treated crops, a freezer storage stability study in animal matrices can be waived.

Crop Field Trials

Supervised crop field trial studies (a total of 44 individual trials) were conducted from 1995 to 2001 in the United States and Canada in/on field corn. Results indicated that the residues of mesotrione and the metabolite MNBA in corn grain were all < 0.01 ppm when corn plants were treated at rates ranging from 100 to1000 g a.i./ha/season (~0.7–7× the proposed maximum seasonal rate) as a combination of timings of application and harvested between 100 and 155 days after treatment. To simulate sweet corn cobs, field corn was harvested at the normal sweet corn timing (preharvest intervals of 49–60 days).

Consequently, a maximum residue limit (MRL) of 0.01 ppm is recommended to cover residues of mesotrione in/on field corn and sweet corn. This proposed MRL is consistent with the American tolerances established at 0.01 ppm. No Codex MRLs have been established.

Processed Food/Feed

The active ingredient mesotrione was applied to field corn at a rate of 2.8 kg a.i./ha/season (20×), and the field corn grains were processed into wet-milled fractions (starch, crude oil and refined oil) and dry-milled fractions (grits, meal, flour, crude oil and refined oil). A comparison of the residues in the raw agricultural commodity with those in each processed fraction resulted in no concentration of the residues in any of the processed fractions. MRLs will not need to be established to cover residues of mesotrione in corn processed fractions.

Meat/Milk/Poultry/Eggs

The requirement for livestock and poultry feeding studies was not triggered since mesotrione residue levels in harvested corn grain, forage and fodder samples were consistently below the LOQ of 0.01 ppm. Based on the results from the cow and hen metabolism studies and on the maximum theoretical dietary burden, mesotrione residues are not expected in animal tissues following feeding of the treated crops.

Dietary Risk Assessment

Chronic dietary exposure analyses were performed to determine the exposure and risk estimates that resulted from the use of mesotrione on field corn and sweet corn in Eastern Canada. Risk estimates for the representative population subgroups ranged from 2.9% to 22.7% of the ADI. The analysis showed that dietary risk estimates were below the level of concern (100% of the ADI) for the general population and all population subgroups. The currently proposed use for mesotrione encompassed only agricultural use sites. Therefore, when addressing aggregate exposures, only the dietary pathways of food and drinking water were considered. Chronic aggregate exposures were considered acceptable and did not exceed the level of concern.

5.0 Fate and Behaviour in the Environment

5.1 Physical and Chemical Properties Relevant to the Environment

Mesotrione was determined to be very soluble in water, which is one of the indicators high potential for the compound to leach in soil or to runoff in surface water. The vapour pressure of mesotrione at 20°C indicates that the compound would be considered relatively non-volatile under field conditions. The Henry's Law constant of mesotrione indicates that the chemical will not be volatile from water and moist soil surfaces. The magnitude of the *n*-octanol–water partition coefficient for mesotrione indicates that there is little potential for bioaccumulation. The dissociation constant, pK_a, of the compound indicated a potential for mobility in soil under conditions of neutral pH. The UV–visible absorption spectrum of mesotrione indicates that the compound is not likely to phototransform at environmentally relevant wavelengths of light.

5.2 Abiotic Transformation

Mesotrione was stable to hydrolysis in pH 4, pH 5 and pH 9 solutions at 25°C and in pH 4, pH 7 and pH 9 at 50°C. There were no major hydrolytic transformation products. These results indicated that mesotrione was stable to hydrolysis over a wide range of pH values and temperatures. The results of a phototransformation study on soil yielded a half-life of 28.9 days, with the formation of one major phototransformation product: MNBA. The results of phototransformation study in aqueous solution at pH 7 yielded a half life of 86–96 days, equivalent to 92 days in Southern Ontario (37°56'N). There were no major photolytic transformation products formed in water. Abiotic transformation, therefore, will not be an important route of transformation of mesotrione in the environment.

5.3 Biotic Transformation

Results of biotransformation studies with mesotrione in 14 soils from the United States under aerobic conditions at 20°C yielded half lives of approximately 8 to 31.5 days, with the formation of 2 minor transformation products: MNBA and AMBA. It was shown that MNBA further biotransformed in soil, with a half-life ranging from 1 to 30 days. These results indicate that mesotrione will be slightly persistent in the soil according to the classification system of Goring et al. (1975). The half-life of mesotrione in an anaerobic water/soil system at 25°C was 3.6 to 11 days for the entire system, with the formation of one major transformation product: AMBA.

Results of biotransformation studies in an aerobic sediment/water system at 20°C yielded a half-life value of 3 to 6 days, with the formation of one major transformation product: AMBA. These results indicate that mesotrione will be non-persistent in aerobic aquatic systems according to the classification scheme of McEwen and Stephenson (1979). Biotransformation of mesotrione in aquatic systems under anaerobic conditions was not

investigated; however, based on the results of anaerobic soil biotransformation study, mesotrione will be non-persistent under anaerobic conditions.

Biotransformation, therefore, will be an important route of dissipation of mesotrione under aerobic and anaerobic conditions in the environment.

5.4 Mobility

The adsorption K_d and K_{oc} values for mesotrione in 4 soils (Whitakers and Delavan, United States; Garonne, France; Pickett Piece, United Kingdom) and 2 soils from Ontario (sandy loam from Cambridge and clay from Jarvis) ranged from 0.32 to 0.97 mL/g and from 39 to 70 mL/g, respectively. The adsorption K_d and K_{oc} values for the transformation product MNBA in 5 soils (Delavan, Visalia, Wisborough Green, Toulouse and Garrone) ranged from 0.05 to 0.16 mL/g and < 6 to 6.08 mL/g, respectively. The adsorption K_d and K_{oc} values for the transformation product AMBA in the 5 soils ranged from 0.18 to 3.21 mL/g and 18 to 122 mL/g, respectively. These results indicate that mesotrione will be of high to very high mobility in soil based on K_{oc} values. Minor transformation product MNBA will be of very high mobility and AMBA will be of high to very high mobility in the soil. It should also be noted that mesotrione was determined to be very soluble in water, which indicates high potential for the compound to leach in soil or to runoff in surface water. Based on the values for vapour pressure and Henry's Law constant, volatilization of mesotrione is not expected to be a route of dissipation.

5.5 Dissipation and Accumulation under Field Conditions

Results of terrestrial field studies of dissipation and accumulation conducted in Canada indicated that mesotrione was non-persistent in soil, with dissipation time 50% (DT_{50}) values ranging from 3 to approximately 7 days. No significant carryover of residues to the next field season is expected based on these results. The transformation product of mesotrione, MNBA, dissipated during the course of the study. The other transformation product, AMBA, was not detected above the LOD at any soil depth in either trial throughout the field study. There was no evidence of leaching of mesotrione or its transformation products though the soil profile. Field dissipation studies conducted in Illinois yielded DT_{50} values ranging from 8 to 9 days. Mesotrione and its transformation products were not detected below the top (0–15 cm) depth of soil. These results indicate that mesotrione will dissipate rapidly in soil under field conditions with little or no leaching.

5.6 Bioaccumulation

A study of bioaccumulation of mesotrione in fish was not submitted. Given the low magnitude of the *n*-octanol–water partitioning coefficient; however, mesotrione is not expected to bioaccumulate in organisms.

5.7 Summary of Fate and Behaviour in the Terrestrial Environment

Mesotrione was determined to be very soluble in water, which is one of the indicators of high potential for a compound to leach in soil or to runoff in surface water. The vapour pressure of mesotrione at 20°C indicates that the compound would be considered relatively non-volatile under field conditions. The Henry's Law constant of mesotrione indicates that the chemical will not be volatile from water and moist soil surfaces. The magnitude of the *n*-octanol–water partition coefficient for mesotrione indicates that there is no potential for bioaccumulation. The dissociation constant, pK_a, of the compound indicated a potential for mobility in soil under conditions of neutral pH. The UV–visible absorption spectrum of mesotrione indicates that the compound is not likely to phototransform at environmentally relevant wavelengths of light.

Mesotrione was stable to hydrolysis in pH 4, pH 5 and pH 9 solutions at 25°C and in pH 4, pH 7 and pH 9 at 50°C. There were no major hydrolytic transformation products. These results indicated that mesotrione was stable to hydrolysis over a wide range of pH values and temperatures. The results of a phototransformation study on soil yielded a half-life of 28.9 days, with the formation of one major phototransformation product: MNBA. Abiotic transformation, therefore, will not be an important route of transformation of mesotrione in the environment.

Results of biotransformation studies with mesotrione in 14 soils from the United States under aerobic conditions at 20°C yielded half life values of approximately 8 to 31.5 days, with the formation of 2 minor transformation products: MNBA and AMBA. It was shown that MBNA further biotransformed in soil, with a half-life ranging from 1 to 30 days. These results indicate that mesotrione will be slightly persistent in the soil according to the classification system of Goring et al. (1975). Studies of biotransformation of mesotrione in soil under anaerobic conditions indicated that mesotrione will be non-persistent under anaerobic conditions. Biotransformation, therefore, will be an important route of dissipation of mesotrione under aerobic and anaerobic conditions in the terrestrial environment.

The adsorption K_d and K_{oc} values for mesotrione in 4 soils (ERTC, Delavan from the United States, Garonne from France and Pickett Piece from the United Kingdom) and 2 soils from Ontario (sandy loam from Cambridge and clay from Jarvis) ranged from 0.32 to 0.97 mL/g and from 39 to 70 mL/g, respectively. The adsorption K_d and K_{oc} values for the transformation product MNBA in 5 soils (Delavan, Visalia, Wisborough Green, Toulouse and Garrone) ranged from 0.05 to 0.16 mL/g and < 6 to 6.08 mL/g, respectively. The adsorption K_d and K_{oc} values for the transformation product AMBA in the 5 soils ranged from 0.18 to 3.21 mL/g and 18 to 122 mL/g, respectively. These results indicate that mesotrione will be of high to very high mobility in soil based on K_{oc} values. Minor transformation product MNBA will be of very high mobility and AMBA will be of high to very high mobility in the soil. It should also be noted that mesotrione was determined to be very soluble in water, which indicates high potential for the compound to leach in soil or to runoff in surface water. Based on the values for vapour pressure and

Henry's Law constant, volatilization of mesotrione is not expected to be a route of dissipation.

Results of terrestrial field studies of dissipation and accumulation conducted in Canada indicated that mesotrione was non-persistent in soil, with DT_{50} values ranging from 3 to approximately 7 days. No significant carryover of residues to the next field season is expected to occur based on these results. The major transformation product of mesotrione, MNBA dissipated during the course of the study. The other major transformation product, AMBA was not detected above the limit of detection at any depth in either trial throughout the field study. There was no evidence of leaching of mesotrione or its major transformation products though the soil layers. Field dissipation studies conducted in the northern United States yielded DT_{50} values ranging from 8 to 9 days. Mesotrione and its major transformation products were not detected below the top (0–15 cm) depth of soil. These results indicate that mesotrione will dissipate in the soil under field conditions.

5.8 Summary of Fate and Behaviour in the Aquatic Environment

Mesotrione was stable to hydrolysis in pH 4, pH 5 and pH 9 solutions at 25°C and in pH 4, pH 7 and pH 9 at 50°C. There were no major hydrolytic transformation products. These results indicated that mesotrione was stable to hydrolysis over a wide range of pH values and temperatures. The results of a phototransformation study on soil yielded a half-life of 28.9 days, with the formation of one major phototransformation product: MNBA. Abiotic transformation, therefore, will not be an important route of transformation of mesotrione in the environment.

The results of phototransformation study in aqueous solution at pH 7 yielded a half life of 86–96 days. There were no major photolytic transformation products formed in water. Abiotic transformation, therefore, will not be an important route of transformation of mesotrione in the aquatic environment.

Results of biotransformation studies in an aerobic sediment/water system at 20°C yielded a half-life value of 3 to 6 days, with the formation of one major transformation product: AMBA. These results indicate that mesotrione will be non-persistent in aerobic and anaerobic aquatic systems according to the classification scheme of McEwen and Stephenson (1979). Biotransformation of mesotrione in anaerobic aquatic systems was not investigated, but based on the results of anaerobic soil biotransformation study, mesotrione will be non-persistent under anaerobic conditions. Biotransformation, therefore, will be an important route of dissipation of mesotrione under aerobic and anaerobic conditions in the aquatic environment.

A study of bioaccumulation of mesotrione in fish was not submitted. Given the magnitude of the *n*-octanol–water partitioning coefficient; however, mesotrione is not expected to bioaccumulate in aquatic organisms.

5.9 Expected Environmental Concentrations

The concentrations of mesotrione in various environmental compartments were estimated based on calculations using maximum-exposure scenarios. It was assumed that a maximum of 1 application per growing season was made at the maximum rate of 140 g a.i./ha applied either as a preplant, pre-emergence, early postemergence, or late postemergence broadcast spray.

5.9.1 Soil

Assuming a soil bulk density of 1.5 g/cm^3, a soil depth of 15 cm and a scenario in which the product is applied to bare soil, the expected environmental concentration (EEC) of residues in soil would be 0.062 mg a.i./kg soil.

5.9.2 Aquatic Systems

Assuming a water density of 1.0 g/mL, a water depth of 30 cm and a scenario in which a body of water is oversprayed with the product, the EEC in water would be 0.046 mg a.i./L water.

5.9.3 Drinking Water

Mesotrione residues in potential drinking water sources (groundwater and surface water) were modelled at Level 2. The maximum drinking water concentration of mesotrione in groundwater sources as a result of leaching was estimated using the Leaching Estimation and Chemistry Model (LEACHM). Drinking water concentrations in surface water sources (reservoir) as a result of surface run-off were estimated using the linked Pesticide Root Zone Model / Exposure Analysis Modeling System (PRZM/EXAM) models. As the proposed registration is for the Eastern Canada, the scenario representing the proposed use pattern is used for the Level 2 assessment. The Level 2 EECs of mesotrione in drinking water sources are given in Appendix V, Table 5.

5.9.4 Vegetation and Other Food Sources

The applicant did not submit data on the concentrations of mesotrione on crops immediately after application. Therefore, residue concentrations on vegetation were estimated using a nomogram developed by the USEPA from the data of Hoerger and Kenaga (1972), modified by Fletcher et al. (1994), for use in ecological risk assessment (Urban and Cook 1986) (Appendix V, Table 6). A wet weight to dry weight conversion was also calculated.

6.0 Effects on Non-target Species

6.1 Effects on Terrestrial Organisms

The 14-day lethal concentration 50% (LC_{50}) and no observed effect concentration (NOEC) of mesotrione to the earthworm, *Eisenia foetida*, were > 2000 mg a.i./kg soil and 1000 mg a.i./kg soil, respectively. The acute oral LC_{50} and NOEC of mesotrione to the honeybee, *Apis mellifera*, were > 100 µg a.i./bee and 100 µg a.i./bee, respectively. The acute contact LD_{50} and NOEL of mesotrione to *Apis mellifera* were > 11 µg a.i/bee and 11 µg a.i./bee, respectively. Mesotrione, therefore, is classified as non-toxic to the honeybee according to the criteria of Atkins et al. (1981).

The contact LR_{50} of formulated mesotrione (WF 2795, 480 g/L suspension concentrate) to the parasitic wasp, *Aphidius rhopalosiphi*, and the predatory mite, *Typhlodromus pyri*, was 159 g a.i./ha and > 150 g a.i./ha, respectively.

The acute (14-d) oral lethal dose 50% (LD_{50}) and no observed effect level (NOEL) of mesotrione to the bobwhite quail, *Colinus virginianus*, were > 2000 mg a.i./kg body weight and 2000 mg a.i./kg body weight, respectively. The subacute (5-d) dietary LC_{50} and NOEC of mesotrione to the bobwhite quail and the mallard duck, *Anas platyrhynchos*, were > 5200 mg a.i./kg diet and 5200 mg a.i./kg diet, respectively, for both species. The NOEC of mesotrione on the reproduction of *Colinus virginianus* and *Anas platyrhynchus* were 3000 mg a.i./kg diet and 120 mg a.i./kg diet, respectively. Based on the results of the toxicity studies, mesotrione is classified as virtually non-toxic to the bobwhite quail on an acute basis in accordance with the classification system of the USEPA.

Mesotrione was determined to be of low toxicity to rats when administered as a single dose via the oral route (LD_{50}: > 5000 mg/kg bw). There were no clinical symptoms in rats dosed at the highest test concentration (5000 mg/kg bw). Mesotrione was reported to be of low toxicity to rats when administered via the dermal route (LD_{50}: > 2000 mg/kg bw). There were no treatment-related systemic findings in the test animals, although scabs and slight edema were reported. Mesotrione was of low toxicity to rats when administered by the inhalation route (LC_{50}: > 4.75 mg/L). Clinical symptoms included hunched posture, piloerection, irregular breathing and loss in body weight. Complete recovery was evident in all animals by the end of the study. Mesotrione was found to be slightly irritating to the skin and minimally irritating to the eye of rabbits, and non-sensitizing to the skin of guinea pig.

Repeated short-term oral dosing of mesotrione to Beagle dogs at low dose levels (100 and 600 mg/kg bw/day did not cause any adverse treatment-related effects. The high dose (1000 mg/kg bw/day), however, resulted in mesothelial proliferation of the artium of the heart in male dogs (NOAEL: 600 mg/kg bw/day for males and 1000 mg/kg bw/day for females). Oncogenicity studies with mice and rats indicated no adverse treatment-related findings in the mice but showed decreased body-weight gain, hepatocyte vacuolation,

fatty vaculoation and thyroid follicular adenomas in rats (NOAEL: 897.7 and 0.57 mg/kg bw/day, respectively). Mesotrione was not genotoxic and non-mutagenic in a standard battery of genotoxicity and mutagenicity tests such as bacterial reverse mutation (Ames test), mammalian gene mutation and mammalian cytogenetics (micronucleus assay); however, it showed equivocal response in the human lymphocyte cultures for chromosomal aberration in vitro. Mesotrione was not neurotoxic to rats and non-teratogenic to rats and rabbits.

In a multigeneration reproduction study with rats (effects on pregnancy and fetuses), mesotrione caused increased plasma tyrosine, eye lesions, bilateral hydronephrosis, decreased litter size, decreased pup survival and increased incidence of bilateral pelvic dilatation (NOAEL: 0.3 mg/kg bw/day for reproductive effects and lowest observed adverse effect level [LOAEL]: 0.3 mg/kg bw/day and offspring toxicity).

Studies on the effect of mesotrione on the seedling emergence and vegetative vigour of corn (*Zea mays*), oats (*Avena sativa*), onions (*Allium cepa*), perennial ryegrass (*Lolium perenne*), cabbages (*Brassica oleracea*), cucumbers (*Cucumis sativus*), lettuce (*Lactuca sativa*), soybeans (*Glycine max*), tomatoes (*Lycopersicon esculentum*) and turnips (*Brassica rapa*) indicated that the most sensitive species was lettuce, with an effect concentration 25% (EC_{25}) for shoot length of 3.695 g a.i./ha. For vegetative vigour, the most sensitive species was lettuce, with an EC_{25} for shoot length of 0.8176 g a.i./ha.

6.2 Effects on Aquatic Organisms

Freshwater

The acute (48 hour) effect concentration 50% (EC_{50}) and NOEC of mesotrione to the water flea, *Daphnia magna*, were 900 mg a.i./L and 622 mg a.i./L, respectively. The chronic (21 day) EC_{50} of mesotrione to the same species was 230 mg a.i./L. The corresponding NOEC for *Daphnia magna* was 180 mg a.i./L. The acute (48 hour) EC_{50} of transformation products MNBA and AMBA to *Daphnia magna* were 130 mg/L and 160 mg/L, respectively. The respective NOECs for *Daphnia magna* were 100 mg/L for both compounds. Based on the results of these studies, mesotrione and transformation products MNBA and AMBA are classified as practically non-toxic to daphnids in accordance with the classification system of the USEPA.

The acute (96 hour) LC_{50} of mesotrione to the rainbow trout, *Oncorhynchus mykiss*, and the bluegill sunfish, *Lepomis macrochirus*, was > 120 mg a.i./L for both species. The corresponding NOEC of mesotrione to these species was 120 mg a.i./L. The chronic (36 day) NOEC and LOEC of mesotrione to the early life stages of the fathead minnow, *Pimephales promelas* were 12.5 mg a.i./L and 24 mg a.i./L, respectively, based on sublethal effects such as loss of balance, spinal deformities and skin lesions. The acute (96 hour) LC_{50} of transformation products MNBA and AMBA to *Oncorhynchus mykiss* were > 120 mg/L and 100 mg/L, respectively. The corresponding NOEC of MNBA and AMBA to *Oncorhynchus mykiss* were 120 mg/L and 100 mg/L, respectively. Based on the results of the acute toxicity studies, mesotrione is classified as practically non-toxic to

rainbow trouts and bluegill sunfish in accordance with the classification system of the USEPA. The transformation products, MNBA and AMBA, are also classified as practically non-toxic to rainbow trouts using the same classification system.

The acute EC_{50} of mesotrione to the algae, *Selenastrum capricornutum* and *Anabaena flos-aquae*, and freshwater diatom, *Navicula pelliculosa*, were 4.5 mg a.i./L, 54 mg a.i./L and 68 mg a.i./L, respectively. The respective NOECs for the 3 species were 0.75 mg a.i./L, 32 mg a.i./L and 48 mg a.i./L. The acute EC_{50} of the transformation products MNBA and AMBA to *Selenastrum capricornutum* were 38 mg/L and 9.4 mg/L, respectively. The corresponding NOECs for MNBA and AMBA were 32 mg/L and 7.7 mg/L. The acute (14 day) EC_{50} and NOEC of mesotrione to duckweed, *Lemna gibba*, were 7.7 µg a.i./L and 2 µg a.i./L, respectively.

Marine/Estuarine
The applicant indicated that exposure of marine organisms was unlikely, given the short half-life in water and the geographic distribution of the proposed area(s) of use. Therefore, no data on the toxicity of mesotrione to marine organisms were submitted.

6.3 Effects on Biological Methods of Sewage Treatment

Not applicable for the proposed use.

6.4 Risk Characterization

6.4.1 Environmental Behaviour

Mesotrione is non-persistent under aerobic aquatic conditions as well as in aerobic and anaerobic soil under field conditions. Therefore, no significant carryover of residues to the next field season is expected. Mesotrione and its transformation product MNBA are not likely to leach through soil layers. The principal routes of transformation are biotransformation in soil and in aquatic environments. Mesotrione is not expected to volatilize from water and moist soils. Transformation product MNBA will dissipate in soil under field conditions. Mesotrione will not bioaccumulate in organisms.

6.4.2 Terrestrial Organisms

The risk to non-target organisms was calculated using EEC values of 0.062 mg a.i./kg in a 15-cm depth of soil and 0.046 mg a.i./L in a 30-cm depth of water. The EECs in wildlife food sources, expressed in mg a.i./kg dw, are shown in Table 5. Risk quotients were calculated using the NOEC or an estimated NOEC equivalent to 1/10 of the EC_{50} or LC_{50} and EC_{25} for terrestrial plants, for the most sensitive species per group.

6.4.2.1 Non-target Terrestrial Invertebrates

The 14-day acute NOEC of mesotrione to the earthworm, *Eisenia foetida*, is 1000 mg a.i./kg soil. Given that the EEC of mesotrione in soil will be 0.062mg a.i./kg, mesotrione will not pose a risk to the earthworms. The risk quotient (RQ) to earthworms is 6.2×10^{-5}.

The acute contact NOEC of mesotrione to the honeybee (*Apis mellifera*) is 100 µg a.i./bee. Mesotrione is classified as non-toxic to honeybees according to the classification scheme of Atkins (1981). This compound, therefore, will not pose a hazard to honeybees exposed to direct application.

The acute contact NOEC (estimated to be 1/10th of LR_{50}) of mesotrione to the parasitic wasp, *Aphidius rhopalosiphi*, and the predatory mite, *Typhlodromus pyri*, is ~15 g a.i./ha. Given that the proposed rate of application is 140 g a.i./ha, mesotrione will pose a moderate risk (RQ = 9.3) to beneficial arthropods.

6.4.2.2 Terrestrial Plants

The results of a multidose phytotoxicity study conducted with mesotrione indicated that the EC_{25} for the most sensitive endpoint for vegetative vigour, shoot length and plant weight in lettuce was 0.82 g a.i./ha; and the EC_{25} for the most sensitive endpoint for seedling emergence, shoot length in lettuce was 3.7 g a.i./ha.

These results indicate that, mesotrione will pose a very high risk (RQ = 170) to the vegetative vigour and a high risk (MOS = 37) to seedling emergence in non-target vegetation, if exposure of the non-target vegetation occurs by overspray.

6.4.2.3 Wild Birds

The most sensitive endpoint is adverse effects on reproduction of the mallard duck, *Anas platyrhynchos*, with a NOEC of 120 mg a.i./kg diet.

Wild birds, such as mallard ducks, could be exposed to mesotrione residues as a result of spray drift or consumption of sprayed vegetation or contaminated prey. The mallard duck diet may consist of approximately 10% large insects or snails, 10% leafy plants and 80% grain (USEPA 1993). Since the EECs of mesotrione on large insects, leaves/leafy plants and grain are 4.74, 172.5 and 4.74 mg a.i./kg dry weight, respectively (Appendix V, Table 6), the estimated ingestion of mesotrione through contaminated food sources by the mallard can be calculated as follows:

$(0.10 \times 4.74) + (0.10 \times 172.5) + (0.80 \times 4.74) = 21.51$ mg a.i./kg dry weight.

The mallard duck (live weight 1.2 kg) daily consumes food equivalent to 4.17% of its body weight (Urban and Cook 1986). Therefore, the bird would acquire a dose of:

$$(0.041 \times 1200) \times 21.51 \div 1000 = 1.05 \text{ mg a.i./day}$$
$$\text{equivalent to: } (1000 \div 1200) \times 1.05 = 0.87 \text{ mg a.i./kg bw/day}$$

This value is lower than the NOEC for the mallard duck (converted to 5 mg a.i./kg bw/day) at which there were no adverse reproductive effects on the test birds. Therefore, mesotrione will not pose a risk to the mallard duck (RQ = 0.17) on a reproductive effects basis.

6.4.2.4 Wild Mammals

The most likely route for exposure of wild mammals to mesotrione would be through consumption of contaminated prey or vegetation following operational applications of mesotrione herbicide. Assuming a maximum residue of 98.87 mg a.i./kg in short range grass (dry weight basis) and 27.66 mg a.i./kg in small insects (dry weight basis), dosage levels immediately following application resulting from several maximum-exposure scenarios can be estimated. For example, the eastern cottontail rabbit, *Sylvilagus floridanus* (live weight of 1.3 kg), consuming short grass at a rate of 4.4% of its body weight/day (Dalke and Sime 1941, Banfield 1974), would consume 57.2 g of food/day and acquire a dose of 4.35 mg a.i./kg bw/day. The masked shrew, *Sorex cinereus* (live weight of 4 g), ingesting 25–75% of its body weight/day of contaminated small insects (Banfield 1974) would consume 1 to 3 g of food per day and acquire a dose of 6.9 to 20.7 mg a.i./kg bw/day. The meadow vole, *Microtus pennsylvanicus* (live weight of 3.5 g), ingesting 15–24% of its body weight/day in grasses (Peterson 1966) would consume 0.52 to 0.84 g of food per day and acquire a dose of 14.68 to 23.72 mg a.i./kg bw/day.

These estimated exposure dosages are less than the LD_{50}s from any of the acute toxicity studies, but exceed the NOELs from some of the subchronic/chronic studies. The results from some of these latter studies, however, likely overstate the effects that may occur in the field. The proposed use of mesotrione herbicide in the field will result in limited exposure of wild mammals to the product and, therefore, is not expected to pose an appreciable risk to wild mammals.

6.4.3 Aquatic Organisms

6.4.3.1 Non-target Aquatic Invertebrates

The most sensitive endpoint is chronic effects on the water flea, *Daphnia magna*, with an NOEC of 180 mg a.i./L. Given that the EEC of mesotrione in water will be 0.046 mg a.i./L, mesotrione will not pose a risk ($RQ = 2.5 \times 10^{-4}$) to aquatic invertebrates, such as the water flea.

6.4.3.2 Fish

The most sensitive endpoint is effects on the early life stages of fathead minnow, *Pimephales promelas*, with a NOEC of 12.5 mg a.i./L. Given that the EEC of mesotrione in water will be 0.046 mg a.i./L, mesotrione will not pose a risk (RQ = 3.6×10^{-3}) to fish.

6.4.3.3 Aquatic Plants and Algae

The most sensitive endpoint is adverse effects on the duckweed, *Lemna gibba*, with an acute NOEC of 2 µg a.i./L. Given that the EEC of mesotrione in water will be 0.046 mg a.i./L, mesotrione will pose a high risk (RQ = 23) to aquatic organisms, such as the duckweed.

6.4.4 Species at Risk / Endangered Species

The provisions of the *Species at Risk Act*, which came into effect in June 2004, include prohibitions against harming or killing listed species as well as destroying their critical habitat. The PMRA is developing an approach that will ensure that pesticide regulatory decisions are consistent with the purposes of *Species at Risk Act* to protect species at risk and their habitats.

6.5 Risk Mitigation

Mesotrione is non-persistent under aerobic aquatic conditions, as well as in aerobic and anaerobic soil. Therefore, no significant carryover of residues to the next field season is expected. Mesotrione and its transformation product MNBA are not likely to leach through soil layers. The principal routes of transformation are biotransformation in soil and in aquatic environments. Mesotrione is not expected to volatilize from water and moist soils. The transformation product MNBA will dissipate in soil under field conditions. Mesotrione will not bioaccumulate in organisms.

Mesotrione will pose a high risk to aquatic vascular plants, such as the duckweed, and a very high risk to the vegetative vigour of terrestrial plants. Mesotrione will pose a moderate risk to beneficial arthropods such as parasitic wasps and predatory mites exposed to direct treatment. However, mesotrione is unlikely to pose a risk to beneficial arthropods in the corn field habitat when used as a preplant, pre-emergence, early postemergence or late postemergence application.

The risk to aquatic and terrestrial plants can be mitigated by the establishment of terrestrial and aquatic buffer zones.

Mitigative Measures
A buffer zone of 10 meters for application by groundboom sprayer should be established between the last spray swath and the edge of aquatic systems such as rivers, lakes, ponds, streams and other bodies of water.

A buffer zone of 15 meters for application by groundboom sprayer should be established between the last spray swath and the edge of terrestrial habitats such as hedgerows, windbreaks, woodlots, vegetative strips and other vegetation.

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended Use

Mesotrione is contained in one EP, Callisto 480SC Herbicide. The EP is formulated as a suspension containing 480 g/L mesotrione. Callisto 480SC Herbicide is proposed for preplant surface, pre-emergence, early postemergence and late postemergence use in field corn grown in conventional, reduced or no-tillage systems on soils containing from 1 to 10% organic matter in Eastern Canada for control of several annual/winter annual broadleaved weed species. The product is proposed for use alone and in several tank mixtures at 140 or 175 g a.i./ha (0.3 or 0.36 L/ha) for the preplant surface, pre-emergence and early postemergence application timings to control lamb's-quarters, redroot pigweed, velvetleaf, common ragweed, mustard (not species specific), lady's thumb, shepherd's purse, eastern black nightshade and stinkweed (pre-emergence only). The product is proposed for use alone and in several tank mixtures at 100 g a.i./ha (0.21 L/ha) plus 0.2% v/v of a non-ionic surfactant, such as Agral 90 or AgSurf, at the late postemergence application timing to control lamb's-quarters, redroot pigweed, velvetleaf, common ragweed and mustard (not species specific).

Callisto 480SC Herbicide is proposed for ground application in a water carrier of 100 to 200 L/ha at pressures ranging from 206 to 300 kPa using flat fan nozzles at a downward 90º angle. It is also proposed that Callisto 480SC Herbicide can be applied either preplant surface or pre-emergence in fluid fertilizers, which serves the carrier, with the particular instruction that the compatibility of Callisto 480SC Herbicide or tank mixes with the fertilizer should be predetermined by mixing small proportional quantities in advance.

For the preplant surface timing, Callisto 480SC Herbicide is proposed for application in a number of tank mixtures, including tank mixtures with glyphosate, as Roundup Transorb or Touchdown IQ at 900 g a.i./ha, without or with addition of 2.16–2.88 kg a.i./ha Primextra II Magnum (s-metolachlor and atrazine), 1.14–1.6 kg a.i./ha Dual II Magnum (s-metolachlor) without or with 1.0–1.5 kg a.i./ha atrazine as either Aatrex Nine-O or Aatrex Liquid 480.

For the pre-emergence and early postemergence timings, Callisto 480SC Herbicide is proposed for application in tank mixtures with 1.14–1.6 kg a.i./ha Dual II Magnum without or with 1.0–1.5 kg a.i./ha atrazine, as either Aatrex Nine-O or Aatrex Liquid 480, or 2.16–2.88 kg a.i./ha Primextra II Magnum.

For the late postemergence timing, Callisto 480SC Herbicide is proposed for application in tank mixtures with 25 g a.i./ha Accent (nicosulfuron) or 25 g a.i./ha Ultim (nicosulfuron and rimsulfuron). It is also proposed in tank mixtures with a reduced rate of atrazine, 280 g a.i./ha, as Aatrex Nine-O or Aatrex Liquid 480, or with a combination of the reduced rate of atrazine and either 25 g a.i./ha Accent or Ultim. Each of these tank mixtures are proposed for use with a non-ionic surfactant, such as Agral 90 or AgSurf.

Notwithstanding the reduced rate of atrazine as a tank mixture partner for the late postemergence timing, these tank mixture component products are included at their registered rates as when used alone; therefore, the weed claims proposed for each tank mixture are those that are registered for the tank mixture component products and those proposed for Callisto 480SC Herbicide alone. It is indicated on the draft label that the labels of the tank mixture component products should be consulted for precautions, use rates and weeds controlled. This indicates that control claims are being made for atrazine-labelled weed species for the postemergence tank mixtures that include atrazine, even though atrazine is included at a reduced rate.

Rotational crop intervals, being the time between application of Callisto 480SC Herbicide and planting of the next crop in rotation, are proposed for several crops. It is proposed that corn (field, silage, seed, sweet) can be planted immediately after application (a 0 month interval), a 3 month interval for winter wheat and a 10 month interval for spring wheat, soybeans, dry beans (black, white, cranberry, kidney, etc.), potato, tomato and alfalfa. It is indicated on the proposed label that other crops can only be grown after completion of a field bioassay that shows the concerned crop can be successfully grown.

7.1.2 Mode of Action

Mesotrione is a member of the triketones class of herbicides. Mesotrione inhibits the enzyme 4-hydroxyphenyl-pyruvate-dioxygenase (4-HPPD), which converts 4-hydroxyphenyl-pyruvate to homogentisate, a key step in plastoquinone biosynthesis.

7.1.3 Crops

Value data were provided in support of field corn, sweet corn and production seed corn.

7.1.4 Effectiveness Against Pests

7.1.4.1 Preplant Surface

The efficacy of Callisto 480SC Herbicide applied alone at surface preplant at the proposed rates of 140 or 175 g a.i./ha for control of weed species for which a control claim is proposed was evaluated in 16 trials conducted in 2001 on a range of soils. Data from 2 trials conducted in London, Ontario, were excluded from consideration because they were pre-emergence trials conducted under conventional tillage, and efficacy was

assessed only after applying Accent. The remaining 14 trials were conducted in Ontario at 7 sites in mid- to long-season areas and in Quebec at 1 site.

No data for rates lower than the two proposed were provided. In all trials, to include treatments of Callisto 480SC Herbicide alone, a postemergence application of 25 g a.i./ha Accent plus a non-ionic surfactant was made for grassy weed control. Evaluations after Accent was applied could not be considered in support of the proposed weed claims because Accent, while registered for control of several grass weed species, has considerable activity on many broadleaved weeds, thereby confounding the effect of Callisto 480SC Herbicide. A postemergence application of Accent was also made to treatments of Callisto 480SC Herbicide tank mixed with glyphosate.

Data were insufficient to support the proposed preplant surface use of Callisto 480SC Herbicide alone or in tank mixtures in field corn. Furthermore, data were available from one year only, no lower than proposed rates of Callisto 480SC Herbicide were tested, treatments of Callisto 480SC Herbicide alone or tank mixed with glyphosate were followed by a postemergence application of Accent in the 14 preplant surface trials to include a Callisto 480SC Herbicide alone treatment, and the tested three- or four-way tank mixture treatments included Callisto 480SC Herbicide only at the higher proposed rate of 175 g a.i./ha. Additionally, no trials were submitted that evaluated tank mixtures of Callisto 480SC Herbicide plus Primextra II Magnum or Dual II Magnum without or with atrazine as Aatrex Nine-O or Aatrex Liquid 480 at the preplant surface timing in a no-tillage scenario.

The proposed preplant surface use of Callisto 480SC Herbicide alone or in tank mixtures is unacceptable for labelling from an efficacy standpoint. Data from a second year of preplant surface trials are required before control claims can be considered for each weed species for which control claims are proposed. Additional trials must include treatments of Callisto 480SC Herbicide alone and in the proposed tank mixtures at both of the proposed rates plus at a lower rate, about 75% of 140 g a.i./ha (100–105 g a.i./ha). Treatments of Callisto 480SC Herbicide alone or tank mixed with glyphosate must not be followed with any other herbicide. Trials should be conducted at a variety of locations including short-season areas (CHU ≤ 2500).

7.1.4.2 Pre-emergence

7.1.4.2.1 Callisto 480SC Herbicide Alone

The efficacy of Callisto 480SC Herbicide applied alone at the proposed rates of 140 or 175 g a.i./ha for control of weed species for which a control claim is proposed was evaluated in 49 trials on a range of soils in which Callisto 480SC Herbicide was applied pre-emergence. Trials were conducted in 1997 (4 trials), 1998 (9 trials), 1999 (6 trials), 2000 (8 trials) and 2001 (22 trials) in Ontario (46 trials) and Quebec (3 trials).

A lower than proposed rate of 100 g a.i./ha (0.71×) was included in 15 trials conducted in 1997, 1998 and 1999. Conventional tillage practice was used in 48 trials and reduced tillage practice was used in 1 trial. In most trials, Callisto 480SC Herbicide was followed by a postemergence application of 25 g a.i./ha Accent plus a non-ionic surfactant for grassy weed control. Evaluations after Accent was applied were not considered in support of the proposed weed claims because Accent, while registered for control of several grass weed species, has considerable activity on many broadleaved weeds, thereby confounding the effect of Callisto 480SC Herbicide.

Lamb's-quarters

The efficacy of Callisto 480SC Herbicide applied to the crop at the pre-emergence stage for control of lamb's-quarters was evaluated in 38 trials conducted from 1997 to 2001, mainly in Ontario. The efficacy of Callisto 480SC Herbicide was assessed in 31 trials, 13–31 days after application. Control of lamb's-quarters averaged 88% following application of 140 g a.i./ha Callisto 480SC Herbicide in 30 trials. In 11 trials, control averaged 71% for Callisto 480SC Herbicide at a reduced rate of 100 g a.i./ha. The efficacy of the 100 and 140 g a.i./ha rates of Callisto 480SC Herbicide for lamb's-quarters control was directly compared in 10 trials conducted over 3 years. In these trials, control averaged 74 and 79% for Callisto 480SC Herbicide applied at 100 and 140 g a.i./ha, respectively. In 20 trials conducted in 1999 and 2001, control averaged 92% following pre-emergence application of Callisto 480SC Herbicide at either 140 or 175 g a.i./ha, and was similar to the control observed in the Primextra II Magnum treatments.

Trials conducted in 1997 and 1998 as well as most trials conducted in 2000 included Callisto 480SC Herbicide treatments that were not followed by postemergence applications of Accent, thereby permitting later season evaluation of the efficacy of Callisto 480SC Herbicide for lamb's-quarters control.

Control of lamb's-quarters averaged 84% at 33–41 days after application of 140 g a.i./ha over 8 trials conducted in 1998 and 2000. In the 5 trials conducted in 2000, complete control of this weed was observed for Callisto 480SC Herbicide treatments of 140 or 175 g a.i./ha.

In 6 trials, control averaged 98% when assessed from 58 to 65 days after application of 140 g a.i./ha Callisto 480SC Herbicide. Control was similar for the 140 and 175 g a.i./ha rates of Callisto 480SC Herbicide in the 3 trials that included the latter rate.

In 5 trials, control averaged 98% at 76–100 days after application of 140 g a.i./ha Callisto 480SC Herbicide, about 4% greater than that observed for the higher rate.

A total of 12 trials conducted over 3 years included Callisto 480SC Herbicide at both the 100 and 140 g a.i./ha rates. When only the latest evaluation was considered in each trial (13–65 days after application), control was similar between these 2 rates, averaging about 80%.

A control claim for lamb's-quarters is acceptable for Callisto 480SC Herbicide applied pre-emergence at the lower proposed rate of 140 g a.i./ha in conventional till corn. It is not clear whether this is the lowest effective rate since, in 12 trials conducted from 1997–1999, efficacy was similar between rates of 100 and 140 g a.i./ha.

Redroot Pigweed

The efficacy of Callisto 480SC Herbicide applied to the crop at the pre-emergence stage for control of redroot pigweed was evaluated in 24 trials conducted from 1997 to 2001 in Ontario at 14 sites. The efficacy of Callisto 480SC Herbicide was assessed in 17 trials, 13–31 days after application. Control of redroot pigweed averaged 90% following application of 140 g a.i./ha Callisto 480SC Herbicide in 17 trials. The efficacy of 100 and 140 g a.i./ha Callisto 480SC Herbicide for redroot pigweed control was directly compared in 6 trials conducted over 3 years; control averaged 84 and 90%, respectively. In 11 trials conducted in 1999 and 2001, control averaged 90 and 92% following pre-emergence application of 140 and 175 g a.i./ha Callisto 480SC Herbicide.

Trials conducted in 1998 and most trials conducted in 2000 included Callisto 480SC Herbicide treatments that were not followed by postemergence applications of Accent, thereby permitting later season evaluation of the efficacy of Callisto 480SC Herbicide for redroot pigweed control.

Control of redroot pigweed averaged close to 100% when evaluated 33–41 days after application in 5 trials. Callisto 480SC Herbicide treatments of 100 and 140 g a.i./ha were compared in 1 trial, where the higher rate resulted in 98% control versus 86% control for the lower rate. In 4 trials conducted in 2000, complete control of redroot pigweed was achieved by both the 140 and 175 g a.i./ha rates of Callisto 480SC Herbicide.

In 3 trials, control averaged 96% 61–62 days after application of 140 g a.i./ha Callisto 480SC Herbicide. In 1 trial, Callisto 480SC Herbicide applied at either 100 or 140 g a.i./ha resulted in 98% control. In 2 trials, control averaged 95 and 85% for Callisto 480SC Herbicide applied at 140 and 175 g a.i./ha, respectively.

In 5 trials, control averaged 95 and 90% at 76–100 days after application of 140 and 175 g a.i./ha Callisto 480SC Herbicide, respectively.

A total of 8 trials conducted over 3 years included Callisto 480SC Herbicide at both the 100 and 140 g a.i./ha rates. When only the latest evaluation was considered in each trial (13–61 days after application), control was greater and more consistent for the 140 g a.i./ha rate, where 92% average control was achieved compared with the lower rate of 100 g a.i./ha that provided an average 86% control.

A control claim for redroot pigweed is acceptable for Callisto 480SC Herbicide applied pre-emergence at the lower proposed rate of 140 g a.i./ha in conventional till corn. This rate appears to be the lowest effective rate for control of redroot pigweed at the pre-emergence timing.

Velvetleaf
The efficacy of Callisto 480SC Herbicide applied pre-emergence to the crop for control of velvetleaf was evaluated in 13 trials conducted from 1997 to 2001 in Ontario at 5 sites. The efficacy of Callisto 480SC Herbicide was assessed in 12 trials, 13–27 days after application. Control of velvetleaf averaged 93% following application of 140 g a.i./ha Callisto 480SC Herbicide in 12 trials. In 2 trials conducted in 1997 and 1998, control averaged 87 and 96% for Callisto 480SC Herbicide applied at 100 and 140 g a.i./ha, respectively. In 10 trials conducted in 1999 and 2001, control averaged 92 and 93% following pre-emergence application of 140 and 175 g a.i./ha Callisto 480SC Herbicide, respectively.

In most trials conducted in 2000, Callisto 480SC Herbicide treatments were not followed by postemergence applications of Accent, thereby permitting later season evaluation of the efficacy of Callisto 480SC Herbicide for velvetleaf control. Callisto 480SC Herbicide treatments of 100 and 140 g a.i./ha were compared in 1 trial where the higher rate resulted in 100% control versus 98% control for the lower rate.

In 2 trials, control averaged 97%, 62–65 days after application of 140 g a.i./ha Callisto 480SC Herbicide. In 1 trial, Callisto 480SC Herbicide applied at 100 and 140 g a.i./ha resulted in 98 and 100% control, respectively. In 1 trial conducted in 2000, control averaged 96 and 99% for Callisto 480SC Herbicide applied at 140 and 175 g a.i./ha, respectively.

In 1 trial, control of 94 and 97% was observed for treatments of Callisto 480SC Herbicide applied at 140 and 175 g a.i./ha, respectively, at 91 days after application.

Two trials conducted over 2 years included Callisto 480SC Herbicide at both the 100 and 140 g a.i./ha rates. When only the latest evaluation was considered in each trial (13–61 days after application), control was greater for the 140 g a.i./ha rate where 98% average control was achieved than the lower rate of 100 g a.i./ha which provided an average 89% control. These rates were compared in only 2 trials.

A control claim for velvetleaf is acceptable for Callisto 480SC Herbicide applied pre-emergence at the lower proposed rate of 140 g a.i./ha in conventional till corn. Only 2 trials included Callisto 480SC Herbicide at a lower than proposed rate (100 g a.i./ha). Therefore, there are insufficient data for a determination of the lowest effective rate for velvetleaf control.

Common Ragweed
The efficacy of Callisto 480SC Herbicide applied to the crop at the pre-emergence stage for control of common ragweed was evaluated in 17 trials conducted in 1997 to 2001, mainly in Ontario. In those trials for which information was available on the weed developmental stage at application, common ragweed had either not yet emerged or was at the cotyledon stage. The efficacy of Callisto 480SC Herbicide was assessed in 13 trials, 19–30 days after application. Control of common ragweed averaged 73% following

application of 140 g a.i./ha Callisto 480SC Herbicide. The efficacy of 100 and 140 g a.i./ha Callisto 480SC Herbicide for common ragweed control was directly compared in 5 trials conducted over 3 years. In these trials, control averaged 60 and 67%, respectively, for Callisto 480SC Herbicide applied at 100 and 140 g a.i./ha. In 8 trials conducted in 1999 and 2001, control averaged 77 and 81% following pre-emergence application of 140 and 175 g a.i./ha Callisto 480SC Herbicide.

In trials conducted in 1998 as well as in most trials conducted in 2000, Callisto 480SC Herbicide treatments were not followed by postemergence applications of Accent, thereby permitting later season evaluation of the efficacy of Callisto 480SC Herbicide for common ragweed control. Control of common ragweed averaged 69% when evaluated 35–41 days after application in 5 trials. In the 2 trials conducted in 1998, control was poor at 44% for treatments of 100 and 140 g a.i./ha. In the 3 trials conducted in 2000, control averaged 85 and 90% for treatments of 140 and 175 g a.i./ha Callisto 480SC Herbicide, respectively. In comparison, control averaged 95% for the registered treatment of 105 g a.i./ha Converge 75 WDG (isoxaflutole).

In 4 trials, control averaged 90% when evaluated 58–72 days after application of 140 g a.i./ha Callisto 480SC Herbicide. In 2 trials, Callisto 480SC Herbicide applied at 100 and 140 g a.i./ha resulted in an average 75 and 90% control, respectively. In 2 trials conducted in 2000, control averaged 89% for Callisto 480SC Herbicide applied at either 140 and 175 g a.i./ha.

In 3 trials, common ragweed control of 84 and 90% was observed for treatments of Callisto 480SC Herbicide applied at 140 and 175 g a.i./ha, respectively, when evaluated 82–100 days after application.

A total of 6 trials conducted over 3 years included Callisto 480SC Herbicide at both the 100 and 140 g a.i./ha rates. When only the latest evaluation was considered in each trial (27–72 days after application), the level of control was greater for the 140 g a.i./ha rate (76% control) than for the lower rate of 100 g a.i./ha (68%).

A claim of control was proposed for common ragweed for Callisto 480SC Herbicide applied pre-emergence at either of the 2 proposed rates of 140 and 175 g a.i./ha. Data were sufficient to conclude that the 140 g a.i./ha rate is the lowest effective rate for common ragweed suppression. Moreover, data did not show an advantage of the 175 g a.i./ha rate over the lower proposed rate of 140 g a.i./ha in terms of control level for this weed when evaluated early in the season. The efficacy of the higher proposed rate for common ragweed control was evaluated in the later season in only 3 trials conducted in 2000 where application of Callisto 480SC Herbicide was not followed by a postemergence application of Accent. Therefore, data are insufficient to support the labelling of the 175 g a.i./ha rate for common ragweed control.

Wild Mustard
The efficacy of Callisto 480SC Herbicide applied pre-emergence to the crop for control of wild mustard was evaluated in 7 trials conducted from 1999 and 2001 in Ontario and Quebec. In 7 trials, control averaged 86% and ranged from 71–100%, 20–31 days after application of 140 g a.i./ha Callisto 480SC Herbicide. In 1 trial, Callisto 480SC Herbicide applied at 100 and 140 g a.i./ha resulted in 91 and 98% control of this weed, respectively. In 6 other trials conducted in 2001, control averaged 84 and 87% for Callisto 480SC Herbicide applied at 140 and 175 g a.i./ha, respectively.

A claim of control was proposed for mustard (not species specific) for Callisto 480SC Herbicide applied pre-emergence at either of the 2 proposed rates, 140 and 175 g a.i./ha. Only data for wild mustard were submitted. Control from pre-emergence applications was inconsistent, but was always at least 71%. There was little difference in efficacy between the 140 and 175 g a.i./ha rates. When data from 4 early postemergence trials were considered with the data from pre-emergence trials, it was concluded that Callisto 480SC Herbicide applied at 140 g a.i./ha can be expected to result in control of wild mustard. In the 4 early postemergence trials, control after application of either 140 or 175 g a.i./ha Callisto 480SC Herbicide averaged 97% and ranged from 95–100%, 20–22 days after application. In the 4 early postemergence trials, wild mustard development may have been slightly more advanced at application than in the pre-emergence trials, although this is not clear since weed development stage was not mentioned in most reports of the pre-emergence trials. However, in 3 of the early postemergence trials, wild mustard was at an early stage of development, having developed at up to the 1-leaf stage in 2 trials, up to the 2-leaf stage in 1 trial and up to the 6-leaf stage in the fourth trial. The efficacy of Callisto 480SC Herbicide applied at a lower than proposed rate was evaluated in just 1 trial. Therefore, insufficient data were submitted to make a determination of the lowest effective rate for wild mustard control.

Other Proposed Weed Claims
Insufficient data were submitted in support of control claims for lady's thumb and eastern black nightshade. No data were submitted for other mustard species, stinkweed or shepherd's purse. Control claims for these weed species are not acceptable for labelling.

Conclusions
Sufficient data were submitted to demonstrate that the lowest effective rate for Callisto 480SC Herbicide is 140 g a.i./ha for redroot pigweed control and common ragweed suppression for the pre-emergence application timing. Insufficient data were submitted to demonstrate the lowest effective rate for other weed species for which control claims were proposed.

Claims of control for lamb's-quarters, redroot pigweed, velvetleaf and wild mustard as well as a claim of suppression for common ragweed, are acceptable for labelling for Callisto 480SC Herbicide applied pre-emergence to the crop and weeds at the lower proposed rate of 140 g a.i./ha in conventional till corn. However, these claims are not acceptable for CHU areas of 2500 or less due to a lack of data from short season areas.

7.1.4.2.2 Tank Mix with Dual II Magnum

The efficacy of tank mixtures of 100, 140 or 175 g a.i./ha Callisto 480SC Herbicide plus 1.14 to 1.6 kg a.i./ha Dual II Magnum applied pre-emergence to the crop for the control of weed species for which a control claim is proposed for Callisto 480SC Herbicide plus Dual II Magnum-labelled weed species was evaluated in 35 trials. Trials were conducted on a range of soils from 1998 to 2001 in Ontario (32 trials at 19 sites) and Quebec (3 trials at 2 sites) in mainly mid-long season areas.

In 35 trials, Dual II Magnum, included at rates of 1.14 to 1.6 kg a.i./ha in tank mixtures with 100, 140 or 175 g a.i./ha Callisto 480SC Herbicide, did not inhibit the activity of Callisto 480SC Herbicide for control or suppression of weed species for which claims were determined to be acceptable for Callisto 480SC Herbicide applied alone at 140 g a.i./ha, specifically lamb's-quarters (33 trials), redroot pigweed (23 trials), velvetleaf (11 trials), wild mustard (7 trials) and common ragweed (15 trials). In the 12 pre-emergence trials that included a treatment of Dual II Magnum alone, control of Dual II Magnum-labelled grass weed species was similar for 1.14 or 1.6 kg a.i./ha Dual II Magnum alone and Callisto 480SC Herbicide tank mixed with these same rates of Dual II Magnum, specifically for eastern black nightshade (1 trial), green foxtail (9 trials), yellow foxtail (5 trials), large crabgrass (4 trials) and barnyardgrass (3 trials).

A claim of control for Dual II Magnum labelled weed species plus lamb's-quarters, redroot pigweed, velvetleaf and wild mustard as well as suppression of common ragweed for the proposed tank mixture of 140 g a.i./ha Callisto 480SC Herbicide plus 1.14–1.6 kg a.i./ha Dual II Magnum applied pre-emergence to conventional tillage field corn grown is acceptable from an efficacy standpoint, except in geographic areas averaging 2500 seasonal CHU or less.

7.1.4.2.3 Tank Mix with Primextra II Magnum

The efficacy of tank mixtures of 140 or 175 g a.i./ha Callisto 480SC Herbicide plus 2.16 to 2.88 kg a.i./ha Primextra II Magnum applied pre-emergence to the crop for the control of weed species for which a control claim is proposed for Callisto 480SC Herbicide plus Primextra II Magnum-labelled weed species was evaluated in 23 trials conducted on a range of soils from 1999 to 2001 in mainly mid- to long-season areas in Ontario (21 trials) and Quebec (2 trials). Trials were conventional tillage only.

In all the trials conducted in 1999 and 2001 as well as 3 in 2000, applications of Callisto 480SC Herbicide alone were followed by a postemergence application of 25 g a.i./ha Accent plus a non-ionic surfactant for grassy weed control. No herbicides were applied following treatments of Callisto 480SC Herbicide plus Primextra II Magnum. The efficacy of the proposed tank mixture was compared to a registered treatment of 2.16 kg a.i./ha Primextra II Magnum applied alone and to Callisto 480SC Herbicide applied alone (where control was assessed prior to application of Accent as well as in those trials conducted in 2000 where Callisto 480SC Herbicide was not followed by a postemergence

application of Accent). Comparisons to treatments of Callisto 480SC Herbicide alone that were followed by Accent were not made because Accent, while registered for control of several grass weed species, has considerable activity on many broadleaved weeds, thereby confounding the effect of Callisto 480SC Herbicide.

In 5 trials, Primextra II Magnum, included at rates of 2.16-2.88 kg a.i./ha in tank mixtures with 140 or 175 g a.i./ha Callisto 480SC Herbicide, did not inhibit the activity of Callisto 480SC Herbicide for control of velvetleaf, the only weed species for which a control claim was determined to be acceptable for Callisto 480SC Herbicide alone and for which there is no control claim on the Primextra II Magnum label. In 18 pre-emergence trials to include a treatment of Primextra II Magnum alone, control of weed species for which there are registered control claims for Primextra II Magnum and for which claims were either not proposed or acceptable for Callisto 480SC Herbicide was similar for Primextra II Magnum applied alone at 2.16 or 2.491 kg a.i./ha and 140 or 175 g a.i./ha Callisto 480SC Herbicide tank mixed with the same rate of Primextra II Magnum, specifically for eastern black nightshade (1 trial), lady's thumb (3 trials), wild buckwheat (6 trials), pale smartweed (1 trial), green foxtail (12 trials), yellow foxtail (6 trials), large crabgrass (6 trials), barnyardgrass (5 trials) and fall panicum (1 trial).

The tank mixture of 140 g a.i./ha Callisto 480SC Herbicide plus 2.16–2.88 kg a.i./ha Primextra II Magnum applied pre-emergence to conventional tillage field corn is acceptable from an efficacy standpoint, except in geographic areas of 2500 average seasonal CHUs or less, for control of Primextra II Magnum-labelled weeds, velvetleaf and triazine tolerant biotypes of weed species for which there are Callisto 480SC Herbicide-accepted claims.

7.1.4.2.4 Tank Mix with Dual II Magnum and Atrazine

The efficacy of tank mixtures of 175 g a.i./ha Callisto 480SC Herbicide plus 1.14 to 1.6 kg a.i./ha Dual II Magnum plus 1.0 to 1.5 kg a.i./ha atrazine applied pre-emergence to the crop for the control of weed species for which a control claim is proposed for Callisto 480SC Herbicide and weeds for which there are registered control claims for Dual II Magnum and atrazine was evaluated in 10 trials conducted in 2001 on a range of soils in Ontario (9 trials) and Quebec (1 trial). While Dual II Magnum plus atrazine are proposed for tank mixing with Callisto 480SC Herbicide at both proposed rates of 140 and 175 g a.i./ha, tank mixtures that included only the higher Callisto 480SC Herbicide rate were tested. Tillage practice was conventional in 9 trials and minimum (reduced) in 1 trial.

Treatments of Callisto 480SC Herbicide alone were followed by a postemergence application of 25 g a.i./ha Accent plus a non-ionic surfactant for grassy weed control. No herbicides were applied following treatments of Callisto 480SC Herbicide plus Dual II Magnum plus atrazine. The efficacy of the proposed tank mixture was compared to treatments of Callisto 480SC Herbicide alone (where control was assessed prior to application of Accent). Comparisons to treatments of Callisto 480SC Herbicide alone that

were followed by Accent were not made because Accent, while registered for control of several grass weed species, has considerable activity on many broadleaved weeds, thereby confounding the effect of Callisto 480SC Herbicide. The proposed tank mixtures of 175 g a.i./ha Callisto 480SC Herbicide plus 1.14 or 1.6 kg a.i./ha Dual II Magnum plus 1.0 or 1.5 kg a.i./ha atrazine were directly compared to tank mixtures of 175 g a.i./ha Callisto 480SC Herbicide plus 2.491 kg a.i./ha Primextra II Magnum (containing 1.1 kg a.i./ha atrazine and 1.38 kg a.i./ha s-metolachlor) in those trials to include the latter treatment.

In 3 trials, 1.14 or 1.6 kg a.i./ha Dual II Magnum and atrazine as Aatrex Liquid 480 in tank mixtures with 175 g a.i./ha Callisto 480SC Herbicide did not inhibit the activity of Callisto 480SC Herbicide for control of velvetleaf, the only weed species for which a control claim was determined to be acceptable for Callisto 480SC Herbicide alone and for which there is no control claim on either the Dual II Magnum or atrazine (Aatrex Nine-O or Aatrex Liquid 480) labels. Callisto 480SC Herbicide did not appear to compromise the activity of atrazine (as Atrazine 480 or Aatrex Nine-O) for control of atrazine-labelled broadleaved weed species (lady's thumb in 1 trial and wild buckwheat in 2 trials) or the activity of Dual II Magnum for control of labelled weeds (eastern black nightshade in 1 trial, green foxtail in 3 trials, yellow foxtail in 1 trial, large crabgrass in 2 trials, barnyardgrass in 1 trial, fall panicum in 1 trial and old witchgrass in 1 trial) when tank mixed with these products. While proposed tank mixtures with the lower rate of Callisto 480SC Herbicide were not evaluated in any of the trials, it would not be expected that either atrazine or Dual II Magnum would compromise the efficacy of this lower proposed rate of Callisto 480SC Herbicide for control of velvetleaf, particularly given that atrazine could be expected to have activity on velvetleaf. There was only 1 year of data for the tank mixtures of Callisto 480SC Herbicide plus atrazine plus Dual II Magnum. In 4 independent trials conducted during that year, the tank mixtures of 175 g a.i./ha Callisto 480SC Herbicide plus 1.0 kg a.i./ha atrazine plus 1.14 kg a.i./ha Dual II Magnum and 175 g a.i./ha Callisto 480SC Herbicide plus 1.5 kg a.i./ha atrazine plus 1.6 kg a.i./ha Dual II Magnum were compared to 175 g a.i./ha Callisto 480SC Herbicide plus 2.491 kg a.i./ha Primextra II Magnum (1.1 kg a.i./ha atrazine and 1.38 kg a.i./ha s-metolachlor). Since there were 3 years of data for tank mixtures of Callisto 480SC Herbicide plus Primextra II Magnum, 1 year of data for the tank mixtures that include both atrazine and Dual II Magnum was considered sufficient for review.

The tank mixture of 140 g a.i./ha Callisto 480SC Herbicide plus 1.14–1.6 kg a.i./ha Dual II Magnum plus 1.0–1.5 kg a.i./ha atrazine (as Aatrex Nine-O or Aatrex Liquid 480) applied pre-emergence to conventional tillage field corn is acceptable from an efficacy standpoint, except in geographic areas of 2500 average seasonal CHUs or less, for control of Dual II Magnum- and atrazine-labelled weeds, velvetleaf and triazine tolerant biotypes of weed species for which there are Callisto 480SC Herbicide-accepted claims.

7.1.4.3 Early Postemergence

7.1.4.3.1 Callisto 480SC Herbicide Alone

The efficacy of Callisto 480SC Herbicide applied alone at the proposed rates of 140 or 175 g a.i./ha for control of weed species for which a control claim is proposed was evaluated in 14 trials conducted on a range of soils in 2001, 13 of which were conducted in Ontario and 1 of which was conducted in Quebec. No data for rates lower than the 2 proposed (e.g., 0.5×, 0.75×) were provided. Trials were conventional tillage, except for 3 that were reduced tillage. In all trials, Callisto 480SC Herbicide was followed by a postemergence application of 25 g a.i./ha Accent plus a non-ionic surfactant for grassy weed control. Evaluations after Accent was applied were not considered in support of the proposed weed claims because Accent, while registered for control of several grass weed species, has considerable activity on many broadleaved weeds, thereby confounding the effect of Callisto 480SC Herbicide. Therefore, only data collected prior to Accent application were used for review.

Lamb's-quarters
The efficacy of Callisto 480SC Herbicide applied early postemergence for control of lamb's-quarters was evaluated in 14 trials. Lamb's-quarters had not developed to past the 2-leaf stage in most of those trials in which weed developmental stage was reported. Control averaged about 85 and 93% about 1 week after application of 140 and 175 g a.i./ha Callisto 480SC Herbicide, respectively, over 8 trials. At 17–22 days after application of 140 and 175 g a.i./ha Callisto 480SC Herbicide, lamb's-quarters control averaged 95 and 97%, respectively, over 13 trials.

Consistent control of lamb's-quarters was observed for Callisto 480SC Herbicide applied early postemergence at the lower proposed rate and corroborates the data from pre-emergence trials. A control claim for lamb's-quarters is acceptable for Callisto 480SC Herbicide applied early postemergence at up to the weed 2-leaf stage at the lower proposed rate of 140 g a.i./ha in conventional till corn. No data were submitted for lower than proposed rates; therefore, no conclusion can be made on lowest effective rate.

Redroot Pigweed
The efficacy of Callisto 480SC Herbicide applied early postemergence to the crop for control of redroot pigweed was evaluated in 9 trials. Redroot pigweed had not developed past the 2-leaf stage in most of those trials for which weed developmental stage was reported. Control averaged about 92 and 94% about 1 week after application of 140 and 175 g a.i./ha Callisto 480SC Herbicide, respectively, over 4 trials. At 17–22 days after application of 140 and 175 g a.i./ha Callisto 480SC Herbicide, lamb's-quarters control averaged 97 and 98%, respectively, over 9 trials.

Consistent control of redroot pigweed was observed for Callisto 480SC Herbicide applied early postemergence at the lower proposed rate and corroborates the data from pre-emergence trials. A control claim for redroot pigweed is acceptable for Callisto

480SC Herbicide applied early postemergence at up to the weed 2-leaf stage at the lower proposed rate of 140 g a.i./ha in conventional till corn. No data were submitted for lower than proposed rates; therefore, no conclusion can be made on lowest effective rate for the early postemergence timing.

Velvetleaf
The efficacy of Callisto 480SC Herbicide applied early postemergence to the crop for control of velvetleaf was evaluated in 6 trials. At application, velvetleaf had not yet emerged in 1 trial, had developed up to the 1-leaf stage in 4 trials and had developed up to the 2-leaf stage in the remaining trial. Control averaged about 69 and 70% about 1 week after application of 140 and 175 g a.i./ha Callisto 480SC Herbicide, respectively, over 6 trials. At 20–22 days after application of 140 and 175 g a.i./ha Callisto 480SC Herbicide, lamb's-quarters control averaged 97 and 96%, respectively, over 6 trials.

Consistent control of velvetleaf was observed for Callisto 480SC Herbicide applied early postemergence at the lower proposed rate and corroborates the data from pre-emergence trials. A control claim for velvetleaf is acceptable for Callisto 480SC Herbicide applied early postemergence at up to the weed 2-leaf stage at the lower proposed rate of 140 g a.i./ha in conventional till corn. No data were submitted for lower than proposed rates; therefore, no conclusion can be made on lowest effective rate for the early postemergence timing.

Common Ragweed
The efficacy of Callisto 480SC Herbicide applied early postemergence to the crop for control of common ragweed was evaluated in 6 trials. In the 3 trials for which information was available on the weed developmental stage at application, common ragweed had developed up to the 2-leaf stage. Control averaged about 54 and 48% about 1 week after application of 140 and 175 g a.i./ha Callisto 480SC Herbicide, respectively, over 4 trials. At 20–22 days after application of 140 and 175 g a.i./ha Callisto 480SC Herbicide, common ragweed control averaged 76 and 81%, respectively, over 5 trials.

Common ragweed was not consistently controlled by either rate of Callisto 480SC Herbicide applied early postemergence; however, suppression of common ragweed was observed for Callisto 480SC Herbicide applied at both rates and corroborates the data from pre-emergence trials. A claim of suppression for common ragweed at up to the weed 2-leaf stage is acceptable for labelling for Callisto 480SC Herbicide applied early postemergence at 140 g a.i./ha to conventional till corn.

Wild Mustard
The efficacy of Callisto 480SC Herbicide applied early postemergence to the crop for control of wild mustard was evaluated in 4 trials. Wild mustard had not developed past the 2-leaf stage in most of those trials for which weed developmental stage was reported. Over 4 trials, control averaged about 81 and 87% about 1 week after application of 140 and 175 g a.i./ha Callisto 480SC Herbicide, respectively. At 20–22 days after application

of 140 and 175 g a.i./ha Callisto 480SC Herbicide, wild mustard control averaged 97% for both rates.

Control of wild mustard was consistent over the 4 trials for Callisto 480SC Herbicide applied at either rate and was numerically greater than that observed in 7 pre-emergence trials conducted over 2 years where wild mustard control averaged 86% and ranged from 71 to 100% in plots treated with the rate of 140 g a.i./ha. A claim of control for wild mustard at up to the weed 2-leaf stage is acceptable for Callisto 480SC Herbicide applied early postemergence at 140 g a.i./ha to conventional till corn.

Other Weed Species
Insufficient data were submitted in support of control claims for lady's thumb and eastern black nightshade. No data were submitted for other mustard species, stinkweed or shepherd's purse. Control claims for these weed species are not acceptable for labelling.

Conclusions
No data were submitted to demonstrate the lowest effective rate for any of the weed species for which control claims are proposed for this application timing.

Claims of control for lamb's-quarters, redroot pigweed, velvetleaf and wild mustard as well as a claim of suppression of common ragweed are acceptable for labelling for Callisto 480SC Herbicide applied early postemergence at up to the weed 2-leaf stage at the lower proposed rate of 140 g a.i./ha to conventional till corn. However, these claims are not acceptable for areas of 2500 CHU or less due to a lack of data from short season areas.

7.1.4.3.2 Tank Mix with Dual II Magnum

The efficacy of tank mixtures of 140 or 175 g a.i./ha Callisto 480SC Herbicide plus 1.14 to 1.6 kg a.i./ha Dual II Magnum applied early postemergence to the crop for the control of weed species for which a control claim is proposed for Callisto 480SC Herbicide plus Dual II Magnum-labelled weed species was evaluated in 8 trials conducted on a range of soils in 2001 in mid- to long-season areas in Ontario (7 trials) and Quebec (1 trial).

In these trials, application of Callisto 480SC Herbicide alone was followed by a postemergence application of 25 g a.i./ha Accent plus a non-ionic surfactant for grassy weed control. No herbicides were applied following treatments of Callisto 480SC Herbicide plus Dual II Magnum. The efficacy of the proposed tank mixtures was compared to Callisto 480SC Herbicide applied alone (where control was assessed prior to application of Accent) and, in 4 trials, to Dual II Magnum alone (where efficacy was assessed prior to a postemergence application of 10 g a.i./ha Peak (prosulfuron) plus 140 g a.i./ha Banvel II (dicamba) plus 0.2% Ag-Surf). Comparisons to treatments of Callisto 480SC Herbicide alone that were followed by Accent were not made because Accent, while registered for control of several grass weed species, has considerable

activity on many broadleaved weeds, thereby confounding the effect of Callisto 480SC Herbicide.

In 8 trials, Dual II Magnum, included at rates of 1.14 to 1.6 kg a.i./ha in tank mixtures with 140 or 175 g a.i./ha Callisto 480SC Herbicide, did not inhibit the activity of Callisto 480SC Herbicide for control or suppression of weed species for which claims were determined to be acceptable for Callisto 480SC Herbicide applied alone at 140 g a.i./ha, specifically for lamb's-quarters (8 trials), redroot pigweed (5 trials), velvetleaf (3 trials), wild mustard (4 trials) and common ragweed (3 trials). In the 4 postemergence trials to include a treatment of Dual II Magnum alone, control of Dual II Magnum-labelled grass weed species was similar for 1.14 kg a.i./ha Dual II Magnum alone and Callisto 480SC Herbicide tank mixed with this same rate of Dual II Magnum, specifically for green foxtail (2 trials), yellow foxtail (1 trial), large crabgrass (2 trials) and barnyardgrass (2 trials). These data corroborate those from the pre-emergence trials.

A claim of control for Dual II Magnum-labelled weed species plus control of lamb's-quarters, redroot pigweed, velvetleaf and wild mustard as well as suppression of common ragweed for the proposed tank mixture of 140 g a.i./ha Callisto 480SC Herbicide plus 1.14–1.6 kg a.i./ha Dual II Magnum applied early postemergence to conventional tillage field corn is acceptable from an efficacy standpoint, except in areas of 2500 CHU or less.

7.1.4.3.3 Tank Mix with Primextra II Magnum

The efficacy of tank mixtures of 140 or 175 g a.i./ha Callisto 480SC Herbicide plus 2.16 to 2.88 kg a.i./ha Primextra II Magnum applied early postemergence (crop spike to 2-leaf stage) for the control of weed species for which a control claim is proposed for Callisto 480SC Herbicide plus Primextra II Magnum-labelled weed species was evaluated in 8 trials conducted in 2001 on a range of soils at 7 sites in Ontario and 1 site in Quebec.

Applications of Callisto 480SC Herbicide alone were followed by a postemergence application of 25 g a.i./ha Accent plus a non-ionic surfactant for grassy weed control. No herbicides were applied following treatments of Callisto 480SC Herbicide plus Primextra II Magnum. The efficacy of the proposed tank mixture was compared to a registered treatment of 2.16 kg a.i./ha Primextra II Magnum applied alone and Callisto 480SC Herbicide applied alone (where control was assessed prior to application of Accent). Comparisons to treatments of Callisto 480SC Herbicide alone that were followed by Accent were not made because Accent, while registered for control of several grass weed species, has considerable activity on many broadleaved weeds, thereby confounding the effect of Callisto 480SC Herbicide.

In 2 trials, Primextra II Magnum, included at rates of 2.16–2.88 kg a.i./ha in tank mixtures with 140 or 175 g a.i./ha Callisto 480SC Herbicide, did not inhibit the activity of Callisto 480SC Herbicide for control of velvetleaf, the only weed species for which a control claim was determined to be acceptable for Callisto 480SC Herbicide alone and for which there is no control claim on the Primextra II Magnum label. In 5 early

postemergence trials to include a treatment of Primextra II Magnum alone, control of weed species for which there are registered control claims for Primextra II Magnum and for which claims were either not proposed or acceptable for Callisto 480SC Herbicide was similar for Primextra II Magnum applied alone at 2.16 or 2.491 kg a.i./ha and 140 or 175 g a.i./ha Callisto 480SC Herbicide tank mixed with the same rate of Primextra II Magnum, specifically for lady's thumb (1 trial), green foxtail (4 trials), yellow foxtail (1 trial), giant foxtail (2 trials), large crabgrass (2 trials) and barnyardgrass (2 trials).

The tank mixture of 140 g a.i./ha Callisto 480SC Herbicide plus 2.16–2.88 kg a.i./ha Primextra II Magnum applied early postemergence to conventional tillage field corn is acceptable from an efficacy standpoint, except in geographic areas of 2500 average seasonal CHUs or less, for control of Primextra II Magnum-labelled weeds, velvetleaf and triazine tolerant biotypes of weed species for which there are Callisto 480SC Herbicide-accepted claims.

7.1.4.3.4 Tank Mix with Dual II Magnum and Atrazine

The efficacy of tank mixtures of 175 g a.i./ha Callisto 480SC Herbicide plus 1.14 to 1.6 kg a.i./ha Dual II Magnum plus 1.0 to 1.5 kg a.i./ha atrazine applied early postemergence to the crop for the control of weed species for which a control claim is proposed for Callisto 480SC Herbicide and of weeds for which there are registered control claims for Dual II Magnum and atrazine was evaluated in 10 trials conducted in 2001 on a range of soils in Ontario (9 trials) and Quebec (1 trial). While Dual II Magnum plus atrazine are proposed for tank mixing with Callisto 480SC Herbicide at both proposed rates of 140 and 175 g a.i./ha, tank mixtures that included only the higher Callisto 480SC Herbicide rate were tested. Tillage practice was conventional in 8 trials and minimum (reduced) in 2 trials.

Treatments of Callisto 480SC Herbicide alone were followed by a postemergence application of 25 g a.i./ha Accent plus a non-ionic surfactant for grassy weed control. No herbicides were applied following treatments of Callisto 480SC Herbicide plus Dual II Magnum plus atrazine. The efficacy of the proposed tank mixture was compared to treatments of Callisto 480SC Herbicide alone (where control was assessed prior to application of Accent). Comparisons to treatments of Callisto 480SC Herbicide alone that were followed by Accent were not made because Accent, while registered for control of several grass weed species, has considerable activity on many broadleaved weeds, thereby confounding the effect of Callisto 480SC Herbicide. The proposed tank mixtures of 175 g a.i./ha Callisto 480SC Herbicide plus 1.14 or 1.6 kg a.i./ha Dual II Magnum plus 1.0 or 1.5 kg a.i./ha atrazine were directly compared to tank mixtures of 175 g a.i./ha Callisto 480SC Herbicide plus 2.491 kg a.i./ha Primextra II Magnum (containing 1.1 kg a.i./ha atrazine and 1.38 kg a.i./ha s-metolachlor) in those trials to include the latter treatment.

In 4 trials, 1.14 or 1.6 kg a.i./ha Dual II Magnum and atrazine, as Aatrex Nine-O or Aatrex Liquid 480, in tank mixtures with 175 g a.i./ha Callisto 480SC Herbicide did not inhibit the activity of Callisto 480SC Herbicide for control of velvetleaf, the only weed

species for which a control claim was determined to be acceptable for Callisto 480SC Herbicide alone and for which there is no control claim on the Dual II Magnum or atrazine (Aatrex Nine-O or Aatrex Liquid 480) labels. Callisto 480SC Herbicide did not appear to compromise the activity of atrazine (as Atrazine 480 or Aatrex Nine-O) for control of atrazine-labelled broadleaved weed species (lady's thumb in 3 trials and wild buckwheat in 3 trials) or the activity of Dual II Magnum for control of labelled weeds (eastern black nightshade in 1 trial, green foxtail in 3 trials, yellow foxtail in 3 trials, large crabgrass in 1 trial, barnyardgrass in 2 trials and fall panicum in 1 trial) when tank mixed with these products. While proposed tank mixtures with the lower rate of Callisto 480SC Herbicide were not evaluated in any of the trials, it would not be expected that either atrazine or Dual II Magnum would compromise the efficacy of this lower proposed rate of Callisto 480SC Herbicide for control of velvetleaf, particularly given that atrazine could be expected to have activity on velvetleaf. There was only 1 year of data for the tank mixtures of Callisto 480SC Herbicide plus atrazine plus Dual II Magnum, but in 4 independent trials, the tank mixtures of 175 g a.i./ha Callisto 480SC Herbicide plus 1.0 kg a.i./ha atrazine plus 1.14 kg a.i./ha Dual II Magnum and 175 g a.i./ha Callisto 480SC Herbicide plus 1.5 kg a.i./ha atrazine plus 1.6 kg a.i./ha Dual II Magnum were compared to 175 g a.i./ha Callisto 480SC Herbicide plus 2.491 kg a.i./ha Primextra II Magnum (1.1 kg a.i./ha atrazine and 1.38 kg a.i./ha s-metolachlor). Since there were 3 years of data for tank mixtures of Callisto 480SC Herbicide plus Primextra II Magnum, 1 year of data for the tank mixtures that include both atrazine and Dual II Magnum were considered sufficient for review.

The tank mixture of 140 g a.i./ha Callisto 480SC Herbicide plus 1.14-1.6 kg a.i./ha Dual II Magnum plus 1.0–1.5 kg a.i./ha atrazine (as Aatrex Nine-O or Aatrex Liquid 480) applied early postemergence to conventional tillage field corn is acceptable from an efficacy standpoint, except in geographic areas of 2500 average seasonal CHUs or less, for control of Dual II Magnum- and atrazine-labelled weeds, velvetleaf and triazine tolerant biotypes of weed species for which there are Callisto 480SC Herbicide-accepted claims.

7.1.4.4 Late Postemergence

Data were submitted from 44 conventional-till field trials conducted in 1999, 2000 and 2001 over at least 26 sites (41 trials in Ontario at 25 sites and 1 additional trial conducted in Ontario in 2001 at an unknown site) and Quebec (2 trials at 1 site) in which the efficacy of Callisto 480SC Herbicide alone and/or in tank mixtures was assessed. Callisto 480SC Herbicide was evaluated at the proposed rate of 100 g a.i./ha; no rates lower than that proposed were assessed.

The majority of the 21 trials conducted in 1999 and 2000 included treatments of 100 g a.i./ha Callisto 480SC Herbicide plus 1% Superior Oil Concentrate (SOC) plus 2.5% urea-ammonium nitrate (UAN); 1 trial conducted in 2000 included treatments of Callisto 480SC Herbicide plus an unspecified crop oil adjuvant plus 2.5% UAN. One trial in 2000 did not include a Callisto 480SC Herbicide alone treatment (only in tank mixtures). In all

except 1 of the 20 trials to include Callisto 480SC Herbicide alone treatments, treatments of Callisto alone were specifically preceded with a pre-emergence application of a reduced rate of 600–800 g a.i./ha Dual II Magnum, i.e., Dual II Magnum was not applied as a blanket treatment. Each of the 23 trials conducted in 2001 included treatments of 100 g a.i./ha Callisto 480SC Herbicide plus 0.2% v/v non-ionic surfactant, either as Agsurf (14 trials) or Agral 90 (9 trials). While 6 of these trials also included treatments of Callisto 480SC Herbicide plus 1% of an unspecified crop oil concentrate (COC) and an additional 8 trials included treatments of 100 g a.i./ha Callisto 480SC Herbicide plus 1% COC plus 2.5% UAN, the specific crop oil was not SOC. Therefore, data from 2001 could not be "bridged" to data from the previous 2 years. In 6 trials, treatments of Callisto 480SC Herbicide were specifically preceded with a pre-emergence application of 1.357 kg a.i./ha Dual II Magnum. No data were submitted for the proposed treatment (with a non-ionic surfactant) from trials in shorter season areas.

Data were insufficient to support proposed efficacy claims for the proposed treatment of Callisto 480SC Herbicide plus a non-ionic surfactant. Efficacy data from 6 to 25 relevant trials were submitted in support of each of the 5 proposed tank mixtures. All or most of the relevant data submitted in support of the tank mixtures were generated in one year.

The efficacy of Callisto 480SC Herbicide applied postemergence without an adjuvant or at lower than proposed rates with a non-ionic surfactant was not assessed. Therefore, the lowest effective rate could not be established. In the trials that were considered relevant to the proposal, spray volumes of 150 L/ha or 196–200 L/ha were assessed; treatments of Callisto 480SC Herbicide alone or in tank mixtures were not evaluated in spray volumes of 100 L/ha.

The proposed late postemergence use of Callisto 480SC Herbicide alone or in tank mixtures is unacceptable for labelling from an efficacy standpoint. Additional data are required before control claims can be considered for each weed species for which control claims are proposed. Additional trials must include treatments of Callisto 480SC Herbicide alone and in the proposed tank mixtures at the proposed rate of 100 g a.i./ha and a lower rate of 75 g a.i./ha. Treatments of Callisto 480SC Herbicide alone or in tank mixtures must not be preceded or followed by other herbicides. Trials should be conducted at a variety of locations including short-season areas (CHU $\leq$ 2500). Treatments of Callisto 480SC Herbicide alone and in proposed tank mixtures made in 100 L/ha are required to support labelling of the lower end of the proposed spray volume range.

7.1.4.5 Rainfastness

No data were submitted from trials in which rainfastness were evaluated. The proposed postemergence rainfast interval of three hours is not acceptable for labelling.

7.1.4.6 Overall Conclusions on Efficacy of Callisto 480SC Herbicide

Efficacy data were insufficient to support proposed weed control claims for Callisto 480SC Herbicide for the preplant surface and late postemergence application timings. Efficacy data were sufficient to support the use of Callisto 480SC Herbicide for pre-emergence and early postemergence use in corn on a conditional basis. Additional efficacy data are required to support the need for a single application rate of 140 g a.i./ha for those weed species for which a control claim is conditionally supported.

The submitted data support claims of control for lamb's-quarters, redroot pigweed, velvetleaf and wild mustard as well as suppression of common ragweed for Callisto 480SC Herbicide applied pre-emergence or early postemergence to the crop at 140 g a.i./ha at up to the weed 2-leaf stage in conventional tillage corn grown in eastern Canada. Insufficient data were submitted in support of control claims for lady's thumb, eastern black nightshade, other mustard species, stinkweed or shepherd's purse. Insufficient data were submitted to demonstrate the lowest effective rate, except for redroot pigweed control and common ragweed suppression at the pre-emergence timing. The submitted data support the labelling of tank mixtures of Callisto 480SC Herbicide with Dual II Magnum, Primextra II Magnum, and the combination of Dual II Magnum plus atrazine (as Aatrex Nine-O or Aatrex Liquid 480) at the pre-emergence and early postemergence application timings for broader spectrum weed control, including annual grasses.

7.2 Phytotoxicity to Target Plants or Target Plant Products

7.2.1 Field Corn

7.2.1.1 Preplant Surface

Crop tolerance data were submitted from the 22 efficacy field trials conducted in 2001 on a range of soils. Two trials conducted in London, Ontario were excluded because Callisto 480SC Herbicide was applied pre-emergence and both trials were conducted under conventional tillage. The remaining 20 surface preplant trials were conducted in Ontario (18 trials) and Quebec (2 trials). Trials were either no-till (16 trials) or reduced tillage (4 trials). Surface preplant treatments of Callisto 480SC Herbicide alone or in tank mixture with glyphosate were followed by a postemergence application of 25 g a.i./ha Accent plus non-ionic surfactant.

The crop tolerance data submitted were insufficient to support the proposed preplant surface use of Callisto 480SC Herbicide alone or in tank mixtures in field corn grown under no- or reduced tillage scenarios. Furthermore, data were available from 1 year only, grain yield data were available from only 2 trials, and no data were available for 2× treatments. No crop tolerance data were submitted for short season hybrids. Therefore the proposed preplant surface use of Callisto 480SC Herbicide alone or in tank mixtures is unacceptable for labelling from a non-safety adverse effects standpoint. Data from a second year of preplant surface trials are required before crop tolerance claims can be

considered for field corn in no- or reduced tillage. Additional trials should be situated over a wide geographic area and include short-season areas (CHU ≤ 2500). Short season hybrids should be evaluated and trials should include proposed treatments at 2× rates. Grain yield data are required to support this application timing.

7.2.1.2 Pre-emergence

7.2.1.2.1 Callisto 480SC Herbicide Alone

Crop tolerance data were submitted from 42 field trials conducted on a range of soils in 1997 (2 trials), 1998 (2 trials), 1999 (6 trials), 2000 (8 trials) and 2001 (24 trials) in Ontario (39 trials at 21 sites) and Quebec (3 trials at 2 sites) in which field corn was treated with a pre-emergence application of 140 or 175 g a.i./ha Callisto 480SC Herbicide. Two pre-emergence trials conducted in London, Ontario, that were identified in the data package as surface preplant trials were included in the above total. All trials were conducted under a conventional tillage regime, except for 1 trial that was conducted under minimum tillage.

In trials conducted in 1999 and 2001, Callisto 480SC Herbicide was followed by a postemergence application of 25 g a.i./ha Accent plus 0.2% v/v Agral 90 or Agsurf. In most of these trials, the first crop tolerance assessment was done prior to Accent application, but later assessments were conducted after Accent application. No postemergence herbicides were applied after the pre-emergence Callisto 480SC Herbicide treatments in 2000. Three trials conducted in 1999 included a rate twice the maximum proposed rate of 175 g a.i./ha. No data from dedicated crop tolerance trials (in which general weed control was achieved with a maintenance herbicide applied over the entire trial area) were submitted. A range of registered treatments were included for comparison. At least 17 hybrids with CHU ratings 2650–3300 (except for 2 which were 2150–2250 CHU) were evaluated in these trials (hybrids were not identified in 2 trials). No trial assessed the response of more than 1 hybrid.

Early season injury to corn 15–31 days after application of 140 or 175 g a.i./ha Callisto 480SC Herbicide did not exceed 3% in any one trial and averaged 0.3% over 37 trials. Injury was similar to registered treatments, including Primextra II Magnum, Banvel II, the tank mixture of Primextra II Magnum plus Banvel II as well as Dual II Magnum followed by a postemergence application of Peak plus Banvel II. Mid-season injury to corn 32–56 days after application was assessed in 31 trials. The greater injury observed at the mid-season evaluation (up to 15% and averaging nearly 2%) was probably due to the sequential postemergence application of Accent in the 1999 and 2001 trials. Injury to corn treated with Callisto 480SC Herbicide followed by Accent was greater than that observed for pre-emergence applications of Primextra II Magnum or of the tank mixture of Primextra II Magnum plus Banvel II, but similar to that of Dual II Magnum followed by Peak plus Banvel II. In 1 trial conducted at St-Augustin, Quebec, in which a short-season hybrid of 2150 CHU was tested, high injury (11 and 15%) was observed at the second evaluation timing for treatments of 140 and 175 g a.i./ha.

Yield was determined in thirteen trials. The grain yield of corn treated with Callisto 480SC Herbicide and followed by Accent was greater than that of the untreated check and similar to or greater than the registered treatments. It should be noted that postemergence application of Accent may have augmented yield over that which would be expected with a pre-emergence application of Callisto 480SC Herbicide alone. The submitted data indicate that Callisto 480SC Herbicide applied alone at up to 175 g a.i./ha could be expected to be safe to field corn grown in higher CHU areas.

The data submitted support a crop tolerance claim on a conditional basis for conventional till field corn treated pre-emergence with Callisto 480SC Herbicide, except for hybrids rated at 2500 CHU or less and in geographic areas with a seasonal average of 2500 CHU or less since data were submitted from trials that were conducted mainly in Ontario in mid- to long-season areas. Additional crop tolerance data are required for short-season hybrids and geographic areas (CHU ≤ 2500).

7.2.1.2.2 Tank Mix with Dual II Magnum

Crop tolerance data were submitted from 24 field trials conducted on a range of soils in 1999 (6 trials), 2000 (8 trials) and 2001 (10 trials) in Ontario (21 trials at 17 sites) and Quebec (3 trials at 2 sites) in which field corn was treated with a pre-emergence application of 140 or 175 g a.i./ha Callisto 480SC Herbicide tank mixed with 1.14, 1.357 or 1.6 kg a.i./ha Dual II Magnum. All trials were conventional tillage. No data from dedicated crop tolerance trials (in which general weed control was achieved with a maintenance herbicide applied over the entire trial area) were submitted. At least 18 hybrids of CHU ratings 2650–3300 (except for 2, which were 2150–2250 CHU) were evaluated in these trials (hybrid was not identified in 1 trial). None of the trials assessed the response of more than 1 hybrid.

Early season injury to field corn, assessed from 15–31 days after application, did not exceed 2% in any one trial and averaged 0.4% over 17 trials in the tank mixture treatment of 175 g a.i./ha Callisto 480SC Herbicide plus 1.6 kg a.i./ha Dual II Magnum. Injury was similar to 175 g a.i./ha Callisto 480SC Herbicide applied alone or to the registered pre-emergence treatments of 2.16 kg a.i./ha Primextra II Magnum, or 2.491 kg a.i./ha Primextra II Magnum plus 600 g a.i./ha Banvel II. In 4 trials, no injury to corn was observed following a pre-emergence application of a tank mixture of 175 g a.i./ha Callisto 480SC Herbicide plus 1.357 kg a.i./ha Dual II Magnum. Mid-season injury to corn 32–56 days after application was assessed in 16 trials. In 15 trials, injury to corn treated with a tank mixture of 175 g a.i./ha Callisto 480SC Herbicide plus 1.6 kg a.i./ha Dual II Magnum averaged 0.6% and ranged from 0–7%. In the 3 trials where corn was treated with 175 g a.i./ha Callisto 480SC Herbicide plus 1.357 kg a.i./ha Dual II Magnum, injury averaged 3%. Over the 12 trials in which direct treatment comparisons could be made, the tank mixtures of 140 or 175 g a.i./ha Callisto 480SC Herbicide plus 1.6 kg a.i./ha Dual II Magnum resulted in similar injury, about 1%, as Callisto 480SC Herbicide applied alone (followed by a postemergence application of Accent) or 2.16 kg a.i./ha Primextra II Magnum.

Yield was assessed in 9 trials. The 6 trials conducted in 2000 and 2001 included treatments of 2.16–2.491 kg a.i./ha Primextra II Magnum. Yield of the Callisto 480SC Herbicide plus Dual II Magnum tank mixture treatments were compared to that of Primextra II Magnum, since both treatments are to control both broadleaved and grassy weeds. The grain yield of corn treated with tank mixtures of 140 or 175 g a.i./ha Callisto 480SC Herbicide plus 1.357–1.6 kg a.i./ha Dual II Magnum was similar to Callisto 480SC Herbicide applied alone (and followed by the postemergence application of Accent) or the registered treatments of 2.16–2.49 kg a.i./ha Primextra II Magnum.

The data submitted support a crop tolerance claim on a conditional basis for conventional till field corn treated pre-emergence with tank mixtures of Callisto 480SC Herbicide plus Dual II Magnum, except for hybrids rated at 2500 CHU or less and in geographic areas with a seasonal average of 2500 CHU or less since data were submitted from trials that were conducted mainly in Ontario in mid- to long-season areas. Additional crop tolerance data are required for short-season hybrids and geographic areas (CHU ≤ 2500).

7.2.1.2.3 Tank Mix with Primextra II Magnum

Crop tolerance data were submitted from 21 field trials conducted on a range of soils in 1999 (3 trials), 2000 (8 trials) and 2001 (10 trials) in Ontario (19 trials at 17 sites) and Quebec (2 trials at 2 sites) in which field corn was treated with a pre-emergence application of 140 or 175 g a.i./ha Callisto 480SC Herbicide tank mixed with 2.16, 2.49 or 2.88 kg a.i./ha Primextra II Magnum. All trials were conventional tillage. No data from dedicated crop tolerance trials (in which general weed control was achieved with a maintenance herbicide applied over the entire trial area) were submitted. At least 15 hybrids of CHU ratings 2650–3300 (except for 1, which was 2150 CHU) were evaluated in these trials (hybrid was not identified in 1 trial). No trial assessed the response of more than 1 hybrid.

Early season injury to corn, assessed 15–31 days after application, did not exceed 2% in any one trial and averaged 0.4% over 14 trials in the tank mixture treatment of 175 g a.i./ha Callisto 480SC Herbicide plus 2.16 kg a.i./ha Primextra II Magnum. Injury was similar to 140 g a.i./ha Callisto 480SC Herbicide applied alone or to the registered pre-emergence treatment of 2.16 kg a.i./ha Primextra II Magnum. In 11 trials, injury to corn treated with 175 g a.i./ha Callisto 480SC Herbicide plus 2.16 kg a.i./ha Primextra II Magnum averaged 0.5%. Injury to the proposed tank mixture at the maximum application rate was assessed in 8 trials conducted in 2001. Injury averaged 0.1% in these trials and was similar to 175 g a.i./ha Callisto 480SC Herbicide applied alone. Injury was not visually detectable in 4 trials after application of a tank mixture of 175 g a.i./ha Callisto 480SC Herbicide plus 2.491 kg a.i./ha Primextra II Magnum. Injury was assessed mid-season (32–56 days after application) in 15 trials. Injury to corn treated with a tank mixture of 140 g a.i./ha Callisto 480SC Herbicide plus 2.16 kg a.i./ha Primextra II Magnum in 12 trials or 175 g a.i./ha Callisto 480SC Herbicide plus 2.16 kg a.i./ha Primextra II Magnum in 10 trials was less than corn treated with a pre-emergence treatment of Callisto 480SC Herbicide alone followed by a postemergence application of

25 g a.i./ha Accent plus non-ionic surfactant. Injury to field corn following application of 175 g a.i./ha Callisto 480SC Herbicide tank mixed with 2.88 kg a.i./ha Primextra II Magnum averaged 1.4% over 9 trials and ranged from 0–6%, similar to that observed for the pre-emergence Callisto 480SC Herbicide alone treatment that was followed by a postemergence application of Accent. No visually detectable injury was observed mid-season to corn treated with 175 g a.i./ha Callisto 480SC Herbicide plus 2.491 kg a.i./ha Primextra II Magnum in 3 trials conducted in 2001. Corn treated with a tank mixture of Callisto 480SC Herbicide plus the maximum rate of Primextra II Magnum (2.88 kg a.i./ha) sustained about 1% greater injury than that treated with a tank mixture that included Primextra II Magnum applied at the minimum rate (2.16 kg a.i./ha).

Six trials were taken to yield. The grain yield of corn treated with tank mixtures of 140 or 175 g a.i./ha Callisto 480SC Herbicide plus 2.16–2.88 kg a.i./ha Primextra II Magnum was usually greater than the weedy check and similar to Callisto 480SC Herbicide applied alone (and followed by a postemergence application of Accent) or the registered treatments of 2.16–2.491 kg a.i./ha Primextra II Magnum.

The data submitted support a crop tolerance claim on a conditional basis for conventional till field corn treated pre-emergence with tank mixtures of Callisto 480SC Herbicide plus Primextra II Magnum, except for hybrids rated at 2500 CHU or less and in geographic areas with a seasonal average of 2500 CHU or less since data were submitted from trials that were conducted mainly in Ontario in mid- to long-season areas. Additional crop tolerance data are required for short-season hybrids and geographic areas (CHU $\leq$ 2500).

7.2.1.2.4 Tank Mix with Dual II Magnum plus Atrazine

Crop tolerance data were submitted from 10 field trials conducted on a range of soils in 2001 in Ontario (9 trials at 9 sites) and Quebec (1 trial) in which field corn was treated with a pre-emergence application of 175 g a.i./ha Callisto 480SC Herbicide tank mixed with 1.0 or 1.5 kg a.i./ha atrazine (as Aatrex Nine-O or Aatrex Liquid 480) plus 1.144 or 1.6 kg a.i./ha Dual II Magnum. All trials were conventional tillage. No data from dedicated crop tolerance trials (in which general weed control was achieved with a maintenance herbicide applied over the entire trial area) were submitted. At least 9 hybrids of CHU ratings of 2650 to 3300 (except for 1, which was 2150 CHU), were evaluated in these trials (hybrid was not identified in 1 trial). No trial assessed the response of more than 1 hybrid.

Early season injury to corn 19–31 days after application of 175 g a.i./ha Callisto 480SC Herbicide tank mixed with either 1.0 kg a.i./ha atrazine plus 1.14 kg a.i./ha Dual II Magnum or the maximum proposed rate of 1.5 kg a.i./ha atrazine plus 1.6 kg a.i./ha Dual II Magnum averaged 0.2% and never exceeded 2%. This was similar to the injury observed for the treatment of Callisto 480SC Herbicide alone in 10 trials, or that observed in 6 trials for the treatments of 1.5 kg a.i./ha atrazine alone and the registered treatment of 2.49 kg a.i./ha Primextra II Magnum plus 600 g a.i./ha Banvel II. Injury was similar or higher when assessed mid-season in 9 trials (47–56 days after application). Injury to corn

treated with a tank mixture of 175 g a.i./ha Callisto 480SC Herbicide plus 1.5 kg a.i./ha atrazine plus 1.6 kg a.i./ha Dual II Magnum averaged 1.1%, which was 0.8% greater than that observed for the same tank mixture that included minimum proposed rates of atrazine (1.0 kg a.i./ha) and Dual II Magnum (1.14 kg a.i./ha). In 6 trials, injury to corn treated with the registered pre-emergence treatment of 2.49 kg a.i./ha Primextra II Magnum (containing 1.11 kg a.i./ha atrazine and 1.38 kg a.i./ha s-metolachlor) plus 600 g a.i./ha Banvel II was similar to the proposed tank mixture applied at the maximum rate.

Yield was assessed in 3 trials with severe weed infestations. The grain yield of corn treated with tank mixtures of 175 g a.i./ha Callisto 480SC Herbicide plus either a combination of 1.0 kg a.i./ha atrazine plus 1.14 kg a.i./ha Dual II Magnum or a combination of 1.5 kg a.i./ha atrazine plus 1.6 kg a.i./ha Dual II Magnum was similar to that of treatments of 140 and 175 g a.i./ha Callisto 480SC Herbicide followed by a postemergence application of Accent.

The data submitted support a crop tolerance claim on a conditional basis for conventional till field corn treated pre-emergence with tank mixtures of Callisto 480SC Herbicide plus Dual II Magnum plus atrazine as Aatrex Nine-O or Aatrex Liquid 480, except for hybrids rated at 2500 CHU or less and in geographic areas with a seasonal average of 2500 CHU or less since data were submitted from trials that were conducted mainly in Ontario in mid- to long-season areas. Additional crop tolerance data are required for short-season hybrids and geographic areas (CHU $\leq$ 2500).

7.2.1.3 Early Postemergence

7.2.1.3.1 Callisto 480SC Herbicide Alone

Crop tolerance data were submitted from 20 field trials conducted in 2001 in Ontario (19 trials at 12 sites) and Quebec (1 trial) in which field corn was treated with an early postemergence application of 140 or 175 g a.i./ha Callisto 480SC Herbicide. Six of these trials were dedicated crop tolerance trials, each of which received either a preplant incorporated application of 2.491 kg a.i./ha Primextra II Magnum (5 trials) or an application of 400 g a.i./ha Liberty 200SN (glufosinate ammonium). The dedicated crop tolerance trials evaluated rates of 175 and 350 g a.i./ha Callisto 480SC Herbicide. Trials were conventional tillage, except for 3 that were reduced tillage; 1 did not indicate tillage practice. A total of 13 hybrids of CHU ratings 2650 to 3350 (except for 1 of 2150 CHU), were evaluated in these trials, although no trial assessed the response of more than 1 hybrid.

In the early season, slight injury to field corn of 1 to 3% was observed 6–17 days after application of 175 g a.i./ha Callisto 480SC Herbicide in 13 trials, with injury averaging 1.3% over 18 trials. At 20–29 days after application, slight injury to field corn of 1 to 3% was observed in the 175 g a.i./ha Callisto 480SC Herbicide treatment in 7 trials, with injury averaging 0.8% over all 20 trials. The maximum injury observed in a Callisto 480SC Herbicide treatment was 4% at the 140 g a.i./ha rate at the second evaluation

timing. When both Callisto 480SC Herbicide rates were considered, slight injury was observed in 10 of 20 trials. At both evaluation timings, injury was similar or less than that observed in registered treatments of 2.491–2.88 kg a.i./ha Primextra II Magnum tank mixed with 288 g a.i./ha Banvel II, 2.88 kg a.i./ha Primextra II Magnum or 1.6 kg a.i./ha Dual. In the dedicated crop tolerance trials, Callisto 480SC Herbicide applied at 2× the maximum proposed rate (350 g a.i./ha) resulted in similar or slightly greater injury than the maximum 1× rate; however, the 2× rate did not result in greater injury than the included registered treatments.

Grain yield was evaluated in 10 trials, including the 6 dedicated crop tolerance trials and 4 trials in which efficacy was assessed. Grain yield of field corn treated with 140 and 175 g a.i./ha Callisto 480SC Herbicide was significantly greater than that of the weedy check in each trial and similar to that of the registered treatments. In the 6 dedicated crop tolerance trials, mean grain yield of either the 175 or 350 g a.i./ha Callisto 480SC Herbicide treatments was about 8% greater than that of the untreated check.

The data submitted support a crop tolerance claim on a conditional basis for conventional till field corn treated early postemergence with Callisto 480SC Herbicide, except for hybrids rated at 2500 CHU or less, and in geographic areas with a seasonal average of 2500 CHU or less since data were submitted from trials that were conducted mainly in Ontario in mid- to long-season areas. Additional crop tolerance data are required for short-season hybrids and geographic areas (CHU ≤ 2500).

7.2.1.3.2 Tank Mix with Dual II Magnum

Crop tolerance data were submitted from 14 field trials conducted on a range of soil types in 2001 in Ontario (13 trials at 10 sites) and Quebec (1 trial) in which field corn was treated with an early postemergence application of 140 or 175 g a.i./ha Callisto 480SC Herbicide tank mixed with 1.14 to 1.6 kg a.i./ha Dual II Magnum. Six of these trials were dedicated crop tolerance trials, each of which received either a preplant incorporated application of 2.491 kg a.i./ha Primextra II Magnum (5 trials) or an application of 400 g a.i./ha Liberty 200SN. The dedicated crop tolerance trials included treatments of the tank mixture at the maximum proposed 1× and 2× rates. Trials were conventional tillage, except for 2 that were reduced tillage; 1 did not indicate tillage practice. A total of 11 hybrids with CHU ratings of 2650 to 3350 (except for 1 of 2150 CHU) were evaluated in these trials, although no trial assessed the response of more than 1 hybrid.

In the early season, slight injury to field corn of 1 to 4% was observed in 10 of 13 trials when evaluated 6–17 days after application of 140 or 175 g a.i./ha Callisto 480SC Herbicide tank mixed with 1.357 or 1.6 kg a.i./ha Dual II Magnum. At 20–29 days after application, slight injury to field corn of 1 to 4% was observed in these tank mixture treatments in 8 of 14 trials. At both evaluation timings, injury in the proposed tank mixture treatments was similar to or less than that observed for registered treatments of 2.491–2.88 kg a.i./ha Primextra II Magnum plus 288 g a.i./ha Banvel II, 2.88 kg a.i./ha Primextra II Magnum, 1.6 kg a.i./ha Dual, or 25 g a.i./ha Ultim plus 236 g a.i./ha Striker.

Callisto 480SC Herbicide applied at the 2× rate in the 6 dedicated crop tolerance trials resulted in greater early season injury (4.8%) than the 1× rate (2.3%); however, injury in the 2× treatment had declined to about 2% by the second evaluation timing, similar to that of the 1× rate treatment.

Grain yield was evaluated in 8 trials, including 2 trials in which efficacy was evaluated and the 6 dedicated crop tolerance trials. Grain yield of field corn treated with 140 or 175 g a.i./ha Callisto 480SC Herbicide tank mixed with 1.357 or 1.6 kg a.i./ha Dual II Magnum was significantly greater than that of the weedy check in each of the 2 efficacy trials and was similar to that of the registered treatments. In the 6 dedicated crop tolerance trials, mean grain yield of the tank mixture treatment of 175 g a.i./ha Callisto 480SC Herbicide plus 1.6 kg a.i./ha Dual II Magnum was about 14% greater than that of the untreated check. Grain yield of the 2× rate treatment of the Callisto 480SC Herbicide plus Dual II Magnum tank mixture was similar to that of the 1× rate.

The data submitted support a crop tolerance claim on a conditional basis for conventional till field corn treated early postemergence with tank mixtures of Callisto 480SC Herbicide plus Dual II Magnum, except for hybrids rated at 2500 CHU or less, and in geographic areas with a seasonal average of 2500 CHU or less since data were submitted from trials that were conducted mainly in Ontario in mid- to long-season areas. Additional crop tolerance data are required for short-season hybrids and geographic areas (CHU ≤ 2500).

7.2.1.3.3 Tank Mix with Primextra II Magnum

Crop tolerance data were submitted from 14 field trials conducted on a range of soil types in 2001 in Ontario (13 trials at 10 sites) and Quebec (1 trial) in which field corn was treated with an early postemergence application of 140 or 175 g a.i./ha Callisto 480SC Herbicide tank mixed with 2.16 to 2.88 kg a.i./ha Primextra II Magnum. Six of these trials were dedicated crop tolerance trials, each of which received either a preplant incorporated application of 2.491 kg a.i./ha Primextra II Magnum (5 trials) or an application of 400 g a.i./ha Liberty 200SN. The dedicated crop tolerance trials included treatments of the tank mixture at the maximum proposed 1× and 2× rates. Trials were conventional tillage, except for 2 that were reduced tillage; 1 trial report did not indicate tillage practice. A total of 11 hybrids of CHU ratings of 2650 to 3350 (except for 1 of 2150 CHU) were evaluated in these trials, although no trial assessed the response of more than 1 hybrid.

In the early season, slight to moderate injury to field corn of 1 to 6% was observed in 10 of 13 trials when evaluated 6–17 days after application of 140 or 175 g a.i./ha Callisto 480SC Herbicide tank mixed with 2.16 to 2.88 kg a.i./ha Primextra II Magnum. At 20–29 days after application, slight injury to field corn of 1 to 5% was observed in these tank mixture treatments in 8 of 14 trials. At both evaluation timings, injury in the proposed tank mixture treatments was similar to that observed for registered treatments of 2.491–2.88 kg a.i./ha Primextra II Magnum plus 288 g a.i./ha Banvel II, 2.88 kg a.i./ha Primextra II Magnum or 25 g a.i./ha Ultim plus 236 g a.i./ha Striker. Callisto 480SC

Herbicide applied at the 2× rate in the 6 dedicated crop tolerance trials resulted in greater early season injury (5%) than the 1× rate (3%); however, injury in the 2× treatment had declined to about 3% by the second evaluation timing, similar to that of the 1× rate treatment.

Grain yield was evaluated in 8 trials, including the 6 dedicated crop tolerance trials and 2 trials in which efficacy was evaluated . Grain yield of field corn treated with 140 or 175 g a.i./ha Callisto 480SC Herbicide tank mixed with 2.16–2.88 kg a.i./ha Primextra II Magnum was significantly greater than that of the weedy check in each of the 2 efficacy trials and was similar to that of the registered treatments. In the 6 dedicated crop tolerance trials, mean grain yield of field corn treated with 175 g a.i./ha Callisto 480SC Herbicide tank mixed with 2.88 kg a.i./ha Primextra II Magnum was the same as that for this tank mixture at the 2× rate and 11% greater than that of the untreated check.

The data submitted support a crop tolerance claim on a conditional basis for conventional till field corn treated early postemergence with tank mixtures of Callisto 480SC Herbicide plus Primextra II Magnum, except for hybrids rated at 2500 CHU or less, and in geographic areas with a seasonal average of 2500 CHU or less since data were submitted from trials that were conducted mainly in Ontario in mid- to long-season areas. Additional crop tolerance data are required for short-season hybrids and geographic areas (CHU ≤ 2500).

7.2.1.3.4 Tank Mix with Dual II Magnum plus Atrazine

Crop tolerance data were submitted from 10 field trials conducted on a range of soil types in 2001 in Ontario (9 trials at 9 sites) and Quebec (1 trial) in which field corn was treated with an early postemergence application of 175 g a.i./ha Callisto 480SC Herbicide tank mixed with both 1.14 to 1.6 kg a.i./ha Dual II Magnum and 1.0 or 1.5 kg a.i./ha atrazine, as Aatrex Nine-O or Atrazine 480. No trials included assessment of a 2× rate. A registered early postemergence treatment of 2.491 kg a.i./ha Primextra II Magnum tank mixed with 288 g a.i./ha Banvel II was included for comparison in all trials. All trials were conventional tillage except for 2 that were reduced tillage; 1 trial report did not indicate tillage practice. A total of 9 hybrids with CHU ratings of 2650 to 3300 (except for 1 of 2150 CHU) were evaluated in these trials, although no trial assessed more than 1 hybrid.

At 6–17 days after application of the proposed tank mixture at the maximum proposed rate of 175 g a.i./ha Callisto 480SC Herbicide plus 1.5 kg a.i./ha atrazine plus 1.6 kg a.i./ha Dual II Magnum, slight to moderate injury of 1–7% was observed in 4 of 9 trials. Injury of 1 to 4% to field corn treated with the proposed tank mixture that included atrazine at either 1.0 or 1.5 kg a.i./ha and Dual II Magnum at either 1.14 or 1.6 kg a.i./ha was observed in 3 of 10 at 20–29 days after application. At both evaluation timings, injury to field corn treated with the proposed tank mixture treatment was similar to that observed for 2.491 kg a.i./ha Primextra II Magnum tank mixed with 288 g a.i./ha Banvel II.

The grain yield of corn treated with the proposed tank mixtures of Callisto 480SC Herbicide plus Dual II Magnum plus atrazine was greater than the weedy check and was similar to other treatments including the registered treatments of atrazine alone followed by a postemergence application of Accent, or a pre-emergence treatment of Primextra II Magnum tank mixed with Banvel II. Yield of the proposed tank mixtures with atrazine and Dual II Magnum was similar to that of the proposed tank mixture with Primextra II Magnum in 1 trial, where Primextra II Magnum was included in the tank mixture at an application rate of s-metolachlor and atrazine that fell between that of the two tank mixture treatments that included Dual II Magnum and atrazine.

The data submitted support a crop tolerance claim on a conditional basis for conventional till field corn treated early postemergence with tank mixtures of Callisto 480SC Herbicide plus Dual II Magnum plus atrazine as Aatrex Nine-O or Aatrex Liquid 480, except for hybrids rated at 2500 CHU or less and in geographic areas with a seasonal average of 2500 CHU or less since data were submitted from trials that were conducted mainly in Ontario in mid- to long-season areas. Additional crop tolerance data are required for short-season hybrids and geographic areas (CHU ≤ 2500).

7.2.1.4 Late Postemergence

Crop tolerance data were submitted from 37 conventional-till field trials conducted over 3 years at a minimum of 26 sites (33 trials in Ontario at 25 sites and 1 additional trial at an unknown site as well as 2 trials in Quebec at 1 site). Crop injury was assessed in 36 trials and yield was determined in 12 trials. Callisto 480SC Herbicide was evaluated at the proposed rate of 100 g a.i./ha in all trials, and applications always included an adjuvant as SOC, a COC, or a non-ionic surfactant.

The majority of the 16 trials conducted in 1999 and 2000 included treatments of 100 g a.i./ha Callisto 480SC Herbicide plus 1% SOC plus 2.5% UAN; 2 trials conducted in 2000 included a treatment of Callisto 480SC Herbicide plus an unspecified crop oil adjuvant plus 2.5% UAN. A treatment of Callisto 480SC Herbicide alone was not evaluated in 1 trial; in this trial, Callisto 480SC Herbicide was only included in tank mixtures. In all except 1 of the 15 trials, the Callisto 480SC Herbicide alone treatment was specifically preceded with a pre-emergence application of a reduced rate of 600–800 g a.i./ha Dual II Magnum, i.e., Dual II Magnum was not applied as a blanket treatment over the entire trial site. A 2× rate of 200 g a.i./ha was included in 5 trials conducted in 1999 only, in which Callisto 480SC Herbicide was applied with SOC.

Each of the 21 trials conducted in 2001 included a treatment of 100 g a.i./ha Callisto 480SC Herbicide plus 0.2% v/v non-ionic surfactant, as Agsurf or Agral 90 in all trials, a treatment of Callisto 480SC Herbicide plus 1% COC without UAN in 6 trials and with UAN in 7 trials. The specific crop oil used was not Superior Oil Concentrate in these trials; therefore, data from 2001 could not be “bridged” to data from the previous 2 years. Furthermore, there were yield data from just 3 trials in which Callisto 480SC Herbicide was applied with a non-ionic surfactant. In these 3 trials, Callisto 480SC Herbicide was

preceded with a pre-emergence application of 1.357 kg a.i./ha Dual II Magnum. No data were submitted for the proposed treatment (with a non-ionic surfactant) in short season areas, or in the Quebec and Atlantic regions.

7.2.2 Production Seed (inbred) Corn

7.2.2.1 Pre-emergence

Crop tolerance data were submitted from 3 field trials conducted over 3 years from 1999 to 2001 at 2 locations in southern Ontario. The number of inbred lines evaluated was trial specific, with 68 inbred lines tested in 1999, 19 of the 68 were again tested in 2000, and 16 of those tested in both 1999 and 2000 were again evaluated in 2001. Nineteen inbred lines were common to the trials conducted in the latter 2 years. The treatment rates of Callisto 480SC Herbicide were 140 and 280 g a.i./ha.

The data submitted indicate that production seed corn can be expected to be tolerant of Callisto 480SC Herbicide applied pre-emergence at the lower proposed rate of 140 g a.i./ha, since standcount and yield response of most production seed corn inbreds treated with 140 or 280 g a.i./ha Callisto 480SC Herbicide was similar to that of the registered postemergence treatment of 25 g a.i./ha Accent. However, there was some variability in response, as observed in the 1999 trial in which some inbred lines treated with either rate of Callisto 480SC Herbicide were significantly higher or lower yielding than where treated with the registered postemergence treatment of Accent.

The data submitted support a crop tolerance claim for production seed corn inbreds treated pre-emergence with Callisto 480SC Herbicide at rates up to 140 g a.i./ha. While most of the evaluated inbred lines responded similarly to Callisto 480SC Herbicide as they did to the registered treatment, there was some minor variability in standcount and seed yield response among inbreds. Due to potential for yield reduction in some inbred lines, the following statement must be included on the label: “Not all seed corn inbreds have been tested; the use of Callisto 480SC Herbicide must be approved by the seed corn company and comply with the directions given by the seed corn company” (a similar statement appears on the label of Accent 75DF herbicide). No crop tolerance data were submitted in support of the proposed tank mixtures for production seed corn. Therefore, from a crop tolerance standpoint, Callisto 480SC Herbicide is acceptable for pre-emergence application to production seed corn at rates of up to 140 g a.i./ha, but is not acceptable for use in tank mixtures.

7.2.3 Sweet Corn

7.2.3.1 Pre-emergence

Crop tolerance data from 7 field trials conducted from 1999–2001 at 3 locations in southern Ontario were submitted in support of the proposed use in sweet corn. A total of 13 hybrids were evaluated, 4 of which were included in all trials, 5 of which were

included in 4 trials conducted in 1999 and 2000, and 4 of which were included in 4 trials conducted in 2001. Trials conducted in 1999 and 2000 included treatments of Callisto 480SC Herbicide at 140 and 280 g a.i./ha, and trials conducted in 2001 included Callisto 480SC Herbicide at 175 and 350 g a.i./ha. None of the proposed tank mixture treatments were included in any of the trials.

Pre-emergence applications of Callisto 480SC Herbicide did not usually result in visually detectable injury. Injury of 1 to 3% was observed in treatments of 280 g a.i./ha Callisto 480SC Herbicide (2× the lower proposed rate) for 3 hybrids in 1 trial each. In 1 of these trials, injury of 3%, observed at 14 days after application, had disappeared by 28 days after application. Injury of 1% was observed in 1 trial for 1 hybrid in the 350 g a.i./ha Callisto 480SC Herbicide treatment (2× the higher proposed rate). Injury of 4% was observed in the 140 g a.i./ha Callisto 480SC Herbicide treatment for 1 hybrid in 1 trial at 14 days after application, which had disappeared by 28 days after application. In 2 trials conducted in 2001, some whitening of leaf tissue was observed for 4 hybrids in 1 trial and 2 in a second trial during the growing season after the final visual injury evaluation had been conducted at 28–39 days after application. It was reported that this injury had disappeared later.

Total yield data were available from all 7 trials, and marketable yield data from 5 trials. In 1999 and 2000, the total yield of sweet corn treated with a pre-emergence application of Callisto 480SC Herbicide at 140 and 280 g a.i./ha averaged 105% and 104%, respectively, that of the weed-free check over 36 data points (9 hybrids × 4 trials). In 2001, the total yield of sweet corn treated with 175 and 350 g a.i./ha Callisto 480SC Herbicide averaged 105% and 98%, respectively, that of the weed-free check over 24 data points (8 hybrids × 3 trials). Marketable yield generally reflected total yield. The data indicate that sweet corn can be expected to be tolerant to Callisto 480SC Herbicide at up to 140 g a.i./ha when applied pre-emergence to the crop.

The data submitted support a crop tolerance claim for sweet corn treated with a pre-emergence application of Callisto 480SC Herbicide alone at up to 140 g a.i./ha. However, since no crop tolerance data were submitted in support of the tank mixtures proposed for pre-emergence application in this crop, the proposed tank mixtures are not acceptable for labelling.

7.2.4 Overall Conclusions on Tolerance of Corn to Callisto 480SC Herbicide

The data submitted support a crop tolerance claim on a conditional basis for conventional till field corn treated pre-emergence or early postemergence with 140 g a.i./ha Callisto 480SC Herbicide, whether applied alone or in a tank mixture with Dual II Magnum, Primextra II Magnum, or Dual II Magnum plus atrazine (as Aatrex Nine-O or Aatrex Liquid 480) at the registered rates. The data submitted do not support the labelling of fluid fertilizer as a carrier. Data were insufficient to support use of Callisto 480SC

Herbicide on corn hybrids with CHU ratings of 2500 or less or in geographic regions of 2500 or less average seasonal CHUs. The data submitted supported the pre-emergence use of Callisto 480SC Herbicide alone at 140 g a.i./ha on production seed corn and sweet corn.

7.3 Impact on Succeeding Crops, Adjacent Crops and on Treated or Plant Products Used for Propagation

7.3.1 Impact on Succeeding Crops

7.3.1.1 Corn

No rotational crop tolerance data were submitted in support of a rotational crop tolerance claim for field corn, silage corn, production seed corn or sweet corn. Data were submitted for field corn, sweet corn and production seed corn from trials in which the product was applied pre-emergence. A review of the crop tolerance data indicate that these corn types can be expected to exhibit acceptable tolerance to pre-emergence applications of Callisto 480SC Herbicide at 140 g a.i./ha. Therefore, these corn types are acceptable for planting as salvage crops, i.e., in the case of crop failure. However, as no rotational crop data were submitted for corn planted in the year following application, it cannot be determined whether corn would be adequately tolerant of mesotrione transformation products that may remain in the soil at time of seeding and subsequent germination. Therefore, an unrestricted rotational crop tolerance claim is not acceptable.

Data from dedicated rotational crop tolerance trials for corn in which an interval of 10 months is evaluated are required to support an unconditional unrestricted rotational crop tolerance claim for this crop. Grain yield data are required to confirm visual assessments of injury and emergence.

7.3.1.2 Winter Wheat

No rotational crop tolerance data were submitted from trials in which the proposed interval of 3 months was evaluated. Instead, rotational crop tolerance data were submitted from 3 trials that were conducted at 1 location in southern Ontario. The evaluated rotational crop intervals were 120, 135, 150 and 165 days. One type of winter wheat (soft red, soft white, hard red) was evaluated per trial. Callisto 480SC Herbicide was applied at 0 (untreated check), 175 and 350 g a.i./ha in each trial.

None of the data submitted could be used in support of the proposed 3-month rotational cropping interval, as the minimum interval tested was 120 days (4 months). No injury was visually detectable for any of the 3 types of winter wheat planted 120 days after application of 175 or 350 g a.i./ha. Standcount of winter wheat planted on Callisto 480SC Herbicide-treated soil was similar to that planted on untreated soil. The data submitted suggest that winter wheat was not adversely affected by Callisto 480SC Herbicide when planted from 120 days after planting; however, no grain yield data or fresh/dry weight

data from the year after planting were available to corroborate the visual injury and standcount data.

A claim of rotational crop tolerance for winter wheat planted no less than 4 months after application is acceptable for conditional registration. Data from additional dedicated rotational crop tolerance trials for winter wheat in which the proposed interval of 3 months, or the conditionally accepted interval of 4 months, is evaluated are required to support an unconditional rotational crop tolerance claim for this crop. Grain yield data are required to confirm visual assessments of injury and emergence.

7.3.1.3 Spring Wheat

No rotational crop tolerance data were submitted from trials in which the proposed interval of 10 months was evaluated. Instead, rotational crop tolerance data were submitted from 3 "same season" trials conducted in 2001 at 3 locations in southern Ontario. At each site, the 4 intervals between application and planting of spring wheat evaluated were 0, 14, 28 and 42 days. Callisto 480SC Herbicide was applied at 0 (untreated check), 175 and 350 g a.i./ha in each trial.

The data submitted indicated that at a 42 day interval, injury to spring wheat was either not detectable or slight, and standcount was unaffected. Due to the high variability in grain yield in the two trials that were not maintained weed-free and did not receive a maintenance herbicide treatment, this attribute was minimally useful in evaluating tolerance of spring wheat to mesotrione residues in soil. However, in the trial conducted in Ridgetown, Ontario, the dry weight of spring wheat was similar among the untreated check and the two treatments of Callisto 480SC Herbicide. When these data are considered with those for winter wheat, the tolerance of which was evaluated for application-to-planting intervals of 4 to 5.5 months, it would appear that spring wheat would be sufficiently tolerant to residues of mesotrione and any of its transformation products remaining in the soil 10 months after application.

A claim of rotational crop tolerance for spring wheat planted no less than 10 months after application is acceptable for conditional registration. Data from additional dedicated rotational crop tolerance trials for spring wheat in which the proposed interval of 10 months is evaluated are required to support an unconditional rotational crop tolerance claim for this crop. Grain yield data are required to confirm visual assessments of injury and emergence.

7.3.1.4 Soybeans, Dry Beans (black, white, cranberry, kidney), Potatoes, Tomatoes and Alfalfa

No rotational crop tolerance data were submitted from trials in which the proposed interval of 10 months was evaluated. Instead, rotational crop tolerance data were submitted from 3 "same season" trials conducted in 2001 at 3 locations in southern Ontario: Ridgetown, Plattsville and Tavistock. At each site, the 4 intervals between

application and planting that were evaluated were 0, 14, 28 and 42 days. Callisto 480SC Herbicide was applied at 0 (untreated check), 175 and 350 g a.i./ha in each trial. Soybeans, kidney beans, cranberry beans, white beans and alfalfa were included in all 3 trials. Tomatoes and black beans were included in the Ridgetown trial only, and potatoes were included in the trials conducted in Plattsville and Tavistock. Trials conducted in Plattsville and Tavistock were not maintained weed-free. Therefore, the yield data were not considered to be reliable, since yield in treated plots may have been augmented by Callisto 480SC Herbicide application as compared to the untreated (weedy) check, thereby potentially masking injury that may have been observed had the trials been maintained weed free, either by hand weeding or by means of application of a maintenance herbicide treatment(s).

The data submitted are insufficient to support the proposed rotational crop interval of 10 months for these crops since data were submitted from same season trials only. The applicant indicated that evaluating tolerance of these crops planted 0 to 42 days after application of the 1× and 2× rates of Callisto 480SC Herbicide would represent a worst case scenario. While it is recognized that such trials do represent a "worst case scenario" with respect to the parent compound, mesotrione, it is not clear whether these crops are sufficiently tolerant of its transformation products that may remain in the soil 10 months after application.

A claim of rotational crop tolerance is not acceptable for soybeans, dry beans (including white beans, cranberry beans, kidney beans and black beans), tomatoes, potatoes and alfalfa 10 months after application of Callisto 480SC Herbicide at the proposed rates of 140 or 175 g a.i./ha.

7.3.1.5 Overall Conclusions on Tolerance of Rotational Crops Grown Following Corn Treated with Callisto 480SC Herbicide

The data submitted support the following recropping intervals on a conditional basis:

- corn (field, silage, seed, sweet): salvage only;
- winter wheat: 4 months; and
- spring wheat: 10 months.

Data were insufficient to support the proposed recropping interval of 10 months for soybeans, dry beans (including white beans, cranberry beans, kidney beans and black beans), tomatoes, potatoes and alfalfa.

7.4 Economics

The applicant indicated that yield losses in corn due to unchecked weed growth can be economically significant. It was indicated that for a corn crop with an average grain yield potential of 7.0 tonnes per hectare (112 bushels per acre), but sustaining a yield loss of

34%[1] due to weed competition, the resulting yield of 74 bushels per acre (4.6 tonne/ha) would represent a loss of $340 per hectare ($136.80 per acre) for corn valued at $142 per tonne ($3.60 per bushel). Additionally, it was indicated that the contribution of seed from uncontrolled weeds would result in chronic weed problems in following years.

7.5 Sustainability

7.5.1 Survey of Alternatives (chemical and non-chemical)

7.5.1.1 Non-chemical Control Practices

Callisto 480SC Herbicide, as for other herbicides, may be used in conjunction with cultivation.

7.5.1.2 Chemical Control Practices

Many pre-emergent/early postemergent herbicides are registered for broadleaved weed control in field corn in eastern Canada, many of which may be used alone or in tank mixtures (Appendix VI, Table 1).

7.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

Pre-emergence or early postemergence application of Callisto 480SC Herbicide would not exclude the sequential use of other herbicides with different modes of action or the use of mechanical weed control. Crop rotation is an important component of integrated pest management. Additional recropping data are required to determine which crops can be safely grown following Callisto 480SC Herbicide application.

7.5.3 Contribution to Risk Reduction

Callisto 480SC Herbicide will provide control of particular annual and winter annual broadleaved weeds in field corn at a low amount of active ingredient per hectare.

7.5.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

The proposed Callisto 480SC Herbicide label includes the resistance management statement outlined in Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*, as follows:

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[1] Knezevic, S., S. Weise and C. Swanton. 1994. *Weed Science*. 42: 568–573.

RESISTANCE-MANAGEMENT RECOMMENDATIONS

For resistance management, CALLISTO 480SC HERBICIDE is a Group 28 herbicide. Any weed population may contain or develop plants naturally resistant to CALLISTO 480SC HERBICIDE and other Group 28 herbicides. The resistant biotypes may dominate the weed population if these herbicides are used repeatedly in the same field. Other resistance mechanisms that are not linked to site of action, but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed.

To delay herbicide resistance:

Where possible, rotate the use of CALLISTO 480SC HERBICIDE or other Group 28 herbicides with different herbicide groups that control the same weeds in a field.

Use tank mixtures with herbicides from a different group when such use is permitted.

Herbicide use should be based on an IPM program that includes scouting, historical information related to herbicide use and crop rotation, and considers tillage (or other mechanical), cultural, biological and other chemical control practices.

Monitor treated weed populations for resistance development.

Prevent movement of resistant weed seeds to other fields by cleaning harvesting and tillage equipment and planting clean seed.

Contact your local extension specialist or certified crop advisors for any additional pesticide resistance-management and/or integrated weed management recommendations for specific crops and weed biotypes.

For further information and to report suspected resistance, contact company representatives at 1-800-459-2422 (Eng) / 1-800-850-4685 (Fr) or at www.syngenta.ca.

7.6 Conclusions

7.6.1 Summary

The proposed uses that are supported by the value assessment are summarized in Appendix VI, Table 2.

8.0 Toxic Substances Management Policy Considerations

8.1 Conclusions

During the review of Mesotrione Technical Herbicide and the EP Callisto 480SC Herbicide, the PMRA has considered the implications of the federal Toxic Substances Management Policy[2] and PMRA Regulatory Directive DIR99-03[3].

The TSMP criteria for persistence of mesotrione and transformation products MNBA and AMBA were not exceeded. Mesotrione is unlikely to volatilize, based on its low vapour pressure and Henry's Law constant. Therefore, a study of persistence in air is not triggered. Both transformation products dissipated in the environment. Mesotrione is not bioaccumulative. Studies have shown that the *n*-octanol–water partitioning coefficient (log K_{ow}) is < -1, which is below the TSMP Track 1 cut-off criterion of ≥ 5.0. Mesotrione does not contain any byproducts or microcontaminants known to be Track 1 substances. Impurities of toxicological concerns are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process. The formulated products do not contain any formulants that are known to contain TSMP Track 1 substances.

9.0 Regulatory Decision

The PMRA has carried out an assessment of available information for the following products in accordance with the Pest Control Products Regulations:

i) Mesotrione Technical Herbicide for use as a technical grade active ingredient (TGAI);
ii) Mesotrione Wet Paste Herbicide for use as a manufacturing concentrate; and
iii) Callisto 480SC Herbicide as a herbicide for pre-emergence use in field, seed and sweet corn and early postemergence use in field corn for control of specific annual broadleaf weeds.

The Agency has concluded that the use of Mesotrione Technical Herbicide, Mesotrione West Paste Herbicide and Callisto 480SC Herbicide has merit and value consistent with the Pest Control Products Regulations and does not entail an unacceptable risk of harm.

The Agency has determined that Mesotrione Technical Herbicide and Callisto 480SC Herbicide are eligible for temporary registration, subject to the provision of required data and of label amendments. Mesotrione Wet Paste Herbicide is being granted a temporary

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2 The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics

3 Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1 800 267-6315 within Canada or (613) 736-3799 outside Canada (long distance charges apply); Fax: (613) 736-3798; E-mail: pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca

registration until the terms and conditions of temporary registration are met for Mesotrione Technical Herbicide and Callisto 480SC Herbicide. There are no outstanding data requirements for Mesotrione Wet Paste Herbicide; however, this product is contingent upon the fulfilment of outstanding data gaps for Mesotrione Technical Herbicide, Pest Control Product Number 27831, and Callisto 480SC Herbicide, Pest Control Product Number 27833.

Syngenta Crop Protection Canada, Inc., will be required to submit additional data to support the registration of the above products, including the following:

- a mouse developmental neurotoxicity study;
- a swine metabolism study;
- raw data demonstrating the UV detector linearity for Method TMR 0914B over the concentration range of interest;
- data for the radiovalidation of Method TMR 0914B in animal matrices (including liver);
- a reliable and validated analytical methodology for the analysis of mesotrione residues in liver samples;
- the final QA/GLP report for study numbers TMJ4676B and TMJ4675B.
- small scale efficacy trials;
- additional crop tolerance trials; and
- additional rotational crop tolerance trials.

List of Abbreviations

a.i.	active ingredient
ACN	acetonitrile
AD	administered dose
ADI	acceptable daily intake
AMBA	2-amino-4-methylsulfonylbenzoic acid
APPL	applicator
ARfD	acute reference dose
AUC	area under the curve
bw	body weight
CD	cluster of differentiation (for naming cell surface molecules expressed on lymphocytes in immunology)
CHU	corn heat units
CI	confidence interval
COC	crop oil concentrate
d	day(s)
DAP	days after planting
DFR	dislodgeable foliar residues
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50%
EC_{50}	effect concentration 50%
EEC	expected environmental concentration
EXAMS	Exposure Analysis Modeling System
F_0	parental animals
F_1	1st generation offspring
F_2	2nd generation offspring
F_3	3rd generation offspring
FLD	fluorescence detector
GC	gas chromatography
GIT	gastrointestinal tract
GLP	good laboratory practice
GSD	geometric standard deviation
ha	hectare
HAFT	highest average field trial
HPLC	high-performance liquid chromatography
HPPA	4-hydroxyphenylpyruvate
HPPD	hydroxyphenylpyruvate dioxygenase
ILV	independent laboratory validation
IV	intravenous
K_d	adsorption quotient
K_{oc}	adsorption quotient normalized to organic carbon
K_{ow}	*n*-octanol–water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%

LEACHM	Leaching Estimation and Chemistry Model
LR_{50}	lethal rate 50%
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
M/L	mixer/loader
M/L/A	mixer/loader/applicator
MIS	maximum irritation score
MAS	maximum average score (at 24, 48 and 72 h)
mg	milligram
MMAD	mass median aerodynamic diameter
MNBA	methylsulfonyl-2-nitrobenzoic acid
MOE	margin of exposure
MRL	maximum residue limit
MSD	mas selective detection
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
ppb	parts per billion
PRZM	Pesticide Root Zone Model
QA	quality assurance
r^2	correlation coefficient
ROC	residue of concern
RQ	risk quotient
RSD	relative standard deviation
SDEV	standard deviation
SOC	Superior Oil Concentrate
SPE	solid phase extraction
TAT	tyrosine aminotransferase
TC	transfer coefficient
TGAI	technical grade active ingredient
TRR	total radioactive residue
TSMP	toxic substances management policy
UAN	urea-ammonium nitrate
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
UV	ultraviolet
µg	micrograms
µL	microlitre

Appendix I Method of Residue Analysis

Table 1 Methods for Environmental Residue Analysis

Matrix	Method	Spike Level	Parent Compound		MNBA		AMBA		LOQ	Method
			% mean rec'y (n)	% RSD	% mean rec'y (n)	% RSD	% mean rec'y (n)	% RSD		
Soil	HPLC/FLD	0.005 and 0.05 ppm	90 (10)	10	112 (10)	7	89	9	0.005 ppm	Accepted
Sediment	Syngenta has a waiver to extend the method for soil to sediment based on the following: 1. The aqueous extraction solvent (0.05 N NH_4OH) for soil is expected give comparable extraction efficiencies for aqueous sediment. 2. Based on metabolism studies, the residues of interest for both soil and sediment are the parent compound, MNBA and AMBA.									Accepted
Water [1]	GC/MSD	0.1–1.0 µg/kg	86.5 (21)	4.6					0.1 µg/kg	Accepted
Plant [2]	LC/MS/MS	0.01–0.10 ppm	94 (12)	9.1	79	7.7			0.01 ppm	Accepted
Animal [3]	HPLC/FLD	10–100 ppb	86 (12)	4	Not detected (based on the PMRA's review).				0.003 ppm	Accepted

[1] Samples should not be previously treated with chlorine
[2] For corn silage
[3] For ground beef

Appendix II Toxicology Summary Table

Table 1 Toxicology Summary Table

MOUSE METABOLISM—TGAI
In a metabolism study, [aromatic]^{14}C-mesotrione (radiochemical purity 99.3%) was administered to 4 CD-1 mice/sex/dose as a single gavage dose of 1 or 100 mg/kg bw. Urinary excretion accounted for 40.6% (single low dose) and 62.9% (single high dose) of the AD for males, and 58.6% (single low dose) and 69.8% (single high dose) of the AD for females, respectively. Fecal elimination for males accounted for 37.7% (single low dose) and 27.3% (single high dose) of the AD, and for females accounted for 20.9% (single low dose) and 24.5% (single high dose) of the AD. Tissue distribution and bioaccumulation accounted for ~14.0% (single low dose) and ~0.4% (single high dose) of the AD. The highest tissue concentration was seen in the liver, with 13.7% of the AD in males and 12.8% of the AD in females at 1 mg/kg bw, and 0.16% of the AD in males and 0.25% of the AD in females at 100 mg/kg bw. The major radioactive component excreted was mesotrione (at 1 mg/kg bw: 49% and 65% of the AD for males and females, respectively; at 100 mg/kg bw: 70% and 78% of the AD for males and females, respectively). The minor identified metabolites, i.e., hydroxy mesotrione, MNBA and AMBA, accounted for 2%-6% of the AD. The unidentified metabolites accounted for up to 8% of the AD, and were considered to possibly be the result of metabolism of ZA1296 by the intestinal microflora. Metabolic profiles were essentially the same regardless of sex or dose. The first metabolic pathway involved hydroxylation of the cyclohexane ring on the parent compound to form hydroxy mesotrione. The second pathway involved an aromatic nitro reduction of the parent compound, forming an aromatic amide intermediate. This postulated intermediate is then cleaved at the cyclohexane ring, resulting in AMBA. The final pathway involves cleaving the C=O bridge from the cyclohexane (MNBA as the intermediate), followed by aromatic nitro reduction to form AMBA.

RAT METABOLISM—TGAI

In a metabolism study, [aromatic-^{14}C]-mesotrione (radiochemical purity ≥ 98.1%) was administered to Sprague Dawley rats as a single gavage dose of 1 or 100 mg/kg bw, 5 rats/sex/group, or 14 daily doses (1 mg/kg bw) of unlabelled mesotrione (purity 99.3%) followed by a single gavage dose of 1 mg/kg bw [aromatic-^{14}C]-mesotrione on day 15, 8 rats/sex. In addition, 8 rats/sex were given a single intravenous (IV) dose of 1 mg/kg bw.

Study results indicated that radiolabelled mesotrione is rapidly absorbed, distributed and excreted following oral administration in rats. Total 72-hour recoveries of the radioactivity were high for all groups (~80% to 92% of the orally AD and ~97% of the intravenously AD). The major route of elimination was via the urine, accounting for ~55% to 67% of the AD after oral dosing, and ~80% of the AD after IV administration. Fecal elimination accounted for ~23% to 30% of the AD after oral dosing, and ~2% to 7% of the AD after intravenous dosing. Radioactivity in the tissues 72 hours postdosing ranged from 5% to 12% of the AD for orally dose animals, and ~10% of the AD after IV administration. Highest tissue concentrations were in the liver and kidneys. There were no significant sex-related differences in excretion pattern or tissue distribution of radioactivity.

In a metabolite characterization study, Sprague Dawley rats were dosed once by oral gavage with [^{14}C-dione]-mesotrione (purity 99.5%) at the single dose level of 50 mg/kg bw, or with [aromatic-^{14}C]-mesotrione (radiochemical purity 100%) at dose levels of 50 or 100 mg/kg bw, 2 rats/sex/group. Oral administration of mesotrione resulted in absorption of at least 60% of the administered dose. The major portion was excreted unchanged in urine, i.e., ~90% of the urinary radioactivity, or 47–59% of the administered dose (AD). Smaller amounts of mesotrione were excreted via the bile, i.e., up to 11% of the AD in males and up to 3% in females. Analyses of excreta and bile revealed a total of 15 minor metabolites, of which 4 were identified, i.e., 4-hydroxy-mesotrione, MNBA, AMBA and 5-hydroxy-mesotrione. Each of these 4 metabolites was individually present at levels of ≤ 5% of the AD. The unabsorbed dose was excreted fairly rapidly in feces. Mesotrione was eliminated largely unchanged in bile. Feces from the cannulated rats contained only small amounts of unchanged mesotrione, indicating that mesotrione was metabolized by the gut microflora. Differences were noted in the metabolic profiles of [^{14}C-dione]-mesotrione and [^{14}C-aromatic]-mesotrione, indicating cleavage of the molecule into its 2 constituent rings. MNBA and AMBA were only isolated from [^{14}C-aromatic]-mesotrione. The presence of these 2 metabolites in urine may in part be attributable to their absorption from the gastrointestinal tract and subsequent systemic circulation. This is supported by the fact that there was no evidence of the cleaved dione ring in urine or feces in metabolite characterization using [^{14}C-dione]-mesotrione.

Proposed metabolic pathway: At least 60% of an oral dose of ZA1296 is absorbed, but undergoes limited metabolism, represented by hydroxylation in either the 4- or 5-position on the dione ring. The polarity of the ZA1296 molecule enables excretion directly via urine, which was shown to be the major route of excretion of the absorbed dose. However, since its molecular weight exceeded the biliary exclusion factor in the rat, a lesser proportion of the absorbed dose was also eliminated via the bile, both sexes (higher proportion in males, however). Small amounts of aromatic ring cleavage products, resulting from metabolism of ZA1296 by the intestinal flora, appeared to have been absorbed and eliminated in the urine. Results indicated that the extent of biotransformation of ZA1296 was slightly more extensive in males.

In an autoradiography study [^{14}C] dione ring-labelled ZA1296 (> 99% radiochemical purity) and [^{14}C] aromatic ring-labelled ZA1296 (>97% radiochemical purity) were administered to Alpk:AP$_f$SD rats by gavage as a single oral dose of 5 mg/kg bw, 2 rats/sex. For each radiolabelled compound, 1 rat/sex was sacrificed at 24 hours after dosing and 1 rat/sex was sacrificed at 48 hours.

The major route of excretion for the aromatic ring-labelled ZA1296 was the urine (67% in the male and 42% in the female after 24 hours; 72% in the male and 53% in the female after 48 hours). For dione ring-labelled ZA1296, the urine was the major route of elimination after 48 hours (59% in the male and 63% in the female), but the feces was the major route of elimination after 24 hours (34% in the male and 28% in the female). The total radioactive dose recovered for the dione ring-labelled compound, after 48 hours was 90% for the male and 92% in the female, and for the aromatic ring-labelled compound was 93% for the male and 76% for the female. Expired air was monitored for 24 hours only, with < 1% of the radioactive dose being recovered, regardless of the position of the ^{14}C in the ZA1296 test compound.

Autoradiography confirmed that both the kidney and the liver were subject to tagging by the radiolabelled compounds or their respective metabolites. The GIT and contents appear to have incorporated the greatest amount of radiolabelled compound, which would be expected in association with faecal elimination.

METABOLISM—MNBA

In a metabolite characterization study, [^{14}C]-MNBA, purity 97.1%, was administered to 4 male Sprague Dawley rats at the single dose level of 75 mg/kg bw. At 12 hours postdosing, 44% of the AD was present in the GIT contents, 16% of the AD was in the urine, 27% of the AD was in the feces and 2% was in the residual carcass (total recovery was 91%). The major metabolite of MNBA was AMBA, which accounted for 58% of urinary radioactivity and 100% of the radioactivity present in the solvent extract of the GIT contents. MNBA is almost quantitatively reduced to AMBA in the GIT. MNBA was present in quantity in urine only at 6 hours postdosing; at 12 hours, AMBA was the major radioactive component in the urine and the GIT. MNBA and AMBA were not well absorbed within the first 12 hours postdosing.

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
ACUTE STUDIES—TGAI			
Oral	Rat—Sprague Dawley, 5000 mg/kg bw, 5/sex.	LD_{50} > 5000 mg/kg bw	**5000 mg/kg bw:** No treatment-related findings. **LOW TOXICITY**
Dermal	Rat—Sprague Dawley, 2000 mg/kg bw; 5/sex	LD_{50}> 2000 mg/kg bw	No treatment-related systemic findings. Scabs, slight oedema. **LOW TOXICITY**
Inhalation, 4-hour, nose-only	Rat—Sprague Dawley, 4.75 mg/L; 5/sex	LC_{50} > 4.75 mg/L	MMAD = 2.09 µm, GSD = 2.13. General clinical signs of toxicity were first observed 1 hour postdosing (hunched posture, piloerection, breathing irregularities, abnormal respiratory noises); loss in body weight on study day 2 only. Complete recovery was evident for all animals by study day 11. **LOW TOXICITY**
Skin irritation	Rabbit—New Zealand White, 6 females; 500 mg dose	MAS = 0.8/8.0	**SLIGHTLY IRRITATING**

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
Eye irritation	Rabbit—New Zealand White, 9 females; 100 mg dose	MIS = 8.3/110	**MINIMALLY IRRITATING**
Skin sensitization (Maximization method of Magnusson and Kligman)	Guinea pig—Albino, Hsd/Poc:DH, 20 females/group Test material administered 3% and 75% for intradermal and topical induction, respectively; 75% and 30% for challenge. Positive control 2-mercaptobenzothiazole.	Test material did not elicit any dermal reactions. No evidence of sensitization. Positive control was sensitizing, demonstrating responsiveness of assay.	**NOT A SENSITIZER**
ACUTE STUDIES—FORMULATION (CALLISTO 480 SC HERBICIDE)			
Oral	Rats—Sprague Dawley, 5000 mg/kg bw; 5/sex	LD_{50} > 5000 mg/kg bw	Slight piloerection and diarrhoea; complete recovery by day 8. **LOW TOXICITY**
Dermal	Rats—Sprague Dawley, 5000 mg/kg bw; 5/sex	LD_{50} > 5000 mg/kg bw	Signs of slight irritation **LOW TOXICITY**
Inhalation, 4-hour, nose-only.	Rats—Sprague Dawley, 5.19 mg/L; 5/sex	LC_{50} > 5.19 mg/L	MMAD = 3.61, 3.40 µm, GSD = 2.62, 2.43. General clinical signs of toxicity were first observed during dosing (salivation, abnormal respiratory noise, decreased activity, stains around the nose, piloerection). Complete recovery was evident for all animals by study day 7. **LOW TOXICITY**
Skin irritation	Rabbits—New Zealand White, 0.5 mL dose; 3 males	MIS = 1.67/8.0	**MILDLY IRRITATING** **<u>Primary Label Recommendation</u>** **CAUTION EYE IRRITANT.** **<u>Secondary Label Recommendation</u>** **May irritate eyes.** **Avoid contact with eyes.**
Eye irritation	Rabbits—New Zealand White, 0.1 mL dose; 3 males	MIS = 4/110	**MINIMALLY IRRITATING**

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
Skin sensitization (Buehler method)	Guinea pig—Dunkin Hartley; 20 /group, sex not stated Test material administered undiluted for induction; 75% and 50% for challenge. Positive control 2-mercaptobenzothiazole.	Test material elicited dermal reactions in 2/20 test animals. Therefore, evidence of sensitization. Positive control was sensitizing, demonstrating responsiveness of assay.	**POSITIVE SENSITIZER** **<u>Primary and Secondary Label Recommendation</u>** **POTENTIAL SKIN SENSITIZER**
ACUTE STUDIES—Metabolites			
Oral; AMBA	Rats—Sprague Dawley, 5000 mg/kg bw; 5/sex	LD_{50} > 5000 mg/kg bw	No treatment-related findings. **LOW TOXICITY**
Oral; MNBA	Rats—Sprague Dawley; 5000 mg/kg bw; 5/sex	LD_{50} > 5000 mg/kg bw	No treatment-related findings. **LOW TOXICITY**
Dermal: MNBA	Rats—Sprague Dawley, 2000 mg/kg bw; 5/sex	LD_{50} > 2000 mg/kg bw	No treatment-related systemic findings. Slight desquamation. **LOW TOXICITY**
SHORT TERM—TGAI			
21-day dermal	Rabbits—New Zealand White, 5/sex/group; 0, 10, 500 or 1000 mg/kg bw/day	**Systemic toxicity** LOAEL could not be determined since there were no treatment-related systemic effects. NOAEL = 1000 mg/kg bw/day **Dermal toxicity** LOAEL = 500 mg/kg bw/day NOAEL = 10 mg/kg bw/day	**Systemic findings:** No treatment-related systemic effects at any dose level tested. **Dermal findings:** **10 mg/kg bw/day:** No treatment-related findings. **500 and 1000 mg/kg bw/day:** Slight erythema, first observed on day 5. Complete recovery for all animals by day 21.

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
28-day dietary	Rats—Sprague Dawley; 6/sex/group; 0, 1000, 5000, 10000, 15000 or 20000 ppm (equal to 0, 131.4, 656.2, 1315.3, 1871.3 or 2463.7 mg/kg bw/day for males, and 0, 133.3, 651.1, 1323.8, 1915.5 or 2423.6 mg/kg bw/day for females).	LOAEL = 131.4/133.3 mg/kg bw/day NOAEL could not be determined since there were treatment-related findings at all dose levels tested.	**131.4/133.3 and 656.2/651.1 mg/kg bw/day:** Renal tubular hyaline droplets. **1315.3/1323.8 mg/kg bw/day:** Lower body-weight gain, males only; renal tubular hyaline droplets. **1871.3/1915.5 and 2463.7/2423.6:** Lower body-weight gain and food consumption; renal tubular hyaline droplets.
3-month dietary	Mouse—C57, 10/sex/group; 0, 100, 1000, 3500 or 7000 ppm (equal to 0, 19.7, 201.1, 744.2 or 1396.6 mg/kg bw/day for males, and 0, 23.3, 250.7, 794.8 or 1648.8 mg/kg bw/day for females)	**Males** LOAEL = 1396.6 mg/kg bw/day NOAEL = 744.2 mg/kg bw/day **Females** LOAEL could not be determined since there were no adverse, treatment-related findings. NOAEL = 1648.8 mg/kg bw/day	**19.7/23.3, 201.1/250.7 and 744.2/794.8 mg/kg bw/day:** No adverse, treatment-related effects. **1396.6/1648.8 mg/kg bw/day:** Lower body-weight gain, males only. There were no treatment-related findings for females. No ocular lesions noted at clinical or histopathological examination. Opthalmological examinations were not conducted.
3-month dietary	Mouse —C57; 20/sex/group; 0, 0, 10, 50, 350 or 7000 ppm (equal to 0, 0, 1.7, 8.4, 61.5 or 1212.4 mg/kg bw/day for males, and 0, 0, 2.4, 12.4, 80.1 or 1537.1 mg/kg bw/day for females).	LOAEL could not be determined since there were no adverse, treatment-related systemic effects. NOAEL = 1212.4/1537.1 mg/kg bw/day	There were no adverse, treatment-related findings at any dose level tested. No ocular lesions were observed at clinical, ophthalmological, gross or histopathological examination.

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
3-month dietary	Rat—Sprague Dawley; 12/sex/group; 0, 1, 125, 1250 or 12500 (equal to 0, 0.09, 10.96, 112.09 or 1110.86 mg/kg bw/day for males, and 0, 0.10, 12.81, 125.58 or 1212.53 mg/kg bw/day for females)	LOAEL=10.96/12.81mg/kg bw/day NOAEL=0.09/0.10 mg/kg bw/day	**0.09/0.10 mg/kg bw/day:** No adverse, treatment-related findings. **10.96/12.81 and 112.09/125.58 mg/kg bw/day:** Corneal opacity/vascularization; unilateral/bilateral keratitis; decreased body-weight gain (males); decreased food efficiency (males). **1110.86/1212.53 mg/kg bw/day:** Corneal opacity/vascularization; unilateral/bilateral keratitis; decreased body-weight gain; decreased food intake; decreased food efficiency (males); renal tubular hyaline droplet formation (males).
3-month dietary	Rat—Sprague Dawley, 12/sex/group; 0, 2.5, 5.0, 7.5 or 150 ppm (equal to 0, 0.21, 0.41, 0.63 or 12.46 mg/kg bw/day for males, and 0, 0.23, 0.47, 0.71 or 14.48 mg/kg bw/day for females).	**Males** LOAEL= 0.63 mg/kg bw/day. NOAEL= 0.41 mg/kg bw/day. **Females** LOAEL= 14.48 mg/kg bw/day. NOAEL= 0.71 mg/kg bw/day.	**0.21/0.23 and 0.41/0.47 mg/kg bw/day:** No treatment-related findings. **0.63/0.71 mg/kg bw/day:** Corneal opacity and vascularization; keratitis (males). No treatment-related findings for females. **12.46/14.48 mg/kg bw/day:** Corneal opacity and vascularization; keratitis.

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
3-month dietary	Rat—Sprague Dawley, 12 males/group; 0, 10, 20, 50 or 125 ppm (equal to 0, 0.9, 1.7, 4.3 or 10.7 mg/kg bw/day)	The purpose of this study was to define the dose-response relationship for body weights and selective organ weights across a wide range of ZA1296 in male rats, and to aid dose level selection for a 2-year dietary study in rats. **Non-ocular Toxicity** LOAEL could not be determined since there were no adverse, treatment-related findings at any dose level tested. NOAEL=10.7 mg/kg bw/day **Ocular Toxicity** LOAEL=0.9 mg/kg bw/day NOAEL could not be determined since ocular effects were observed at all dose levels tested.	 **0.9, 1.7, 4.3 and 10.7 mg/kg bw/day:** There were no adverse, treatment-related findings. **0.9, 1.7, 4.3 and 10.7 mg/kg bw/day:** Corneal opacity and vascularization were observed at all dose levels tested.
6-week oral, gelatin capsules	Dog—Beagle, 1/sex/group; 0, 40, 400, 800 or 1000 mg/kg bw/day	LOAEL could not be determined since there were no adverse, treatment-related findings. NOAEL = 1000 mg/kg bw/day	**40, 400, 800 and 1000 mg/kg bw/day:** No adverse, treatment-related findings.
3-month oral, gelatin capsules	Dog—Beagle, 4/sex/group; 0, 100, 600 or 1000 mg/kg bw/day	**Males** LOAEL = 1000 mg/kg bw/day NOAEL = 600 mg/kg bw/day **Females** LOAEL = could not be determined since there were no adverse, treatment-related findings. NOAEL = 1000 mg/kg bw/day	**100 and 600 mg/kg bw/day:** No adverse, treatment-related findings. **1000 mg/kg bw/day:** Decreased body-weight gain and mesothelial proliferation of the atrium of the heart, males only. NOTE: Although the relationship to treatment of mesothelial proliferation of the atrium was unclear, it could not be ruled out as unrelated to treatment.

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
1-year oral, gelatin capsules	Dog—Beagle, 4/sex/group, 10, 100 or 600 mg/kg bw/day	LOAEL = 600 mg/kg bw/day NOAEL = 100 mg/kg bw/day	**10 and 100 mg/kg bw/day:** Plasma tyrosine and urinary phenolic acid concentrations were increased, but were not considered adverse in the absence of any other treatment-related findings. **600 mg/kg bw/day:** Increased plasma tyrosine, increased urinary phenolic acid, corneal/lenticular opacities and keratitis; decreased body-weight gain (females only); generalized lymphocytolysis (1 female).
SHORT TERM—Metabolites			
28-day oral gavage, MNBA	Rat—Sprague Dawley, 5/sex/group; 0, 15, 150 or 1000 mg/kg bw/day	LOAEL could not be determined since there were no adverse, treatment-related findings. NOAEL = 1000 mg/kg bw/day.	**15, 150 and 1000 mg/kg bw/day:** There were no treatment-related findings.
3-month dietary, MNBA	Rat—Sprague Dawley, 12/sex/group; 0, 100, 650 or 3000 ppm (equal to 0, 7.7, 50.6 or 231.0 mg/kg bw/day for males, and 0, 8.8, 56.9 or 263.7 mg/kg bw/day for females)	LOAEL could not be determined since there were no adverse, treatment-related findings. NOAEL = 231.0/263.7 mg/kg bw/day	**7.7/8.8, 50.6/56.9 and 231.0/263.7 mg/kg bw/day:** No adverse, treatment-related findings.
CHRONIC TOXICITY/ONCOGENICITY—TGAI			
One-year, dietary	Mouse—C57, 60/sex/group; 0, 0, 10, 50, 350 or 7000 ppm (equal to 0, 0, 1.5, 7.8, 56.2 or 1114.0 mg/kg bw/day for males, and 0, 0, 2.1, 10.3, 72.4 or 1494.5 mg/kg bw/day for females)	**Males:** LOAEL = 1114.0 mg/kg bw/day NOAEL = 56.2 mg/kg bw/day **Females:** LOAEL could not be determined since there were no adverse, treatment-related findings. NOAEL = 1494.5 mg/kg bw/day	**1.5/2.1, 7.8/10.3 and 56.2/72.4 mg/kg bw/day:** No treatment-related findings. **1114.0/1494.5 mg/kg bw/day:** Decreased body-weight gain and food efficiency, males only. There were no treatment-related findings for females.

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
80-week dietary	Mouse—C57, 55/sex/group; 0, 10, 350 or 3500/7000 ppm (equal to 0, 1.4, 49.7 or 897.7 mg/kg bw/day for males, and 0, 1.8, 63.5 or 1102.9 mg/kg bw/day for females) NOTE: Animals received 3500 ppm for the first 7 weeks of the study, which was then increased to 7000 ppm for the remainder of the study due to lack of effects on body weights or food consumption.	**Chronic Effects** LOAEL could not be determined since there were no adverse, treatment-related findings. NOAEL = 897.7/1102.9 mg/kg bw/day **Oncogenicity** No evidence of treatment-related oncogenicity.	**1.4/1.8 and 49.7/63.5 mg/kg bw/day:** No adverse, treatment-related findings. **897.7/1102.9 mg/kg bw/day:** Decreased body-weight gain and food efficiency, males only. There were no treatment-related findings for females. No treatment-related oncogenic effects at any dose level tested.

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
105-week dietary	Rats—Sprague Dawley, 64/sex/group; 0, 7.5, 100 or 2500 ppm (equal to 0, 0.48, 6.48 or 159.89 mg/kg bw/day for males, and 0, 0.57, 7.68 or 189.48 mg/kg bw/day for females) NOTE: To aid in the assessent of ocular toxicity only, 20 rats/sex/group were assigned to dose levels of 1.0 or 2.5 ppm (equal to 0.06 or 0.16 mg/kg bw/day for males, and 0.08 or 0.19 mg/kg bw/day for females).	**Chronic Effects** **Males** LOAEL = 0.48 mg/kg bw/day NOAEL could not be determined. **Females** LOAEL = 7.68 mg/kg bw/day NOAEL = 0.57 mg/kg bw/day **Ocular Effects** **Males** LOAEL=0.48 mg/kg bw/day NOAEL=0.16 mg/kg bw/day **Females** LOAEL=7.68 mg/kg bw/day NOAEL=0.57 mg/kg bw/day **Oncogenicity** **Males:** No evidence of treatment-related oncogenicity **Females:** Increased incidence of thyroid follicular cell adenomas (benign) at 189.48 mg/kg bw/day.	**0.57 (females) mg/kg bw/day:** No adverse, treatment-related findings. **0.48 (males) mg/kg bw/day:** Decreased body-weight gain (males only); hepatocyte fatty vacuolation (males only). **6.48/7.68 and 159.89/189.48 mg/kg bw/day:** Decreased body-weight gain (males); hepatocyte fatty vacuolation; thyroid follicular cysts (males); thyroid squamous cysts (females). **0.06/0.08, 0.16/0.19 and 0.57 (females) mg/kg bw/day:** No treatment-related findings. **0.48 (males), 6.48/7.68 and 159.89/189.48 mg/kg bw/day:** Corneal opacitiy/vascularization; keratitis. Increased incidence of thyroid follicular cell adenomas (benign) at 189.48 mg/kg bw/day, females only.

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
REPRODUCTION / DEVELOPMENTAL TOXICITY—TGAI			
Two-generation dietary, one litter per generation	Mouse—CD-1, 26/sex/group; 0, 10, 50, 350, 1500 or 7000 ppm (equal to 0, 2.1, 10.2, 71.4, 311.8 or 1471.9 mg/kg bw/day for males, and 0, 2.1, 10.0, 71.3, 301.6 or 1439.1 mg/kg bw/day for females)	**Parental Toxicity** LOAEL = 1471.9/1439.1 mg/kg bw/day NOAEL = 311.8/301.6 mg/kg bw/day	**2.1/2.1, 10.2/10.0, 71.4/71.3 and 311.8/301.6 mg/kg bw/day:** Plasma tyrosine levels were increased, but were not considered adverse in the absence of any other treatment-related findings. **1471.9/1439.1 mg/kg bw/day:** Cloudy/opaque eyes; unilateral/bilateral cataractous change; retinal detachment; increased plasma tyrosine levels.
		Reproductive Toxicity LOAEL could not be determined since there were no treatment-related findings. NOAEL = 1471.9/1439.1 mg/kg bw/day	No treatment-related effects at any dose level tested.
		Offspring Toxicity LOAEL=311.8/301.6 mg/kg bw/day NOAEL=71.4/71.3 mg/kg bw/day Based on the above data, an increase in the quanitative susceptibility of mouse pups was demonstrated.	**2.1/2.1, 10.2/10.0 and 71.4/71.3 mg/kg bw/day:** Plasma tyrosine levels were increased, but were not considered adverse in the absence of any other treatment-related findings. **311.8/301.6 and 1471.9/1439.1 mg/kg bw/day:** Lower pup body weight; cloudy/opaque eyes; unilateral/bilateral cataractous change; increased plasma tyrosine levels.

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
Three-generation dietary, one litter per generation	Rat—Sprague Dawley, 26/sex/group; 0, 2.5, 10, 100 or 2500 ppm (equal to 0, 0.3, 1.1, 11.6 or 278.1 mg/kg bw/day for males, and 0, 0.3, 1.1, 11.7 or 297.2 mg/kg bw/day for females) NOTE: For the F_0 and F_1 generations, exposure to mesotrione was continuous throughout the study period. For the F_2 generation, at 14 weeks after selection, subdivided into continuous treatment group (12/sex/group) and recovery group (14/sex/group). Four weeks later, these groups were mated to produce the F_3 generation.	**Parental Toxicity** **Ocular Effects** LOAEL = 1.1/1.1 mg/kg bw/day NOAEL = 0.3/0.3 mg/kg bw/day **Other Systemic Effects** LOAEL = 1.1/11.7 mg/kg bw/day NOAEL = 0.3/1.1 mg/kg bw/day **Reproductive Toxicity** LOAEL = 278.1/297.2 mg/kg bw/day NOAEL = 11.6/11.7 mg/kg bw/day	**0.3/0.3 and 1.1 (females only) mg/kg bw/day:** Increased plasma tyrosine, F_2 continuous treatment group (only measured for F_2 continuous treatment and recovery groups); not considered adverse in the absence of any other treatment-related findings. **1.1 (males only), 11.6/11.7 and 278.1/297.2 mg/kg bw/day:** a) Eye lesions—corneal opacity/vascularization, keratitis (F_0, F_1 and F_2 continuous treatment and recovery groups). Note that for the F_2 recovery group, after 28 weeks on control diet, the only ocular lesion was ghost vascularization (2500 ppm, both sexes, and 100 ppm, males only), indicating healed lesions. b) Bilateral hydronephrosis (F_1 and F_2 continuous treatment and recovery groups); increased plasma tyrosine, F_2 continuous treatment group (only measured for F_2 continuous treatment and recovery groups). Bilateral hydronephrosis was not observed in the F_0 generation indicating that the development of bilateral hydronephrosis is dependent on in utero exposure. **0.3/0.3, 1.1/1.1 and 11.6/11.7 mg/kg bw/day:** No treatment-related findings. **278.1/297.2 mg/kg bw/day:** Decreased litter size, decreased pup survival to day 22, decreased percentage of pups born live and increased whole litter loss (F_{1A}, F_{2A} and F_{3A} continuous treatment litters).

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
		Offspring Toxicity **Ocular Effects** LOAEL = 0.3/0.3 mg/kg bw/day NOAEL could not be determined since there were treatment-related ocular effects at all dose levels tested. **Other Systemic Effects** LOAEL = 1.1/1.1 mg/kg bw/day NOAEL = 0.3/0.3 mg/kg bw/day Eye lesions were observed at lower dose levels than seen in parental animals, indicating increased quantitative susceptibility of the young. Bilateral hydronephrosis was not observed in the F_0 generation parents, but was observed in the F_1 and F_2 generation parents, and was noted in all generations of offspring, indicating that in utero exposure is required for the development of this finding and is suggestive of increased qualitative susceptibility of the young.	**0.3/0.3 mg/kg bw/day:** Eye lesions, males only—corneal opacity (F_{1A}, F_{2A} and F_{3A} continuous treatment litters); increased plasma tyrosine, F_{3A} continuous treatment group (only measured for F_{3A} continuous treatment and recovery groups); not considered adverse for females since there were no other treatment-related findings. **1.1 mg/kg bw/day:** Eye lesions, males only—corneal opacity/vascularization, keratitis (F_{1A}, F_{2A} and F_{3A} continuous treatment litters); bilateral hydronephrosis (F_{1A}, F_{2A} and F32A continuous treatment litters); increased plasma tyrosine F_{3A} continuous treatment group (only measured for F_{3A} continuous treatment and recovery groups); not considered adverse for females since there were no other treatment-related findings. **11.6/11.7 and 278.1/297.2 mg/kg bw/day:** Eye lesions-corneal opacity/vascularization and keratitis (F_{1A}, F_{2A} and F_{3A} continuous treatment litters); bilateral hydronephrosis (F_{1A}, F_{2A} and F_{3A} continuous treatment litters); increased plasma tyrosine F_{3A} continuous treatment group (only measured for F_{3A} continuous treatment and recovery groups); increased incidence of bilateral renal pelvic dilatation (F_{1A}, F_{2A} and F_{3A} continuous treatment litters).

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
Teratogenicity oral gavage	Female mice—CD-1, 30/group; 0, 0, 10, 60, 150 or 600 mg/kg bw/day	**Maternal Toxicity** LOAEL could not be determined since there were no adverse, treatment-related findings. NOAEL = 600 mg/kg bw/day **Developmental Toxicity** LOAEL could not be determined since there were no adverse, treatment-related findings. NOAEL = 600 mg/kg bw/day **Teratogenicity** LOAEL could not be determined since there were no treatment-related findings. NOAEL = 600 mg/kg bw/day	**0, 10, 60, 150 and 600 mg/kg bw/day:** There were no treatment-related maternal, developmental or teratogenic findings. No teratogenic effects at any dose level tested.
Teratogenicity oral gavage	Rats—Sprague Dawley, 24/group; 0, 100, 300 or 1000 mg/kg bw/day	**Maternal Toxicity** LOAEL = 100 mg/kg bw/day. NOAEL could not be determined since there were treatment-related findings at all dose levels tested. **Developmental Toxicity** LOAEL = 100 mg/kg bw/day. NOAEL could not be determined since there were treatment-related findings at all dose levels tested. **Teratogenicity** LOAEL could not be determined since there were no treatment-related findings. NOAEL = 1000 mg/kg bw/day	**100, 300 and 1000 mg/kg bw/day:** Decreased body-weight gain and food consumption. **100, 300 and 1000 mg/kg bw/day:** Increased incidence of minor anomalies, i.e., unossified cervical centra (3–7) and extra 14th ribs. Increased incidence of variants, i.e., unossified centrum 2 and odontoid; dose-related reduction in the degree of pes and manus ossification. Lower fetal body weight (1000 mg/kg bw/day only). No teratogenic effects at any dose level tested.

STUDY	SPECIES/STRAIN and DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS
Teratogenicity oral gavage	Rabbit—New Zealand white, 20/group; 0, 100, 250 or 500 mg/kg bw/day	**Maternal Toxicity** LOAEL = 250 mg/kg bw/day NOAEL = 100 mg/kg bw/day **Developmental Toxicity** LOAEL could not be determined since there were no adverse, treatment-related effects at any dose level tested. NOAEL = 500 mg/kg bw/day **Teratogenicity** LOAEL could not be determined since there were no treatment-related findings. NOAEL = 500 mg/kg bw/day	**100 mg/kg bw/day:** No adverse, treatment-related findings. **250 mg/kg bw/day:** Slightly increased incidence of abortions. **500 mg/kg bw/day:** Slightly increased incidence of abortions; decreased body-weight gain. **100, 250 and 500 mg/kg bw/day:** Increased incidence of skeletal variants, i.e., partially ossified odontoid, 27 presacral vertebrae and extra 13th ribs of normal length, dose-related reduction in the degree of ossification of the manus and pes. The noted variations are considered transient, reversible delays in ossification and are not regarded to be adverse effects. No teratogenic effects at any dose level tested.
MUTAGENICITY—TGAI			
STUDY	**SPECIES/STRAIN or CELL TYPE**	**DOSE**	**SIGNIFICANT EFFECTS/ COMMENTS**
Reverse gene mutation assay	*S. typhimurium*, strains TA98, TA100, TA1535 and TA1537	100, 200, 500, 1000, 2500 and 5000 µg/plate, ±S9	**Negative** (±S9)
Chromosome aberration assay	Human lymphocyte cultures, in vitro	0, 250, 1000 and 2000 µg/mL, +S9; 0, 250, 1000, 1500 and 2000 µg/mL, -S9	**Negative** (+S9) **Equivocal** (-S9)
Gene mutation assay	L5178Y mouse lymphoma cell cultures, in vitro	0, 125, 250, 500 and 1000 µg/mL, ±S9	**Negative** (±S9)
Micronucleus assay	CD-1 mouse bone marrow cells	500 mg/kg bw, 10 mice/sex	**Negative**

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
MUTAGENICITY—MNBA			
Reverse gene mutation assay	*S. typhimurium*, strains TA98, TA100, TA1535 and TA1537 *E. Coli* strains WP2P and WP2PuvrA.	0, 100, 200, 500, 1000, 2500 and 5000 µg/plate, ±S9	**Negative (±S9)**
Micronucleus assay	Sprague Dawley rat bone marrow cells	2000 mg/kg bw, 10 male rats	**Negative (±S9)**
Cytogenetics assay	Human lymphocytes	Assay 1: 0, 250, 1250 and 2000 µg/mL, ±S9 Assay 2: 0, 250, 1250 and 2451 µg/mL, ±S9	**Negative (±S9)**
Genotoxicity assessment of MNBA and AMBA, using MNBA	i) Micronucleus assay ii) DNA repair assay	i) 2000 mg/kg bw ii) 2000 mg/kg bw	**Negative** **Negative** Conclusion: The results of both in vivo studies were negative for genotoxicity. In addition, based on structure-activity relationship, neither MNBA nor AMBA were potentially gentoxic, and both materials were negative in the Ames assay. Hence, it was concluded that neither MNBA nor AMBA have any significant genotoxic activity in mammals.
MUTAGENICITY—AMBA			
Reverse gene mutation assay	*S. typhimurium*, strains TA98, TA100, TA1535 and TA1537	0, 100, 200, 500, 1000, 2500 and 5000 µg/plate, ±S9	**Negative (±S9)**
Micronucleus assay	CD-1 mouse bone marrow cells	0, 250, 1000 and 2150 µg/mL, ±S9	**Negative (+S9)** **Positive (-S9)**

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
NEUROTOXICITY (acute and subchronic)			
Acute oral	Rat—Sprague Dawley, 10/sex/group; 0, 20, 200 or 2000 mg/kg bw	**Systemic toxicity** LOAEL could not be determined since there were no treatment-related systemic effects noted at any dose level tested. NOAEL = 2000 mg/kg bw **Neurotoxicity** LOAEL could not be determined since there were no treatment-related neurotoxic effects noted at any dose level tested. NOAEL = 2000 mg/kg bw	**20, 200 and 2000 mg/kg bw:** There were no treatment-related findings at any dose level tested.
3-month dietary	Rat—Sprague Dawley, 10/sex/group; 0, 2.5, 100 or 5000 ppm (equal to 0, 0.20, 8.25 or 402.80 mg/kg bw/day for males, and 0, 0.23, 9.29 or 466.64 mg/kg bw/day for females)	**Systemic toxicity** LOAEL=8.25/9.29 mg/kg bw/day NOAEL=0.20/0.23 mg/kg bw/day **Neurotoxicity** LOAEL could not be determined since there were no treatment-related neurotoxic effects noted at any dose level tested. NOAEL = 402.80/466.64 mg/kg bw/day.	**0.20/0.23 mg/kg bw/day:** No treatment-related effects. **8.25/9.29 mg/kg bw/day:** Corneal opacities and/or vascularization; slightly lower body-weight gain (non-adverse). **402.80/466.64 mg/kg bw/day:** Corneal opacities and/or vascularization; slightly lower body-weight gain and food consumption (non-adverse).

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
SPECIAL STUDIES—CONTROL			
Plasma tyrosine, and liver and kidney enzyme parameters in control mouse pups	Not applicable	Not applicable. This study was conducted to provide a data base on the activity/levels of two enzymes involved in tyrosine catabolism, i.e., TAT and p-hydroxyphenylpyruvate dioxygenase (HPPD), in mouse pups from new born to 42 days of age.	**TAT:** In the dams, levels in the liver were high from days 1 to 15 postpartum, with a decline to normal adult values by day 22 postpartum. In the pups, TAT activity was similar to the adult values. Plasma tyrosine was inversely related to TAT levels (dams and offspring). **HPPD:** In the dams, levels in the liver were similar throughout the study period. In offspring, HPPD activity was low from days 1 to 15 postpartum, then increased to adult values by day 22 postpartum. Kidney levels of TAT and HPPD were substantially lower than the activity seen in the liver, but followed a similar pattern of development.
Plasma tyrosine, and liver and kidney enzyme parameters in control rat pups	Not applicable	Not applicable. This study was conducted to provide a data base on the activity/levels of two enzymes involved in tyrosine catabolism, i.e., TAT and p-hydroxyphenylpyruvate dioxygenase (HPPD), in rat pups from new born to 42 days of age.	**TAT:** In the dams, levels in the liver were consistent throughout the study, as were plasma tyrosine levels. In the pups, TAT activity in the liver increase after birth and then decline to adult levels by day 22. The sex difference in HPPD levels becomes apparent after sexual maturity. **HPPD:** In the dams, levels in the liver were increased over time. In offspring, HPPD activity and plasma tyrosine activity increased over time, attaining adult values by day 22 postpartum. The sex difference in HPPD levels becomes apparent after sexual maturity. Kidney levels of TAT and HPPD were substantially lower than the activity seen in the liver, but followed a similar pattern of development.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
SPECIAL STUDIES—TGAI			
28-day dietary	Rats—Sprague Dawley, 8 females/group; 0, 0 ppm ZA1296/0.5% tyrosine, 0 ppm ZA1296/1.0% tyrosine, 0 ppm ZA1296/2.5% tyrosine, 100 ppm ZA1296, 100 ppm ZA1296/0.5% tyrosine, 100 ppm ZA1296/1.0% tyrosine, 100 ppm ZA1296/2.5% tyrosine.	Not applicable. This was a special study designed to investigate the induction of tyrosinaemia in female rats given diets containing tyrosine when small amounts of ZA1296 were also present.	**Plasma tyrosine:** Increased in the 100 ppm ZA1296, 100 ppm ZA1296/0.5% tyrosine, 100 ppm ZA1296/1.0% tyrosine and 100 ppm ZA1296/2.5% tyrosine groups. **TAT:** Increased in the 0 ppm ZA1296/0.5% tyrosine, 0 ppm ZA1296/1.0% tyrosine, 0 ppm ZA1296/2.5% tyrosine, 100 ppm ZA1296 and ZA1296/2.5% tyrosine groups. **4-hydroxyphenylpyruvate dioxygenase (HPPD):** Decreased in the 0 ppm ZA1296/2.5% tyrosine, 100 ppm ZA1296, 100 ppm ZA1296/0.5% tyrosine, 100 ppm ZA1296/1.0% tyrosine, 100 ppm ZA1296/2.5% tyrosine groups. **Ocular effects (cloudy eyes):** Observed in the 100 ppm ZA1296/0.5% tyrosine, 100 ppm ZA1296/1.0% tyrosine and 100 ppm ZA1296/2.5% tyrosine groups. Results of this study indicate that the tyrosinemia and the associated toxic effects seen in rats related to administration of ZA1296 alone in the diet are exacerbated when both ZA1296 and tyrosine are administered to rats in the diet.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
3-month dietary	Mouse—C57; 20/sex/group; 0, 1, 10, 50, 100, 350, 1000, 3500 or 7000 ppm (equal to 0, 0.16, 1.69, 8.49, 18.0, 58.5, 179.3, 599.9 or 1222.5 mg/kg bw/day for males, and 0, 0.19, 1.94, 10.8, 20.5, 72.7, 214.9, 714.8 or 1436.4 mg/kg bw/day for females)	Not applicable. This was a special study designed to investigate ZA1296-induced tyrosinaemia.	**Plasma tyrosine:** At 1 week, increased at all dose levels, both sexes; this effect was maintained through to study termination at 10 ppm and higher. **TAT:** Increased at all dose levels tested, females only. **4-hydroxyphenylpyruvate dioxygenase (HPPD):** Decreased at all dose levels tested, both sexes. **Phenolic acid (in urine):** Increased at all dose levels for females, and at 10 ppm and higher for males. There were no ocular lesions observed at clinical, gross or histopathological examination. Ophthalmological examinations were not conducted.
3-month dietary	Rats—Sprague Dawley, 16 males/group; 0, 0, 0.5, 1, 3, 4, 5, 7.5, 10 or 100 ppm (equal to 0, 0, 0.04, 0.09, 0.27, 0.35, 0.44, 0.67, 0.89 or 8.96 mg/kg bw/day)	Not applicable. This was a special study designed to investigate the correlation between ocular, body weight and organ weight changes with ZA1296-induced tyrosinaemia.	**Plasma tyrosine:** Increased at all dose levels tested. **TAT:** Increased at doses ≥ 0.09 mg/kg bw/day. **4-hydroxyphenylpyruvate dioxygenase (HPPD):** Decreased at all dose levels tested. **Phenolic acid (in urine):** Increased at all dose levels tested. **Ocular effects (corneal opacity and/or vascularization):** ≥ 0.67 mg/kg bw/day No treatment-related adverse effects on body-weight gain, liver weights or kidney weights. These findings indicate a correlation between ZA1296-induced tyrosinaemia, caused by the inhibition of HPPD and modulated by the induction of TAT, and the incidence of corneal opacity.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
3-month dietary	Rats—Sprague Dawley, 20 females/group; 0, 0, 1, 5, 10, 50, 100, 1000 or 2500 ppm (equal to 0, 0, 0.09, 0.48, 0.95, 4.82, 9.54, 94.83 or 236.75 mg/kg bw/day)	Not applicable. This was a special study designed to investigate the correlation between ocular, body weight and organ weight changes with ZA1296-induced tyrosinaemia.	**Plasma tyrosine:** Increased at all dose levels tested. **TAT:** Increased at all dose levels tested at week 2; increased at doses ≥ 0.48 mg/kg bw/day at weeks 5 and 14. **4-hydroxyphenylpyruvate dioxygenase (HPPD):** Decreased at all dose levels tested. **Phenolic acid (in urine):** Increased at ≥9.54 mg/kg bw/day. **Ocular effects (corneal opacity and/or vascularization):** ≥9.54 mg/kg bw/day. No treatment-related adverse effects on body-weight gain, liver weights or kidney weights. These findings indicate a correlation between ZA1296-induced tyrosinaemia, caused by the inhibition of HPPD and modulated by the induction of TAT and the incidence of corneal opacity.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
3-month dietary	Rats—Sprague Dawley, 40 males/group; 0, 5, 100 or 2500 ppm (equal to 0, 0.37, 7.52 and 192 mg/kg bw/day). Recovery periods of 0, 2, 4, 6 or 9 weeks for the 5 and 100 ppm groups, and recovery periods of 0, 1, 2, 4 and 9 weeks for the 2500 ppm group, 8 rats/group/interval.	Not applicable. This study was designed to investigate the reversibility of liver and kidney weight changes in rats induced by dietary administration of ZA1296 for 90 days.	**Plasma tyrosine:** Increased at all dose levels tested. Returned to control levels by the end of the recovery period. **TAT:** Increased at all dose levels tested. Returned to control levels by the end of the recovery period. **4-hydroxyphenylpyruvate dioxygenase (HPPD):** Decreased at all dose levels tested. Partial recovery by the end of the recovery period. **Ocular effects (corneal opacity and vascularization):** Observed at all dose levels tested. Only ghost vascularization (indicating healed lesions) was observed at the end of the recovery period. No treatment-related adverse effects on body-weight gain, liver weights or kidney weights. These findings indicate a correlation between ZA1296-induced tyrosinaemia, caused by the inhibition of HPPD and modulated by the induction of TAT, and the incidence of corneal opacity. The data also indicate reversibility of treatment-related effects upon cessation of treatment.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
3-month dietary	Rats—Sprague Dawley; 0 or 2500 ppm (equal to 0 or 272 mg/kg bw/day). 16 males in the control group, 40 males in the 2500 ppm group. At the end of treatment, 8/16 control males, 15/28 males in the treated group with eye lesions and all of the 12 males in the treated group without eye lesions were sacrificed. The remaining survivors were retained for an 8-week recovery period.	Not applicable. This study was designed to investigate the development of the known ocular lesions in rats fed diet containing ZA1296 and to demonstrate the reversibility of these lesions following cessation of dietary administration.	At the end of an 8-week recovery period, there was complete resolution of the following treatment-related findings: lower body-weight gain, increased plasma tyrosine levels and corneal lesions seen at ophthalmological examination. Histopathological changes in the eyes had completely reversed by the end of the recovery period for 4/13 animals, and had almost completely reversed in 9/13 animals.
Systemic exposure following dietary administration	Rats—Male Sprague Dawley; ZA1296, batch P8 or P11: 40, 125, 1250 or 5000 ppm (equivalent to 0.1, 4, 12.5, 125.0 or 500 mg/kg bw/day)	Not applicable. The purpose of this study was to determine whether feeding diet containing the same concentration of different batches of ZA1296 to male rats for a period of 7 days resulted in any differences in systemic exposure to unchanged test substance.	There were no differences in food consumption between diet prepared with either P8 or P11, nor between dose levels. Comparisons of systemic exposure based on urinary excretion of unchanged ZA1296 and on the effect on plasma tyrosine concentrations showed no significant differences between diet prepared with P8 or P11. Plasma AUC and Cp_{max} increased linearly with dose, for both batches; there was some evidence of divergence in response at high dose levels, resulting in slightly higher systemic exposures with batch P11.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
3-month dietary	Rats—Sprague Dawley, 40 males/group; 0, 5, 100 or 2500 ppm (equal to 0, 0.37, 7.52 or 192 mg/kg bw/day) Recovery periods of 0, 2, 4, 6 or 9 weeks for the 5 and 100 ppm groups, and recovery periods of 0,1, 2, 4 or 9 weeks for the 2500 ppm group, 8 rats/group/time interval.	Not applicable. This study was designed to investigate the reversibility of liver and kidney weight changes in rats induced by dietary administration of ZA1296 for 90 days.	**Plasma, liver and kidney tyrosine:** Increased at all dose levels tested. Returned to control levels by the end of the recovery period. **TAT:** Increased at all dose levels tested. Returned to control levels by the end of the recovery period. **4-hydroxyphenylpyruvate dioxygenase (HPPD):** Decreased at all dose levels tested. Partial recovery by the end of the recovery period. **Ocular effects (corneal opacity and vascularization):** Observed at all dose levels tested. Only ghost vascularization (indicating healed lesions) was observed at the end of the recovery period. No adverse, treatment-related effects on body-weight gain, liver weights or kidney weights. These findings indicate a correlation between ZA1296-induced tyrosinaemia, caused by the inhibition of HPPD and modulated by the induction of TAT, and the incidence of corneal opacity. The data also indicate reversibility of treatment-related effects upon cessation of treatment.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
One-generation dietary	Rat—Sprague Dawley; **Group 1:** 0 ppm, 20 pregnant rats/group **Group 2:** 2500 ppm (equivalent to 125 mg/kg bw/day), 8 pregnant rats/group, from postcoitum day 1 to postpartum day 11, then control diet to termination. **Group 3:** 2500 ppm, 12 pregnant rats/group, from postcoitum day 1 to study termination.	Not applicable. The purpose of this study was to develop a short-term model to investigate the effects of ZA1296 on litter size, decreased pup survivability and/or delayed preputial separation in F_1 males only.	**Group 2:** Decreased pup and litter overall body-weight gain; increased plasma tyrosine (parental and pups). **Group 3:** Decreased parental body-weight gain; decreased pup and litter overall body-weight gain; increase in whole litter loss; increased plasma tyrosine (parental and pups).
One-generation dietary	Rat—Sprague Dawley, 20 pregnant rats/group; 0, 0.5% tyrosine, 1.0% tyrosine, 2.0% tyrosine, 2500 ppm ZA1296, 2500 ppm ZA1296/0.5% tyrosine, 2500 ppm ZA1296/1.0% tyrosine or 2500 ppm ZA1296/2.0% tyrosine Study was terminated on day 5 postpartum. NOTE: Animals in the ZA1296/2.0% tyrosine group were terminated by day 11 for humane reasons.	Not applicable. The purpose of this study was to evaluate the effects of ZA1296 in conjunction with dietary tyrosine on litter size and pup viability.	**Eye lesions (opacity):** ZA1296/0.5% tyrosine, ZA1296/1.0% tyrosine and ZA1296/2.0% tyrosine. **Plasma tyrosine levels:** Markedly increased in the ZA1296, ZA1296/0.5% tyrosine, ZA1296/1.0% tyrosine and ZA1296/2.0% tyrosine groups; slightly elevated in the groups receiving tyrosine alone. **Whole litter loss:** Increased in the ZA1296/0.5% tyrosine and ZA1296/1.0% tyrosine groups. **Pups alive on day 5:** Lower in the ZA1296/0.5% tyrosine and ZA1296/1.0% tyrosine groups; slightly lower in the ZA1296 group. **Pups born dead:** Increased in the ZA1296/1.0% tyrosine group. Treatment with a combination of mesotrione and tyrosine caused more marked effects than treatment with mesotrione alone.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
One-generation dietary	Rat—Sprague Dawley, 20 pregnant rats/group; 0, 0.5% tyrosine, 1.0% tyrosine, 2.0% tyrosine, 2500 ppm ZA1296, 2500 ppm ZA1296/0.5% tyrosine, 2500 ppm ZA1296/1.0% tyrosine or 2500 ppm ZA1296/2.0% tyrosine Study was terminated on day 29 postpartum. NOTE: Animals in the ZA1296/2.0% tyrosine group were terminated by day 11 for humane reasons.	Not applicable. The purpose of this study was to evaluate the role of tyrosine in the ZA1296-induced reproductive effects by adding different dose levels of tyrosine in conjunction with ZA1296 in order to exacerbate any possible tyrosine effects.	**Eye lesions (opacity):** Parents and pups: ZA1296, ZA1296/0.5% tyrosine, ZA1296/1.0% tyrosine and ZA1296/2.0% tyrosine. **Plasma tyrosine levels:** Parents and pups— Markedly increased in the ZA1296, ZA1296/0.5% tyrosine, ZA1296/1.0% tyrosine and ZA1296/2.0% tyrosine groups; slightly elevated in the groups receiving tyrosine alone. **Whole litter loss:** Increased in the ZA1296/0.5% tyrosine and ZA1296/1.0% tyrosine groups. **Litter size:** Decreased in the ZA1296/0.5% tyrosine and ZA1296/1.0% tyrosine groups; slightly decreased in the ZA1296 group. **Pups surviving to day 22:** Decreased in the ZA1296, ZA1296/0.5% tyrosine and ZA1296/1.0% tyrosine groups. **Pups born live:** Decreased in the ZA1296/1.0% tyrosine group.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
			Bilateral/unilateral renal pelvic dilatation: Increased in the ZA1296, ZA1296/0.5% tyrosine and ZA1296/1.0% tyrosine groups. The data indicate that there could be a causal relationship between tyrosine and reduced litter size and increased perinatal mortality. A possible causal relationship between tyrosine and pelvic dilatation was not as convincing since the incidence was similar between the ZA1296 group and the ZA1296/tyrosine groups. It should be noted, however, that treatment with tyrosine alone did not result in reduced litter size, increased perinatal mortality or bilateral renal pelvic dilatation and there was no dose-response relationship associated with the degree of the tyrosinaemia and the observed findings. In addition, a specific mechanism of action was not proposed as to how increased plasma tyrosine levels could induced the noted findings. It was therefore concluded that it was not adequately demonstrated that the tyrosinemia associated with mesotrione administration elicited the observed findings. It was determined, however, that treatment with a combination of mesotrione and tyrosine caused more marked effects than treatment with mesotrione alone.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
Teratogenicity oral gavage	Rabbit— New Zealand white, female, 20/group; 0, 1% tyrosine, 500 mg ZA1296/kg bw/day or 500 mg ZA1296/kg bw/day + 1% tyrosine	Not applicable. The purpose of this study was to investigate the effects of tyrosinaemia on changes in the ossification of the rabbit fetal skeleton, and on the incidence of abortion in rabbits.	**Plasma tyrosine:** Increased in all treatment groups. Returned to predose levels 8 to 9 days postdosing. **TAT:** Decreased in the ZA1296 and ZA1296/tyrosine groups only. **4-hydroxyphenylpyruvate dioxygenase (HPPD):** Decreased in the ZA1296 and ZA1296/tyrosine groups only. Tyrosine group unaffected. A single doe in the ZA1296/tyrosine group was aborted; it is uncertain whether this finding was treatment-related. No effect in any group on the number, growth or survival of the fetuses, nor evidence of any treatment-related teratogenic effects. Increased incidence of minor skeletal anomalies and skeletal variants in the ZA1296 and ZA1296/tyrosine groups. The study data indicated that there could be a causal relationship between the incidence of specific changes in fetal ossification and plasma tyrosine levels rather than a direct effect of ZA1296. It should be noted, however, that treatment with tyrosine alone did not result in the specific changes in fetal ossification, and a specific mechanism of action was not proposed as to how increased plasma tyrosine levels could induce the noted findings. It was therefore concluded that it was not adequately demonstrated that the tyrosinemia associated with mesotrione administration elicited the observed findings.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
Plasma tyrosine determination in the pregnant mouse	Mouse—CD-1; 0, 10, 30, 60, 100, 300 or 600 mg/kg bw/day, 18 females in the control group, 12 females/group in the treated groups	Not applicable. The purpose of this study was to investigate the effects of ZA1296 on plasma levels of tyrosine in the pregnant mouse.	Plasma tyrosine levels peaked 4 to 8 hours postdosing at all dose levels tested, at all intervals measured.
Plasma tyrosine determination in the pregnant rat	Rat—Sprague Dawley; 0, 2, 10, 50, 100, 300 or 1000 mg/kg bw/day, 6 females/group	Not applicable. The purpose of this study was to investigate the effects of ZA1296 on plasma levels of tyrosine in the pregnant rat.	Plasma tyrosine levels were increased at ≥10 mg/kg bw/day. Largest increases were seen 12 hours after the first dose. Increases seen 12 hours after 6th and 10th dose were not as marked as after the 1st dose. Levels at 24 hours postdosing were lower than at 12 hours postdosing.
Plasma tyrosine determination in the pregnant rabbit	Rabbit—New Zealand White; 0, 2, 10, 50, 100, 250 or 500 mg/kg bw/day, 3 females/group	Not applicable. The purpose of this study was to investigate the effects of ZA1296 on plasma levels of tyrosine in the pregnant rabbit.	Plasma tyrosine levels were increased at ≥10 mg/kg bw/day. Largest increases were seen 12 hours after the first dose. Increases seen 12 hours after 8th and 14th dose were not as marked as after the 1st dose. Levels at 24 hours postdosing were lower than at 12 hours postdosing.
Tyrosine determination in the milk of lactating mice	Mouse—CD-1; 0, 10, 100 or 7000 ppm (equivalent to 0, 0.15, 1.5 or 1050 mg/kg bw/day), 5 females/group	Not applicable. The purpose of this study was to compare the level of tyrosine in the milk with the level of tyrosine in the blood of lactating mice exposed to ZA1296 in the diet during gestation and lactation.	There was a dose-related increase in plasma tyrosine levels, i.e., ~5-fold, 9.5-fold and 14-fold in the 10, 100 and 7000 ppm groups, respectively. Tyrosine levels in the milk could not be measured due to insufficient sample size. Conclusion: It could not be determined whether increased tyrosine levels in the plasma would result in an increase in tyrosine levels in the milk of treated dams.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
Tyrosine determination in the milk of lactating rats	Rat—Sprague Dawley; 0, 2.5, 1000 or 2500 ppm (equivalent to 0, 0.25, 100 or 250 mg/kg bw/day)	Not applicable. The purpose of this study was to compare the level of tyrosine in the milk with the level of tyrosine in the blood of lactating rats exposed to ZA1296 in the diet during gestation and lactation.	Plasma tyrosine levels were increased ~2-fold in the 2.5 ppm group, and ~16-fold in the 1000 and 2500 ppm groups. Levels in milk increased in a similar fashion, i.e., ~3-fold in the 2.5 ppm group, and ~13-fold in the 1000 and 2500 ppm groups. Tyrosine levels in milk were ~23% to 35% lower than tyrosine levels in the plasma. Conclusion: Tyrosine concentration in milk samples mey be predicted from plasma tyrosine concentrations. Significant maternal transfer of tyrosine to the neonate can be predicted in studies where the maternal animals are exposed to ZA1296.
Biochemical studies in rat and mouse liver	i) Rat—CD, 0, 1000, 7000 or 16000 ppm (equivalent to 0, 100, 700 or 1600 mg/kg bw/day); males ii) Mouse—CD-1, 0, 1000, 3000 or 7000 ppm (equivalent to 0, 15, 105 or 240 mg/kg bw/day); males Ten animals in each control group, five animals in each treated group.	Not applicable. The purpose of this study was to characterize the biochemical and pathological effects of ZA1296 in rat and mouse liver after administration in the diet for 28 days.	ZA1296 was not hepatotoxic in these studies. It induced minimal induction of CYP 1A1 in the rat, CYP 2B1/2 and CYP 3A1 in the mouse, and minimal induction of their associated enzyme activities. In comparison to the 134-fold and 25-fold increases in CYP enzyme activities produced by the standard inducing agents, the 2- and 3.5-fold increases produced by ZA1296 were not considered to be significant. Conclusion: The absence of liver growth, lack of adverse histopathology and minimal CYP induction at high dose levels, indicates that ZA1296 is unlikely to be hepatocarcinogenic in rats and mice.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
Acute oral	Human—6 males/group; 0.1, 0.5 or 4.0 mg/kg bw	Not applicable. The purpose of this study was to identify suitable urinary markers to allow non-invasive monitoring of worker exposure to ZA1296 and to define the dose response for increased plasma tyrosine levels.	**Plasma tyrosine:** Dose-related increase; peak levels at 5–6 hours, 6–8 hours and 8–12 hours postdosing for the 0.1, 0.5 and 4.0 mg/kg bw groups, respectively. Plasma tyrosine returned to predosing levels by 24 hours, 24 hours and 48 hours for the 0.1, 0.5 and 4.0 mg/kg bw groups, respectively. Peak concentrations seen within 1 hour of dosing. Plasma tyrosine half-life ~1 hour. Rapidly excreted; majority eliminated within 8–12 hours postdosing. **4-hydroxyphenyl acetic acid and 4-hydroxyphenyl pyruvic acid:** Total excretion increased during 24 hours postdosing. Returned to predose levels at 24 hours postdosing. It is concluded that measurement of urinary excretion of phenolic acids could be used to provide a non-invasive marker of systemic exposure to ZA1296 during field application.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
Compiled results from 15 studies using > 50 triketone compounds	Rats—Sprague Dawley	Not applicable. The purpose of this review was to compile the results of 15 studies in which over 50 triketone compounds were evaluated to assess the relationship between plasma and ocular tyrosine levels and between plasma tyrosine and the incidence of corneal lesions in the rat.	**Conclusions:** a) Many triketones caused increased plasma and ocular tyrosine concentrations and induced ocular lesions. b) Structurally similar ketones can have markedly different potencies. c) The least potent test substances included enamine pro-herbicide derivatives of ketones. d) Plasma and ocular tyrosine concentrations increased the risk of corneal lesions. e) Evidence suggests that there may be a tyrosine threshold (1000 nmol/mL in plasma) for ocular lesion development. f) The ocular lesion produced by triketones is due to prolonged tyrosinaemia rather than a direct effect of the triketone on the cornea.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
Data review of mechanism of toxicity of mesotrione and its relevance to humans	Laboratory animals, humans	Not applicable. The purpose of this review was to determine the relevance of the toxicity data for mesotrione in various species to humans. Zeneca and two independent panel of experts conducted the review.	**Conclusions:** There is both direct and indirect evidence to conclude that the toxicity associated with administration of mesotrione to rats is mediated by tyrosine. There is direct and indirect evidence that the species differences in toxic response is the result of different steady-state tyrosine levels, maintained by the differential activities of TAT. The higher steady-state activity of TAT in the mouse maintains a lower plasma level of tyrosine in the mouse, thus precluding the expression of toxicities seen in the rat. The general systemic toxicity related to mesotrione is related to the tyrosine plasma level achieved as a result of TAT activity in each specific species. Therefore, the mouse is considered more predictive of the human dose/effect profile of mesotrione than the rat since human TAT activity is similar to the mouse, and plasma tyrosine levels in the human are maintained at levels below those that cause the systemic toxicity seen in the rat.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
			The PMRA concurs that the mouse is the more appropriate species for human risk assessment with respect to ocular toxicity related to mesotrione administration. However, special reproduction and developmental studies did not adequately demonstrate a direct causal relationship between the tyrosinaemia resulting from mesotrione administration and decreased litter size, decreased pup survival, bilateral hydronephrosis and fetal ossification changes. Therefore, human risk assessment for reproductive and developmental findings should not be restricted to findings observed in mice; rather, data generated from all reproduction and developmental studies, regardless of species, should be considered.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
Data review of mechanism of toxicity of mesotrione and its relevance to humans	Laboratory animals, humans	Not applicable. The proposed mechanism of action for mesotrione was presented.	The primary effect of exposure to ZA1296 is inhibition of the enzyme HPPD. Prolonged inhibition of this enzyme results in an increase in plasma tyrosine levels (tyrosinaemia). Following inhibition of HPPD, the maximal extent of the tyrosinaemia is controlled by the enzyme TAT. This enzyme has relatively low activity in the rat resulting in a severe tyrosinaemia. TAT activity is much greater in the mouse, leading to relatively minor increases in plasme tyrosine levels. The activity of TAT is similar in mice and in humans. The applicant concluded that the findings in the rat at low dose levels of mesotrione are not relevant to humans and that the findings and effect levels established in the mouse should be used in preference when assessing the safety of mesotione to humans. The PMRA concurs that the mouse is the more appropriate species for human risk assessment with respect to ocular toxicity related to mesotrione administration. However, special reproduction and developmental studies did not adequately demonstrate a direct causal relationship between the tyrosinaemia resulting from mesotrione administration and decreased litter size, decreased pup survival, bilateral hydronephrosis and fetal ossification changes. Therefore, human risk assessment for reproductive and developmental findings should not be restricted to findings observed in mice; rather, data generated from all reproduction and developmental studies, regardless of species, should be considered.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS
SPECIAL STUDIES—Tyrosine			
21-day dietary	Rat—Sprague Dawley, 8 males/group; 0, 0.5%, 1.0%, 2.5% or 5.0%. All groups on a low protein diet.	Not applicable. The purpose of this study was to assess the ophthalmoscopic and histological effects of different dose levels of tyrosine when fed in a low protein diet to weanling rats.	**0.5% and 1.0%:** No treatment-related findings. **2.5% and 5.0%:** Corneal opacity, keratitis and iritis with polymorph accumulation at the filtration angle. Epithelial disorganization without inflammation (5.0% only).
SPECIAL STUDIES—NTBC			
Pharmacokinetic crossover in humans, 2 single oral doses, 2 weeks apart	Humans—10 healthy males; 1 mg/kg bw in either liquid or capsule formulation. Fourteen days after dosing, subjects who received the liquid dose were dosed by capsule, and vice versa (1 mg/kg bw).	Not applicable. The purpose of this study was to compare the bioavailability of NTBC, at dose levels used in the clinic, from 2 different formulations in healthy volunteers.	Conclusion: Inhibition of HPPD by NTBC is essentially irreversible and adaptation by humans to the tyrosinaemia is similar to that which occurs in mice. (Maximum tyrosine levels in mice is ~800 nmol/mL, after which a steady state is maintained; in humans it was ~1000 nmol/mL)
SPECIAL STUDIES—METABOLITES			
MNBA: assay of rat liver cytosol for p-hydroxyphenylpyruvate dioxygenase (HPPD)	MNBA: 0, 0.02 and 2.0 μM. Positive controls: i) NTBC: 0.02, 0.2 and 2.0 μM. ii) ZA1296: 0.02, 0.2 and 2.0 μM.	Not applicable. The purpose of this study was to investigate the inhibition of HPPD by MNBA, a ZA1296 metabolite. (ZA1296 is a known inhibitor of HPPD).	Both ZA1296 and NTBC resulted in extensive inhibition of HPPD, i.e., 70% (0.02 μm) nd 100% (2.0 μM). MNBA resulted in only slight inhibition of HPPD at 2.0 μM, i.e., 7.2%. Conclusion: MNBA will not likely interfere significantly with tyrosine catabolism in vivo.
AMBA: assay of rat liver cytosol for p-hydroxyphenylpyruvate dioxygenase (HPPD)	AMBA: 0, 0.02 and 2.0 μM. Positive controls: i) NTBC: 0.02, 0.2 and 2.0 μM. ii) ZA1296: 0.02, 0.2 and 2.0 μM.	Not applicable. The purpose of this study was to investigate the inhibition of HPPD by AMBA, a ZA1296 metabolite. (ZA1296 is a known inhibitor of HPPD).	Both ZA1296 and NTBC resulted in extensive inhibition of HPPD, i.e., 70% (0.02 μm) nd 100% (2.0 μM). AMBA resulted in only slight inhibition of HPPD at 2.0 μM, i.e., 18.7%. Conclusion: AMBA will not likely interfere significantly with tyrosine catabolism in vivo.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSE	SIGNIFICANT EFFECTS/ COMMENTS

Recommended ADI: 0.001 mg/kg bw/day for the general population, based on the NOAEL of 0.3 mg/kg bw/day. The NOAEL was established in the rat reproduction study, based on bilateral hydronephrosis (parents and pups), and using a 300-fold uncertainty factor, i.e., 10× for interspecies differences, 10× for intraspecies differences and an additional 3-fold uncertainty factor due to increased qualitative and quantitative susceptibility of rat pups (bilateral hydronephrosis) and increased quanitative susceptibility of mouse pups (eye lesions).

Eye lesions seen in rats were not considered for human risk assessment since the mouse was considered to be a more appropriate model for eye lesions. In the mouse, eye lesions were only observed in the mouse reproduction study. For parents, findings were observed at the high dose level of 1471.9/1439.1 mg/kg bw/day, and at dose levels of ≥ 311.8/297.2 mg/kg bw/day for offspring.

It was not conclusively demonstrated that non-ocular effects were the direct result of increased plasma tyrosine levels, rather than a direct effect of exposure to mesotrione.

Recommended ARfD: No acute endpoints of concern were identified, and so an ARfD is not required.

There was an increase in the quantitative susceptibility of mouse pups in the mouse reproductive toxicity study.

There was an increase in the qualitative and quantitative susceptibility of rat pups in the rat reproductive toxicity study.

There was an increase in the quantitative susceptibility of rat fetuses in the rat reproduction study.

There was no evidence of oncogenic/carcinogenic potential of mesotrione in rodents.

There was no evidence of neurotoxicity in rats after acute and short-term exposure to mesotrione.

Appendix III Occupational Exposure Summary Tables

Table 1 PHED Exposure Estimates Based on Best Fit[1] Statistical Measure

PHED Scenario	Unit Exposure (µg a.i./kg a.i. handled)						
	Dermal Body	Dermal Hands	Dermal Total	Dermal[2] Absorbed	Inhalation[3]	Total Deposition (D+I)	Total Absorbed (D+I)
Mixer/Loader (liquid)							
Single layer + gloves	36.33	14.81	51.14	0.51	1.6	52.74	2.11
+ coveralls	17.96	14.81	32.77	0.33	1.6	34.37	1.93
Applicator (groundboom)							
Single layer + no gloves + open cab	18.63	14.35	32.98	0.33	0.96	33.94	1.29
+ coveralls	7.18	14.35	21.53	0.22	0.96	22.49	1.18

[1] Best fit estimate based on adding arithmetic means for normal distributions, geometric means for lognormal distributions, medians for other distributions

[2] Dermal absorption factor = 1%

[3] Inhalation exposure adjusted for respiration rate for light work (17 litres per minute)

Table 2 Scenario-specific Exposure Estimates for Mixer + Loader + Applicator

Exposure Scenario	PHED Total Unit Exposure [1] (µg a.i./kg a.i. handled)		Exposure Pattern (kg a.i .handled/day)	Daily Exposure [2] (µg a.i./ kg bw/day)	
	Total deposition	Total [3] absorbed		Deposition	Absorbed
Farmer M/L/A (liquid; groundboom)					
Single layer + gloves (M/L) + open cab	86.68	3.4	80 ha/day × 140 g a.i./ha = 11.2 kg a.i./day	13.87	0.54
+ coveralls	56.86	3.1		9.1	0.5
Custom M/L/A (liquid; groundboom)					
Single layer + gloves (M/L) + open cab	86.68	3.4	140 ha/day × 140 g a.i./ha = 19.6 kg a.i./day	24.27	0.95
+ coveralls	56.86	3.1		15.92	0.87

[1] Sum of mixer + loader + applicator dermal and inhalation exposures (deposition or absorbed)

[2] Calculated as [µg a.i./kg a.i. handled/day × application rate × area treated/day] / body weight (70 kg)

[3] Dermal absorption factor = 1%

Table 3 Operator Exposure Estimates and Margins of Exposure

Exposure Scenario	Daily Systemic Exposure (mg a.i./kg bw/day)	MOE
Farmer mixer/loader/applicator (liquid; groundboom)		
Single layer + gloves (mixer/loader) + open cab	0.00054	556
+ coveralls	0.0005	600
Custom mixer/loader/applicator (liquid; groundboom)		
Single layer + gloves (mixer/loader) + open cab	0.00095	316
+ coveralls	0.00087	345

Table 4 Re-entry Exposure Estimates and Margins of Exposure

Re-entry Exposure Scenario	Daily Systemic Exposure (µg a.i./kg bw/day)	MOE
Scouting—minimal foliage development	0.048	6300
Scouting—full foliage development	0.003	100000
Detasseling production seed corn	0.028	11000
Hand-harvesting sweet corn	0.0007	430000

Appendix IV Residues

Table 1 Integrated Food Residue Chemistry Summary

DIRECTIONS FOR USE OF PESTICIDE ON FIELD CORN, SWEET CORN AND PRODUCTION SEED CORN					
Crop	**Formulation/Type**	**Timing**	**No./ season**	**Rate (g a.i./ha)**	**Preharvest Interval (days)**
Field corn, sweet corn and production seed corn	Suspension concentrate	Pre-emergent; broadcast application	1	140	100 (field corn grain/stover) 90 (field corn forage) 50 (sweet corn)
		or			
		Field corn only Early postemergent; spike to 2-leaf growth stage; Foliar broadcast application	1	140	100 (field corn grain/stover) 90 (field corn forage)

PHYSICOCHEMICAL PROPERTIES	
Water solubility at 20°C (mg/L)	2200 (pH 4.8), 15000 (pH 6.9) and 22000 (pH 9)
Solvent solubility at 20°C (mg/L)	3.7×10^3 in methanol; 1.7×10^4 for ethyl acetate; 2.7×10^3 for toluene; 8.9×10^4 for 1,2-dichloroethane; 10.4×10^3 for acetonitrile; 1.4×10^3 for xylenes; $< 0.3 \times 10^3$ for heptane; and 8.1×10^4 for acetone.
n-octanol–water partition coefficient (Log K_{ow})	0.11 (unbuffered); -1.076 (pH 5) and < -1 (pH 7 and 9)
Vapour pressure at 20°C	$< 5.7 \times 10^{-6}$ Pa

ANALYTICAL METHODOLOGY				
Parameters	**Plant Matrices**			
Method ID	TMR 0689	TMR 0643B	TMR 0882B	RAM 366/01
Type	Data-gathering	Data-gathering	Data-gathering	Data-gathering and Enforcement
Analytes	isopropyl-MNBA (combined residues of parent and MNBA)	AMBA conversion product (Mesotrione and MNBA separately)	AMBA conversion product (Mesotrione and MNBA separately)	Mesotrione and MNBA separately
Instrumentation	GC/MSD	HPLC/UV	HPLC/UV	HPLC/MS/MS
LOQ	0.01 ppm	0.01 ppm	0.01 ppm	0.01 ppm
Standard	An external standard method was used as a marker for retention time, response and calibration.			
ILV	No ILV	Successfully validated by ILV	Successfully validated by ILV	Successfully validated by ILV

Extraction/cleanup	– Extracted with ACN:water and partitioned into methylene chloride. The isopropyl ester of MNBA is formed and extracted with acetone. – No cleanup	– Extracted with ACN: water and partitioned into ethyl acetate – Silica SPE followed by reversed-phase HPLC	– Extracted with ACN: water – Reversed-phase HPLC	– Extracted ACN:ultra-pure water after addition of sodium chloride – OASIS HLB SPE
Radiovalidation	None	Adequately radiovalidated	None	None
ANALYTICAL METHODOLOGY				
Parameters	**Animal Matrices**			
Method ID	TMR 0739B ADD		TMR 0914B	
Type	Data-gathering		Data-gathering and enforcement	
Analytes	Mesotrione as isopropyl-MNBA		Mesotrione as AMBA conversion product	
Instrumentation	GC/MSD		HPLC/UV	
LOQ	0.01 ppm		0.01 ppm	
Standard	An external standard method was used as a marker for retention time, response and calibration.			
ILV	Successfully validated by ILV in ground beef and milk		Successfully validated by ILV in ground beef and milk	
Extraction/cleanup	– Extracted with acetone for milk and egg samples or acetone:water for the other tissues and partitioned into methylene chloride. The isopropyl ester of MNBA is formed and extracted with acetone. – No cleanup		– Extracted with acetone for milk and egg samples or acetone:water for the other tissues and partitioned into methylene chloride – Reversed-phase HPLC	
Radiovalidation	None		None	
Multiresidue method	Protocols A through F not suitable for the analysis of mesotrione.			
NATURE OF THE RESIDUE IN PLANTS—Corn				
Radiolabel position	[^{14}C-phenyl] mesotrione		[^{14}C-cyclohexanedione] mesotrione	
Test site	Outdoor test plots		Outdoor test plots	
Treatment 1 Rate	Preplant incorporated to soil at 280–307 g a.i./ha (~2×)		Preplant incorporated to soil at 280–307 g a.i./ha (~2×)	
Treatment 2 Rate	Foliar application (postemergent) at 161–164 g a.i./ha (~1×)		Foliar application (postemergent) at 161–164 g a.i./ha (~1×)	
Treatment 3 (supplemental study) Total rate	Pre-emergent application at 302 g a.i./ha followed by a foliar postemergent application at 179 g a.i./ha 481 g a.i./ha (~3.4×)		Not applicable	

Preharvest interval	28 days for immature corn forage 130 days for mature corn plants		28 days for immature corn forage 130 days for mature corn plants	
Corn metabolism studies demonstrated that residues of mesotrione resulted from the uptake and metabolism of mesotrione and the major soil metabolite MNBA.				
Metabolites Identified	**Major Metabolites (> 10% TRRs)**		**Minor Metabolites (< 10% TRRs)**	
Radiolabel position	[^{14}C-phenyl] mesotrione	[^{14}C-cyclohexanedione] mesotrione	[^{14}C-phenyl] mesotrione	[^{14}C-cyclohexanedione] mesotrione
Grain	None	None	None	None
Forage * (1) From samples harvested following the preplant treatment. * (2) From samples harvested following the postemergent treatment.	MNBA (1)* Conjugated AMBA (2)*	Carbohydrates (1 and 2)* 4-OH mesotrione (1)*	Mesotrione (1 and 2)* MNBA (2)* AMBA (1 and 2)* Conjugated AMBA(1)* 4-OH mesotrione (1 and 2)*	Mesotrione (1 and 2)* 4-OH mesotrione (2)*
Fodder * (1) From samples harvested following the preplant treatment. * (2) From samples harvested following the postemergent treatment.	Conjugated AMBA (1 and 2)*	Carbohydrates (2)* lignin (2)*	Mesotrione (1 and 2)* MNBA (1 and 2)* AMBA (1 and 2)* Conjugated AMBA (1 and 2)* 4-OH mesotrione (1 and 2)*	Cellulose (2)*
CONFINED ROTATIONAL CROP STUDY—Wheat, Soybean, Endive and Radish				
Radiolabel position	[^{14}C-phenyl] mesotrione or [^{14}C-cyclohexanedione] mesotrione			
Test Site	Greenhouses			
Treatment	Application to bare soil (sandy loam), with wheat and soybeans planted at the 30 DAT interval and wheat soybeans, endive and radish planted at 120 DAT and 300 DAT intervals. Crops were harvested at maturity.			
Application rate	For the 30 DAT interval, rate of 308 g a.i./ha. For the 120 DAT and 300 DAT intervals, rate of 462 g a.i./ha.			
In the phenyl radiolabelled study, MNBA was the predominant metabolite identified in all matrices, except for the 120 and 300 DAT wheat grain and the 300 DAT radish root and top. AMBA (free and conjugated) was also a major metabolite in all the 30 DAT soya and wheat matrices, except wheat grain. The parent was only identified in 30 DAT wheat forage (0.01 ppm) and in 300 DAT wheat hay (<0.01 ppm). In the cyclohexanedione radiolabelled study, none of the identified metabolites (mesotrione, 4-OGlu, 4-OH, 5-OH, xanthanone, glucose and fructose) accounted for more than 0.01 ppm.				

NATURE OF THE RESIDUE IN LAYING HEN			
Species	**Dose Level**	**Length of Dosing (day)**	**Sacrifice**
Hen	10 ppm	10	16 hours
90–99% of the AD eliminated with excreta; < 1% remaining in tissues, organs and eggs.			
Metabolites Identified	**Major Metabolites (> 10% TRRs)**	**Minor Metabolites (< 10% TRRs)**	
Radiolabel position: [^{14}C-phenyl] mesotrione			
Excreta	Mesotrione AMBA	None	
Liver	Mesotrione	None	
Skin and subcutaneous fat	Mesotrione	None	
Egg yolk	Mesotrione	None	
Radiolabel position: [^{14}C-cyclohexanedione] mesotrione			
Excreta	Mesotrione	5-OH-mesotrione	
Liver	Mesotrione	None	
Skin and subcutaneous fat	Mesotrione	None	
Egg yolk	Mesotrione ^{14}C-palmitic/oleic/stearic acids	None	
NATURE OF THE RESIDUE IN RUMINANT—Lactating Cow			
Species	**Dose Level**	**Length of Dosing (days)**	**Sacrifice (hours)**
Cow	10–12 ppm	7	16
91–93% of the AD excreted in via urine (~10–13%) and feces (~80%); < 2% remaining in tissues, organs and milk.			
Metabolites Identified	**Major Metabolites (> 10% TRRs)**	**Minor Metabolites (< 10% TRRs)**	
Radiolabel position: [^{14}C-phenyl] mesotrione			
Urine	AMBA	None	
Feces	AMBA	None	
Liver	Mesotrione	None	
Kidney	Mesotrione AMBA	None	
Milk	None	None	
Radiolabel position: [^{14}C-cyclohexanedione] mesotrione			
Urine	None	1,3-cyclohexadione	
Feces	None	5-OH-mesotrione Tetrahydroxanthone	
Liver	Mesotrione	None	

Kidney	Mesotrione	None
Milk	^{14}C-Lactose	None

CROP FIELD TRIALS—Field Corn

Forty-four individual field corn trials in Canada and the United States (In Zones 1, 2, 5, 5A, 5B and 6) from 1995 to 2001.

Timing of Application	Total Rate (g a.i./ha)	Preharvest Interval (days)	Mesotrione Residue Levels (ppm)					
			n	Min.	Max.	HAFT	Mean	SDEV
Field Corn Grain								
Early postemergence	175 (1.25×)	129–142	24	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Late postemergence	100 (0.7×)	100–133	32	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Pre-emergence + late postemergence	500 (3.6×) (300 + 200)	110–131	16	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Pre-emergence	300 (~2×)	122–155	4	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Pre-emergence	600 (~4×)	122–155	4	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Postemergence	200 (1.4×)	90–126	4	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Postemergence	400 (2.8×)	90–126	4	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Pre-emergence + postemergence	500 (3.6×) (300 + 200)	90–126	4	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Pre-emergence + postemergence	1000 (~7×) (600 + 400)	90–126	4	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Pre-emergent + late postemergent	560 (4×) (336 + 224)	68–114	67	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Kernels and CWHR (to simulate sweet corn)								
Pre-emergence + late-postemergence	500 (4×) (300 + 200)	49–60 (milking stage)	16	< 0.01	< 0.01	< 0.01	< 0.01	N/A

RESIDUE DECLINE

Not applicable since all the residues were < 0.01 ppm (< LOQ).

MAXIMUM RESIDUE LIMITS

Field corn and sweet corn	0.01 ppm
Meat and meat-byproducts, milk and eggs	0.01 ppm

FIELD ACCUMULATION IN ROTATIONAL CROPS—Radish, Soybeans, Millet, Sorghum, Endive and Wheat

Two trials were conducted in the United States, in North Carolina (Zone 2) and in Illinois (Zone 5).

Commodity	Total Rate (g a.i./ha)	Preharvest Interval (days)	Plantback Interval (days)	Mesotrione Residue Levels (ppm)					
				No.	Min.	Max.	HAFT	Mean	SDEV
Soybean forage	340 (~2.4×)	68–71	30	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A

Commodity	Total Rate (g a.i./ha)	Preharvest Interval (days)	Plantback Interval (days)	Mesotrione Residue Levels (ppm)					
				No.	Min.	Max.	HAFT	Mean	SDEV
Soybean hay	340 (~2.4×)	99–121	30	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Soybean seed	340 (~2.4×)	152–189	30	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Endive leaves	560 (4×)	123–179	74–98	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Radish tops	340 (~2.4×)	56–63	30	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Radish tops	560 (4×)	122–166	85–98	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Radish roots	340 (~2.4×)	56–63	30	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Radish roots	560 (4×)	122–166	85–98	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Millet forage	340 (~2.4×)	56–68	30	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Sorghum forage	340 (~2.4×)	118–119	30	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Wheat forage	560 (4×)	172–337	100	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Millet hay	340 (~2.4×)	67–81	30	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Wheat hay	560 (4×)	322–361	100	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Millet straw	340 (~2.4×)	92–98	30	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Wheat straw	560 (4×)	362–386	100	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Millet grain	340 (~2.4×)	92–98	30	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A
Wheat grain	560 (4×)	362–386	100	2	< 0.01	< 0.01	< 0.01	< 0.01	N/A

PROCESSED FOOD AND FEED

The processing study was conducted with field corn treated at a rate of 2.8 kg a.i./ha/season (20-fold the proposed maximum seasonal rate).

Fraction	Mean Residue Levels (ppm)	Concentration Factor
Whole field corn grain	< 0.01	—
Starch	< 0.01	0
Wet-milled crude oil	< 0.01	0
Wet-milled refined oil	< 0.01	0
Grits	< 0.01	0
Meal	< 0.01	0
Flour	< 0.01	0
Dry-milled crude oil	< 0.01	0
Dry-milled refined oil	< 0.01	0

LIVESTOCK FEEDING
Based on the lactating cow and laying hen metabolism studies conducted at exaggerated rates in comparison to the maximum theoretical dietary burden (MTDB of 0.01 ppm for beef cattle, 0.018 ppm for dairy cattle and 0.008 ppm for poultry) and the anticipated dietary burden calculations, no finite residues of mesotrione are expected in the livestock tissues, milk and eggs. Feeding studies can be waived.

Appendix V Environmental Assessment

Table 1 Physical and Chemical Properties of the Active Ingredient Relevant to the Environment

Property	Value	Comments
Water solubility at 20°C	15 g a.i/L at pH 6.9	Very soluble in water. One of the indicators of high potential to leach
Vapour pressure	$< 5.7 \times 10^{-6}$ Pa at 20°C	Non-volatile from water and moist soil surface
Henry's Law constant at 20°C	$1/H = 1.9 \times 10^{10}$ $K = 1.27 \times 10^{-12}$ atm m^3/mole	
log K_{OW}	< -1 at pH 7	Low potential for bioaccumulation
pK_a	3.12 at 20°C	Under neutral pH conditions, mesotrione will be mobile in the soil.
UV–visible absorption	Maximum of 256 nm in methanol	Minimal phototransformation is expected in the natural environment.

Table 2 Fate and Behaviour of Mesotrione in the Terrestrial Environment

Fate process	Endpoint	Interpretation
Hydrolysis	Stable to hydrolysis at pH 4, pH 5 and pH 9 at 25°C and in pH 4, pH 7 and pH 9 at high temperature (50°C)	Hydrolysis will not be a route for transformation or dissipation of mesotrione in the terrestrial environment.
Phototransformation on soil	Half life: 28.9 days	Phototransformation is not likely to be an important route of transformation of mesotrione.
Aerobic biotransformation	DT_{50}: ~ 8–31.5 d in soil	Mesotrione is classed as slightly persistent in soil under aerobic conditions.
Anaerobic biotransformation	DT_{50}: 3.6–11 d in soil	Mesotrione is classed as slightly persistent in soil under anaerobic conditions.
Adsorption/desorption	Adsorption K_{OC}: 39–70 mL/g, for parent Adsorption K_{OC} for MNBA: < 6–6.08 mL/g Adsorption KOCc for AMBA: 18–122 mL/g	Mesotrione has a high to very high potential for mobility in soil. MNBA has a very high potential, and AMBA has a high to very high potential for mobility in soil.
Aged soil column leaching	No studies submitted	—
Field dissipation and leaching (Canada)	DT_{50}: 3–7 d No residues of parent compound and transformation products below the 15 cm soil depth	Mesotrione is non-persistent in soil under field conditions. Mesotrione and its transformation products did not leach under conditions of the field study.

Table 3 Fate and Behaviour of Mesotrione in the Aquatic Environment

Fate process	Endpoint	Interpretation
Hydrolysis	Stable to hydrolysis at pH 4, pH 5 and pH 9 at 25°C and in pH 4, pH 7 and pH 9 at high temperature (50°C)	Hydrolysis will not be a route for transformation or dissipation of mesotrione in the aquatic environment.
Phototransformation	DT_{50} = 86–96 d in water	Phototransformation will not be significant route for transformation or dissipation of mesotrione in the photic zone of clear natural water.
Aerobic biotransformation	DT_{50}: 3–6 d in water	Mesotrione is classed as non-persistent in water under aerobic conditions.
Anaerobic biotransformation	no study submitted	However, based on the results of anaerobic (flooded) soil studies, mesotrione will be non-persistent in water under anaerobic conditions.
Adsorption/desorption	Adsorption K_{oc} : 39–70 mL/g	Mesotrione has a low potential for partitioning into the sediment.
Field dissipation	No study submitted	—

Table 4 Summary of Transformation Products Formed in Fate Studies

Fate Process	Major Transformation Products (≥ 10% of applied mesotrione)	Minor Transformation Products (≤ 10% of applied mesotrione)
Hydrolysis	None identified	None formed
Phototransformation on soil	4-(methylsulfonyl)-2-nitrobenzoic acid (MNBA)	2-amino-4-methylsulfonylbenzoic acid (AMBA)
Phototransformation in water	None formed	MNBA
Aerobic biotransformation in soil	None formed	MNBA and AMBA
Anaerobic biotransformation in soil	No study submitted	No study submitted
Aerobic biotransformation in sediment/water	None formed	AMBA
Anaerobic biotransformation in sediment/water	None formed	AMBA
Terrestrial field dissipation	None formed	MNBA

Table 5 Estimated Environmental Concentrations (Level 2) of Mesotrione in Drinking Water Sources

Groundwater (µg a.i./L)		Surface Water	
		Reservoir (µg a.i./L)	
Acute[1]	Chronic[2]	Acute[3]	Chronic[4]
2.1	1.9	1.9	0.08

1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of yearly peaks
4 90th percentile of yearly averages

Table 6 Maximum EECs of Mesotrione on Vegetation and Other Food Sources Immediately Following Application at the Rate of 173 g a.i./ha

Environmental Compartment	Concentration Fresh Weight (mg a.i./kg)[a]	Fresh Weight / Dry Weight Ratios	Concentration Dry Weight (mg a.i./kg)
Short range grass	29.96	3.3[b]	98.87
Leaves and leafy crops	15.68	11[b]	172.5
Long grass	13.72	4.4[b]	60.37
Forage crops	16.8	5.4[b]	90.72
Small insects	7.28	3.8[c]	27.66
Pods with seeds	1.5	3.9[c]	5.84
Large insects	1.25	3.8[c]	4.74
Grain and seeds	1.25	3.8[c]	4.74
Fruit	1.87	7.6[c]	14.25

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973).
[b] Fresh weight / dry weight ratios from Harris (1975) and Fletcher et al. (1994).
[c] Fresh weight / dry weight ratios from Spector (1956).

Table 7 Summary of Effects of Mesotrione on Terrestrial Organisms

Group	Organism	Study	NOEL/NOEC	$LD_{50}/LC_{50}/EC_{25}$	Degree of Toxicity
Birds	Bobwhite quail	Acute oral	2000 mg a.i./kg bw	> 2000 mg a.i./kg bw	Practically non-toxic
	Mallard duck	Dietary	5200 mg a.i./kg diet	> 5200 mg a.i./kg diet	Virtually non-toxic
	Mallard duck	Acute oral	Study not submitted		
	Bobwhite quail	Dietary	5200 mg a.i./kg diet	> 5200 mg a.i./kg diet	Virtually non-toxic
	Bobwhite quail	Reproduction	3000 mg a.i./kg diet	—	No treatment-related effects on reproductive parameters
	Mallard duck	Reproduction	120 mg a.i./kg diet	—	Treatment-related effects such as reduction in embryo survival and hatching rate
Mammals	Rat	Acute oral	5000 mg a.i./kg bw	> 5000 mg a.i./kg bw	Low toxicity
	Rat	Dermal	—	> 2000 mg a.i./kg bw	Low toxicity
	Rat	Inhalation	—	> 4.75 mg a.i./L	Low toxicity
	Beagle dog	Sub-chronic oral	600 mg a.i./kg bw/d for males; 1000 mg a.i./kg bw/d for females	—	Toxic
	Rat	Two-generation reproduction	0.3 mg/kg bw/d, for reproductive effects	—	Toxic
Soil organisms	Earthworm	Acute	1000 mg a.i./kg soil	> 2000 mg a.i./kg soil	
Beneficial arthropods	Honeybee	Acute oral	11 µg a.i./bee	> 11 µg a.i./bee	Non-toxic
		Acute contact	100 µg a.i./bee	> 100 µg a.i./bee	
	Parasitic wasp	Acute contact	—	LR_{50} = 159 g a.i./ha	
	Predatory mite	Contact	—	LR_{50} > 150 g a.i./ha	

Group	Organism	Study	NOEL/NOEC	$LD_{50}/LC_{50}/EC_{25}$	Degree of Toxicity
Terrestrial plants	Seedling emergence	The most sensitive species was lettuce, with an EC_{25} of 3.695 g a.i./ha for shoot length.			
	Vegetative vigour	The most sensitive species was lettuce, with an EC_{25} of 0.8176 g a.i./ha for shoot length.			

Table 8 Summary of Toxicity of Mesotrione to Aquatic Organisms

Group	Organism	Study	NOEC	$LC_{50}/EC_{50}/EC_{25}$	Degree of Toxicity
Fish	Rainbow trout	Acute	120 mg a.i./L	> 120 mg a.i./L	Practically non-toxic
	Bluegill sunfish	Acute	120 mg a.i./L	> 120 mg a.i./L	Practically non-toxic
	Fathead minnow	Early life stages	12.5 mg a.i./L	—	Slightly toxic
Invertebrates	Water flea	Acute	622 mg a.i./L	900 mg a.i./L	Practically non-toxic
	Water flea	Chronic	180 mg a.i./L	230 mg a.i./L	—
Algae	Blue-green alga	Acute	0.75 mg a.i./L	4.5 mg a.i./L	—
	Green alga	Acute	32 mg a.i./L	54 mg a.i./L	—
	Freshwater diatom	Acute	48 mg a.i./L	68 mg a.i./L	—
Plants	Duckweed	Acute	2 µg a.i./L	7.7 µg a.i./L	—

Table 9 Summary of Risk Assessment for Terrestrial Organisms

Organism	Effect	NOEC or NOEL	EEC	Risk Quotient	Risk	Mitigative Measures
Mallard	Reproductive	120 mg a.i./kg diet	0.87 mg a.i./kg bw/d	0.17	No risk	Not required
Eastern cottontail	Acute (rat study)	5000 mg a.i./kg bw	4.35 mg a.i./kg bw/d	—	No risk	Not required
Masked shrew	Acute (rat study)	5000 mg a.i./kg bw	6.9–20.7 mg a.i./kg bw/d	—	No risk	Not required
Meadow vole	Acute (rat study)	5000 mg a.i./kg bw	14.68–23.72 mg a.i./kg bw/d	—	No risk	Not required
Earthworm	Acute	1000 mg a.i./kg soil	0.062 mg a.i./kg soil	6.2×10^{-5}	No risk	Not required
Honeybee	Acute contact	100 µg a.i./bee	—	—	No risk	Not required
Wasps, mites	Acute contact	15 g a.i./ha	140 g a.i./ha	9.3	Moderate*	Not required
Terrestrial plants	Vegetative vigour	0.82 g a.i./ha	140 g a.i./ha	170	Very high	Buffer zone

* Unlikely to pose a risk in corn field habitat when used as a preplant, pre-emergence, early postemergence or late postemergence application.

Table 10 Summary of Risk Assessment for Aquatic Organisms

Organism	Effect	NOEC or NOEL (mg a.i/L)	EEC (mg a.i./L)	Risk Quotient	Risk	Mitigatory Measures
Water flea	Chronic	180	0.046	2.5×10^{-4}	No risk	Not required
Fathead minnow	Early life stages	12.5	0.046	3.6×10^{-3}	No risk	Not required
Duckweed	Acute	0.002	0.046	23	High risk	Buffer zone

Appendix VI Value Summary

Table 1 Active Ingredients and Examples of End-use Products Registered for Pre-emergence and/or Early Postemergence Use in Field Corn

Active Ingredient (herbicide group number)[1]	Example of EP (registration number)	Types of Weeds Controlled	Control of Weed Species for Which a Claim of Control Is Acceptable for Callisto 480SC Herbicide
Flumetsulam (2)/clopyralid (4)	Fieldstar Corn Herbicide (24451)	Broadleaves	All
Flumestsulam (2)	Flumetsulam 75% WDG (24450)	Broadleaves	All except wild mustard
Dicamba (4)	Banvel II Herbicide (23957)	Broadleaves	All
S-metolachlor (15)	Dual II Magnum Herbicide (25729)	Annual grasses, some broadleaves	Eastern black nightshade, redroot pigweed (pre-emergent suppression)
S-metolachlor (15)/atrazine (5)	Primextra II Magnum (25730)	Annual grasses, broadleaves	All except velvetleaf
Diflufenzopyr (4)/dicamba (4)	Distinct Herbicide (25811)	Broadleaves	All except wild mustard
Dimethenamid (15)	Frontier Herbicide (23462)	Annual grasses, some broadleaves	Eastern black nightshade, redroot pigweed (pre-emergence only)
Linuron (7)	Lorox DF Herbicide (20193)	Annual grasses, broadleaves	All except wild mustard
Atrazine (5)	Aatrex Nine-O Agricultural Herbicide (14842)	Broadleaves, wild oats	All except wild mustard
Atrazine (5)/ 2,4-D (4)	Clean Crop Shotgun Flowable Herbicide (24608)	Broadleaves	All (early postemergence only)
Pyridate (6)	Lentagran 45WP (21561)	Broadleaves	Lamb's-quarters, redroot pigweed
Pendimethalin (3)	Prowl 60 WDG Herbicide (25137)	Annual grasses, broadleaves	Lamb's-quarters, redroot pigweed suppression
Atrazine (5)/dicamba (4)	Marksman Herbicide (19349)	Broadleaves	All

Active Ingredient (herbicide group number)[1]	Example of EP (registration number)	Types of Weeds Controlled	Control of Weed Species for Which a Claim of Control Is Acceptable for Callisto 480SC Herbicide
Isoxaflutole (28)	Converge 75WDG (26142)	Annual grasses, broadleaves	All (pre-emergence only)
Flufenacet (15)/metribuzin (5)	Axiom DF(26233)	Annual grasses, broadleaves	Common ragweed, redroot pigweed, lamb's-quarters (pre-emergence only)
Imazethapyr (2)/atrazine (5)	Patriot (25519)	Annual grasses, broadleaves	All except wild mustard
Imazethapyr (2) for use on imazethapyr-tolerant cultivars	Pursuit Herbicide (21537)	Annual grasses, broadleaves	All

[1] See Appendix 1 of Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action.*

Table 2 Summary of Value Supported Uses

Callisto 480SC Herbicide—Value Supported Uses	
Crop	Field corn (except hybrids of 2500 CHU or less), sweet corn and production seed corn, excluding crops grown in geographic areas averaging a seasonal average of 2500 CHU or less.
Timing	Pre-emergence, Early Postemergence (spike to 2-leaf)
Tillage	Conventional only
Rate	140 g a.i./ha
Weed claims (up to weed 2-leaf stage)	Control: Lamb's-quarter, redroot pigweed, velvetleaf, wild mustard Suppression: Common ragweed
Carrier	Water
Carrier volume	200 L/ha
Tank mixes	Field corn only: • 1.14–1.6 kg a.i./ha Dual II Magnum • 2.16–2.88 kg a.i./ha Primextra II Magnum • 1.14–1.6 kg a.i./ha Dual II Magnum plus 1.0–1.5 kg a.i./ha of either Aatrex Nine-O or Aatrex Liquid 480
Rotational crops (conditionally supported)	Field, silage, sweet, production seed corn (salvage only), winter wheat (4 month), spring wheat (10 month)
Value data required in support of an unconditional registration	• Lowest effective rate data for pre-emergence and early postemergence application timings • Crop tolerance data from short season areas and short season hybrids • Rotational crop tolerance data

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