PRD2008-06

Proposed Registration Decision

Iodosulfuron-Methyl-Sodium Technical Herbicide

(publié aussi en français)

18 April 2008

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6605C
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.pmra-arla.gc.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra_infoserv@hc-sc.gc.ca

Canada

ISBN: 978-0-662-48477-6 (978-0-662-48478-3)
Catalogue number: H113-9/2008-6E (H113-9/2008-6E-PDF)

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Overview

Proposed Registration Decision for Iodosulfuron-Methyl-Sodium Technical Herbicide and End-Use Product Tribute Solo 32 DF Herbicide

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing conversion from conditional to full registration of iodosulfuron-methyl-sodium technical herbicide and Tribute Solo 32 DF Herbicide for control of certain broadleaf and grassy weeds in field corn.

An evaluation of available scientific information found that, under the approved conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

This Proposed Registration Decision is a consultation document that summarizes the science evaluation of iodosulfuron-methyl-sodium and presents the reasons for the decision. It also proposes additional risk-reduction measures that will be required to further protect human health and the environment.

This Overview describes the regulatory process and the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessment of iodosulfuron-methyl-sodium.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (please see contact information on the cover page of this document).

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration.[1] The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

[2] "Value" as defined by Subsection 2(1) of the *Pest Control Products Act* "...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at www.pmra-arla.gc.ca.

Before making a final registration decision on iodosulfuron-methyl-sodium, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Registration Decision document on iodosulfuron-methyl-sodium, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation section of this consultation document.

What Is Iodosulfuron-Methyl-Sodium Technical Herbicide?

Iodosulfuron-methyl-sodium is a postemergence herbicide, i.e. a herbicide applied after the crop has emerged above the ground. It is applied to field corn using ground application equipment to control broadleaf and grassy weeds. Iodosulfuron-methyl-sodium inhibits the activity of acetolactate synthase (ALS), which is the key enzyme in the biosynthesis of the branch-chain amino acids, isoleucine, leucine and valine. Although the actual sequence of phytotoxic processes is unclear, plant death results from events occurring in response to inhibition of the ALS enzyme.

Health Considerations

Can Approved Uses of Iodosulfuron-Methyl-Sodium Technical Herbicide Affect Human Health?

Iodosulfuron-methyl-sodium is unlikely to affect your health when used according to label directions

Exposure to iodosulfuron-methyl-sodium may occur through diet (food and water). When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100 times higher (and often much higher) than levels to which humans are normally exposed when using iodosulfuron-methyl-sodium products according to label directions.

Iodosulfuron-methyl-sodium caused eye irritation in animals and the end-use product, Tribute Solo 32 DF Herbicide, caused dermal irritation and sensitization in animals. Therefore, the label statement *Warning Skin Irritant, Potential Skin Sensitizer* is required. Iodosulfuron-methyl-sodium did not cause cancer in animals and was not genotoxic. There was also no indication that iodosulfuron-methyl-sodium caused damage to the nervous system and there were no effects on reproduction. The first signs of toxicity in animals given daily doses of iodosulfuron-methyl-sodium over longer periods of time were effects on the liver, kidneys and blood parameters. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

When iodosulfuron-methyl-sodium was given to pregnant animals, effects on the developing fetus were observed at doses that were not toxic to the mother, indicating that the fetus was more sensitive to iodosulfuron-methyl-sodium than the adult animal. However, these effects occurred only at doses that were much higher than the doses producing the most sensitive effect in the database, which was used for the risk assessment. Consequently, sufficient protection already exists for the developing fetus. Therefore, there is no need for further reduction in the allowable level of human exposure to iodosulfuron-methyl-sodium as all groups, including sensitive populations, are adequately protected.

Residues in Water and Food

Dietary risks from food and water are not of concern

Aggregate dietary intake estimates (food plus water) revealed that the general population and infants, the subpopulation that would ingest the most iodosulfuron-methyl-sodium relative to body weight, are expected to be exposed to less than 0.10% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from iodosulfuron-methyl-sodium is not of concern for any population subgroup. Animal studies revealed no acute health effects.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Corn residue trials conducted throughout the United States using iodosulfuron-methyl-sodium were acceptable. The MRL for iodosulfuron-methyl-sodium in or on field corn grain has been established in Table II of the *Food and Drugs Act* (15 April 2005).

Occupational Risks From Handling Tribute Solo 32 DF Herbicide

Refer to Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium*, for a detailed assessment of the toxicological database for iodosulfuron-methyl-sodium and the end-use product, Tribute Solo 32 DF Herbicide.

Environmental Considerations

What Happens When Iodosulfuron-Methyl-Sodium Technical Herbicide Is Introduced Into the Environment?

Iodosulfuron-methyl-sodium is toxic to terrestrial plants; therefore, buffer zones are required during application.

Iodosulfuron-methyl-sodium enters the environment when used as a herbicide on corn. Iodosulfuron-methyl-sodium is slightly persistent in soil and water, while the major breakdown products range from non-persistent to persistent in soil and water. Based on laboratory mobility data, iodosulfuron-methyl-sodium and its major breakdown product would be expected to leach through the soil profile beyond 30 cm with the potential to enter groundwater. Under field conditions at an Ontario site, however, this potential was not realized due to rapid breakdown. Based on low volatility, iodosulfuron-methyl-sodium residues are not expected in the air.

Iodosulfuron-methyl-sodium and its major breakdown product presents a low risk to wild mammals, birds, earthworms, bees and other arthropods. As is expected for a herbicide, the end-use product adversely affects terrestrial and aquatic plants in adjacent areas.

Value Considerations

What is the Value of Tribute Solo 32 DF Herbicide?

Tribute Solo 32 DF Herbicide, a postemergence herbicide, controls both grasses and broadleaf weeds in field corn.

A single application of Tribute Solo 32 DF Herbicide provides effective control of a range of broadleaf and grassy weeds in field corn. It is also compatible with integrated weed management practices and with conventional crop production systems. Since Tribute Solo 32 DF Herbicide is applied after weeds have emerged, farmers can better assess whether the herbicide is necessary or suitable for particular weed species.

Tribute Solo 32 DF Herbicide had been granted conditional registration with one of the conditions that the lowest effective rate for common ragweed be established. The registrant has since decided not to support the claim of common ragweed control, and therefore this claim has been removed from the Tribute Solo 32 DF Herbicide label. The condition of registration has now been adequately addressed from a value perspective and no further data are required.

Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Key risk-reduction measures being proposed on the label of Tribute Solo 32 DF Herbicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

- **Human Health**

  Since there is a concern with users coming into direct contact with iodosulfuron-methyl-sodium on the skin, anyone mixing or loading Tribute Solo 32 DF Herbicide must wear a long-sleeved shirt, pants and chemical-resistant gloves, and anyone applying the product must wear a long-sleeved shirt and pants.

- **Environment**

  TOXIC to aquatic organisms and non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers medium classification. Boom height must be 60 cm or less above the crop or ground.

DO NOT apply by air.

Buffer zones:

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, rangelands, riparian areas and shrublands) and sensitive aquatic habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs, wetlands and estuarine/marine habitats).

Method of Application	Crop	Buffer Zones (metres) Required for the Protection of:	
		Aquatic habitat	Terrestrial habitat
Field sprayer	Corn	1	1

When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

Next Steps

Before making a final registration decision to convert iodosulfuron-methyl-sodium from a conditional to full registration, the PMRA will consider all comments received from the public in response to this Consultation Document. The PMRA will then publish a Registration Decision document, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and the Agency's response to these comments.

Other Information

At the time the PMRA makes its registration decision, it will publish a Registration Decision document on iodosulfuron-methyl-sodium (based on the Science Evaluation section of this consultation document and REG2004-04, *Iodosulfuron-methyl-sodium*). In addition, only the test data referenced in this Consultation Document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Iodosulfuron-Methyl-Sodium

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Refer to Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium*, for the identity of the active substance and its impurities.

1.2 Physical and Chemical Properties of the Active Substances and End-Use Product

Technical Product-Iodosulfuron-Methyl-Sodium

Property	Result
Colour and physical state	Beige crystalline powder
Nominal concentration	92.0%
Odour	Weak non-characteristic odour
Density at 20°C	1.76 g/cm^3
Vapour pressure	Temperature (°C) / Vapour pressure (Pa) 20 / 2.6×10^{-9} 25 / 6.7×10^{-9}
pH	Not specified
Solubility in water at 20°C	pH / Solubility (g/L) 7.6 (unbuffered) / 60 4 / 0.02 5 / 0.17 7 / 25 9 / 65 10 / 45

Property	Result	
n-Octanol–water partition coefficient at 25°C	pH	log K_{ow}
	4	1.96
	5	1.07
	6	0.07
	7	- 0.70
	9	- 1.22
	10	- 1.15

Refer to Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium,* for a detailed chemical assessment of iodosulfuron-methyl-sodium.

1.3 Directions for Use

Refer to Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium*, for detailed directions for use of iodosulfuron-methyl-sodium and Tribute Solo 32 DF Herbicide.

1.4 Mode of Action

Refer to Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium,* for the mode of action of iodosulfuron-methyl-sodium.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in iodosulfuron-methyl-sodium have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

A detailed assessment of the methods of analysis for iodosulfuron-methyl-sodium and end-use product Tribute Solo 32 DF Herbicide are presented in Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium.*

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database available for the technical grade active ingredient, iodosulfuron-methyl-sodium, has been completed. Required toxicity data as presented in Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium*, were submitted to the PMRA.

1. Acute neurotoxicity study

Clinical signs suggestive of a neurotoxic potential, such as squatting posture, ataxic and uncoordinated gait, increased salivation, prostration and prone position, were noted in the rat acute oral study at high doses only and in moribund dogs with bronchopneumonia and pleurisy in the 90-day dietary study. Furthermore, in the rat developmental study the incidence of increased salivation (commonly observed in gavage studies) was observed in the absence of any other treatment-related finding. Based on the considerations outlined above, it was determined that the effects observed did not support the requirement for a neurotoxicity study.

2. Rabbit developmental toxicity study with an adequate high dose

The rabbit developmental study did not produce adverse effects at the highest dose tested (400 mg/kg bw/day), which is not the limit dose (1000 mg/kg bw/day). Therefore, the study is considered unacceptable. However, effects would only be expected to occur at doses above 400 mg/kg bw/day, which already provides an adequate margin of safety of 5479 for the acceptable daily intake (ADI). As a result, a new study at higher doses would not impact the risk assessment and is not required.

3. A mouse oncogenicity study with an adequate high dose

The dose levels tested in this study were viewed as inadequate to assess the carcinogenic potential of iodosulfuron-methyl-sodium in this species. In the 80-week dietary study, there was no evidence to indicate that iodosulfuron-methyl-sodium was oncogenic in the mouse at dose levels up to and including 277 mg/kg bw/day (the highest dose tested), which was the lowest observed adverse effect level (LOAEL). The maximum tolerated dose (MTD) was not achieved in this study but when viewed in light of a negative carcinogenicity study (rat two-year dietary) and negative mutagenicity outcomes in various in vitro and in vivo assays, iodosulfuron-methyl-sodium exhibits a very low oncogenic hazard. A new study would not be expected to reveal any positive data with regard to carcinogenicity at doses relevant to the risk assessment given the weight of evidence. Therefore, no further studies are required at this time.

4. A rat 21/28-day repeat dose dermal toxicity study to further characterize potential hazard and risk via the dermal route of exposure

This study was not provided. However, acceptable modes of exposure were obtained using the one-year oral (feeding) dog study no observed adverse effect level (NOAEL) for the current use pattern. Therefore, no study is required unless there is an expansion of the use pattern.

In rats, iodosulfuron-methyl-sodium was rapidly and extensively absorbed, greater than 93, 79 and 70% of the orally administered single low- (10 mg/kg bw), repeat mid- (100 mg/kg bw) and single high-doses (500 mg/kg bw), respectively. Maximal plasma concentrations (C_{max}) were achieved within 3.6–6.0 and 7.3–7.6 hours following single low- and single high-dose administration, respectively. A comparison of the area under the curve following oral and intravenous low-dose administration indicated a calculated absorption rate or bioavailability of approximately 86 and 63% of the administered dose for males and females, respectively. No significant tissue accumulation was evident, i.e. less than 0.5% of the administered dose remaining in the tissue/carcass at sacrifice (72 hours after dosing). The major route of excretion was via the urine with the majority of the administered dose being eliminated within 24 hours, and was generally complete within 72 hours. Elimination was biphasic, showing a fast initial elimination followed by a slower terminal phase. Following single low-dose administration, approximately 93.9–97.6 and 4.3–7.3% of the administered dose was recovered in the urine and feces, respectively. Following high-dose administration, urinary excretion was reduced to 69.1–71.5% of the administered dose in males and approximately 78.4–85.5% of the administered dose in females. Fecal excretion was increased slightly to approximately 24.5–26.5% of the administered dose in males and approximately 14.9–17.0% of the administered dose in females. Radioactivity was not detected in exhaled air following dosing. Absorption, plasma kinetics, distribution and elimination in dogs were comparable to those in rats. The majority of the administered dose was excreted as the unchanged parent compound, accounting for approximately 48.7–86.3 and 1.1–11.1% of the administered dose in the urine and feces, respectively. Metabolites were identified as AE F145740 (approximately 0.9–4.5% of the administered dose), AE F148741 (approximately 1.5–8.2% of the administered dose) and AE F168532 (approximately 0.3–6.6% of the administered dose). Each of these metabolites was present in both the urine and feces. Unidentified metabolites were also isolated in the feces (approximately 0.6–1.2% of the administered dose). Each of the other metabolites was present at less than 0.6% of the administered dose. There were no significant differences in the metabolic profiles between sexes or dose levels, nor following repeated dosing in the rat or between the rat and dog.

Iodosulfuron-methyl-sodium has low acute toxicity by the oral, dermal and inhalation routes of exposure; it is moderately irritating to the eyes, minimally irritating to the skin and is not considered to be a skin sensitizer. The metabolites of iodosulfuron-methyl-sodium tested have low acute toxicity by the oral and dermal routes of exposure. The formulation, Tribute Solo 32 DF Herbicide, has low acute toxicity by the oral, dermal and inhalation routes of exposure; it is mildly irritating to the eyes, moderately irritating to the skin and is considered to be a potential skin sensitizer. The formulants were on the United States Environmental Protection Agency Lists 3, 4A or 4B, and were of no toxicological concern.

Iodosulfuron-methyl-sodium was tested in a battery of in vitro (bacterial and mammalian cell gene mutation assays, an unscheduled DNA synthesis assay, as well as mammalian cell chromosomal aberration assay) and in vivo (mouse micro nucleus assay) mutagenicity studies. There was no evidence of genotoxicity potential in any of these assays; therefore, the weight of evidence suggests that iodosulfuron-methyl-sodium was not genotoxic under the conditions of the tests performed.

The subchronic and chronic toxicity of iodosulfuron-methyl-sodium was investigated in the mouse, rat and dog. No repeat-dose dermal toxicity study was available. In mice, treatment-related findings were noted in the liver in the 90-day and 80-week dietary studies. Increased liver weights, centrilobular hepatocellular hypertrophy and centrilobular fat deposition were noted at 2100 and 7000 ppm in the 90-day dietary study and at 1750 ppm in the 80-week dietary study. In the 90-day dietary study, the hypertrophied cells exhibited lipofuscin deposition, possibly due to a degradation of the subcellular organelles in the cytoplasm. An increased incidence of focal necrosis was also noted at 7000 ppm in the 90-day dietary study. Centrilobular mononuclear infiltration and pigmentation of the centrilobular hepatocytes, possibly due to lipofuscin deposition, were also noted at 1750 ppm in the 80-week dietary study. In the 90-day dietary study, lower body weight (bw) and body weight gain (bwg) were noted in males at 7000 ppm. The NOAEL for the 90-day dietary study was 700 ppm (equal to 119 mg/kg bw/d) for males and 2100 ppm (equal to 401 mg/kg bw/d) for females. The NOAEL for the 80-week dietary study was 350 ppm (equal to 54.2 and 57.6 mg/kg bw/d for males and females, respectively). The MTD was not achieved in this study. However, when viewed in light of negative carcinogenicity in the rat two-year dietary study and negative mutagenicity outcomes in various in vitro and in vivo assays, iodosulfuron-methyl-sodium exhibits very low oncogenic hazard. There was no evidence to indicate that iodosulfuron-methyl-sodium was oncogenic in mice at dose levels up to and including 1750 ppm (the highest dose tested [HDT]). A new study would not be expected to reveal any positive data with regard to carcinogenicity at relevant doses, given the weight of evidence. Therefore, no further studies are required.

In rats, treatment-related findings were limited to lower bw and bwg in the 90-day and two-year dietary studies. Lower bw and bwg were noted at 5000 and 10 000 ppm (approximately 10–15 and 15–20%, respectively) in the 90-day dietary study and at 7000 ppm (approximately 25–33%) in the two-year dietary study. Elevated alanine aminotransferase (ALAT) activity (approximately 11%) and slight centrilobular hepatocyte enlargement were noted in males at 10 000 ppm in the 90-day dietary study; however, in the absence of correlating findings in other liver function markers or changes in liver weight, these findings were considered to be an adaptive response and not treatment-related. The NOAEL for the 90-day dietary study was 1000 ppm (equal to 67 and 74 mg/kg bw/d for males and females, respectively). The NOAEL for the two-year dietary study was 700 ppm (equal to 29.7 and 39.1 mg/kg bw/d for males and females, respectively).

Dogs appear to be the most sensitive species tested. Dietary concentrations of 1200 ppm and above caused dose-dependent hematological and histopathological findings indicative of anaemia in the 90-day and one-year dietary studies. Hematological findings were generally characterized by a lower red blood cell (RBC) count, and hemoglobin (HGB) and hematocrit (HCT) at 1200 ppm and above. At 7200 ppm, the decreased RBC parameters were noted throughout treatment with the decrease gradually developing and becoming more severe as treatment progressed. Peripheral anaemia appeared to develop gradually, probably by natural turnover of erythrocytes, since there was no evidence of hemolytic processes or hemorrhaging. Examination of the bone marrow smears revealed decreased late normoblasts at 1200 ppm and above, decreased erythroblasts at 7200 ppm and an increased myeloid to erythroid ratio (M:E) at 7200 ppm. Histopathological findings were characterized by severe generalized hematopoietic hyperplasia in the bone marrow at 1200 ppm and above, and extramedullary hematopoiesis in the spleen and liver at 7200 ppm. Hematopoietic hyperplasia was evident in sections of the stifle

joint in which the epiphyseal medullary cavities of the femur and tibia were filled with cells of the myeloid and erythroid series as well as developing megakaryocytes. This correlated with increased incidences of juvenile forms of both the myeloid and erythroid series as indicated by an increase in the number of immature granulocytes present, a reduction in the number of erythroblasts present and an increase in the M:E ratio noted at 7200 ppm. There was no clinical chemistry or histopathological finding to indicate peripheral blood loss via hemolysis or hemorrhaging to account for the hematological and histopathological findings indicative of anaemia; this suggests that these findings may be due to interference of the test substance with cell maturation in the hematopoietic tissue.

In the 90-day dietary study, increased ALAT and aspartate aminotransferase (ASAT) activity and increased liver weight were noted at 1200 and 7200 ppm; however, there was no correlating histopathological finding in the liver. Increased creatine phosphokinase (CPK) activity was also noted at 1200 ppm and above in the 90-day dietary study. At 7200 ppm, the increased creatine phosphatase kinase activity correlated with lower creatinine levels and may be due to muscle loss/injury. This would also correlate with lower bw, bwg and food efficiency noted at 7200 ppm. Other treatment-related findings noted at 7200 ppm in the 90-day dietary study included the following:

- unsteady gait
- hunched posture and prostration
- increased liver, spleen and kidney weight
- pigmentation of the Kupffer cells and slight centrilobular congestion in the liver
- subcapsular tubular necrosis with cyst formation
- interstitial nephritis and hyaline droplets in the kidney
- atrophy of the lymphoid tissue in the spleen.

The NOAEL for the 90-day dietary study was 200 ppm (equal to 8.1 and 8.4 mg/kg bw/d for males and females, respectively). The NOAEL for the one-year dietary study was 1200 ppm (equal to 41.8 mg/kg bw/d) for males and 200 ppm (equal to 7.3 mg/kg bw/d) for females.

In the 80-week dietary study, there was no evidence to indicate that iodosulfuron-methyl-sodium was oncogenic in mice at dose levels up to and including 1750 ppm (HDT); however, the MTD was not achieved in this study. In the rat two-year dietary study, there was no evidence to indicate that iodosulfuron-methyl-sodium was oncogenic in rats at dose levels up to and including 7000 ppm, the HDT. Dosing was considered to be adequate based on decreased bw and bwg (greater than 10%). Iodosulfuron-methyl-sodium was negative for mutagenicity in various in vitro and in vivo assays. Furthermore, registered sulfonyl urea compounds (structurally similar compounds) have been found to be non-carcinogenic. Based on the negative carcinogenicity in the rat two-year dietary study and negative mutagenicity, iodosulfuron-methyl-sodium exhibits very low oncogenic hazard. A new mouse study would not be expected to reveal any positive data with regard to carcinogenicity at relevant doses given the weight of evidence. Therefore, no further studies are required.

There was no evidence in the toxicology database to suggest a significant increase in toxicity with increased duration of exposure in the mouse, rat, or dog, or to indicate a significant difference in gender sensitivity. In the rat two-generation reproduction (one litter per generation) study, reproduction function, reproductive parameters and litter parameters were not influenced by treatment in the first and second parental generations at dose levels up to and including 5000 ppm (equal to 346 and 390 mg/kg bw/d in males and females, respectively), the HDT. In addition, there was no treatment-related systemic finding in the P_1/P_2 animals. In the offspring, decreased pup survival and mean litter size were noted in the second generation offspring (F_2) pups on lactation days 0 and 4. There was no treatment-related finding in the first generation offspring pups. The NOAEL for parental toxicity was 5000 ppm (equal to 346 and 390 mg/kg bw/d in males and females, respectively). The NOAEL for offspring toxicity was 500 ppm (equal to 34.2 and 39.7 mg/kg bw/d in males and females, respectively). On the basis of the parental and offspring NOAELs, neonates appear to be both qualitatively and quantitatively more sensitive than adults to the toxic effects of iodosulfuron-methyl-sodium. In the rat developmental toxicity study, increased salivation was noted in the dams at 1000 mg/kg bw/d throughout treatment (gestation days 8–17). In the fetuses, increased incidences of poor ossification or non-ossification of sacral vertebral arch, individual skull bones, sternebrae, metacarpal 5 in the forepaw and phalanx III of the first to fifth toes was noted at 1000 mg/kg bw/d. These findings were generally within the historical control range; however, when considered collectively, they may indicate delayed skeletal development at this dose level. The NOAEL for maternal and developmental toxicity was 315 mg/kg bw/d. In the rabbit developmental toxicity study, there was no adverse treatment-related maternal or developmental finding at dose levels up to and including 400 mg/kg bw/d, the HDT. The NOAEL for maternal and developmental toxicity was 400 mg/kg bw/d. On the basis of the maternal and developmental NOAELs noted in the rat developmental toxicity study, there was no quantitative evidence to indicate an increased susceptibility of the fetus to in utero exposure to iodosulfuron-methyl-sodium. However, based on the severity of the findings noted at the respective NOAELs and LOAELs, there appears to be an increased qualitative susceptibility of the fetus to in utero exposure to iodosulfuron-methyl-sodium. Iodosulfuron-methyl-sodium was not considered teratogenic to rats or rabbits under the conditions tested.

3.2 Determination of Acceptable Daily Intake

The recommended ADI is 0.073 mg/kg bw/d, as calculated in the following equation:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{SF}} = \frac{7.3 \text{ mg/kg bw/d}}{100} = 0.073 \text{ mg/kg bw/d}$$

The most appropriate NOAEL recommended to calculate the ADI is 7.3 mg/kg bw/d as determined in the one-year dog dietary study. Treatment-related findings at the LOAEL (43.7 mg/kg bw/d) included gross and histopathological changes to the hematopoietic system. A safety factor (SF) of 100-fold is recommended to account for intra- and inter-species variations. In the two-generation reproduction study, there was decreased pup viability in the F_2 pups on lactation days 0 and 4 in the absence of maternal toxicity in the rat. There was also an increased incidence of apparent delayed skeletal development in the rat developmental toxicity study. The *Pest Control Products Act* requires an additional 10-fold factor to protect children and pregnant

females from relevant endpoints of concern or any database uncertainty regarding a potential for increased sensitivity in these population subgroups. A different factor may be determined to be appropriate on the basis of reliable scientific data. In the case of iodosulfuron-methyl-sodium, the 10× *Pest Control Products Act* factor can be removed because the sensitivity noted was at doses at least an order of magnitude greater than the NOAEL used for the ADI, and this provides an adequate margin of safety to the effects of concern.

3.3 Determination of Acute Reference Dose

An acute reference dose was not established because iodosulfuron-methyl-sodium was considered unlikely to present an acute hazard. There were no significant treatment-related findings in the acute, short-term, two-generation reproduction or the developmental toxicity studies to indicate a concern in the acute dietary risk assessment.

3.4 Occupational and Bystander Risk Assessment

Refer to Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium*, for a detailed assessment of the occupational and bystander database for iodosulfuron-methyl-sodium and the end-use product, Tribute Solo 32 DF Herbicide.

3.5 Food Residues Exposure Assessment

A detailed assessment of the residue chemistry database for iodosulfuron-methyl-sodium and the end-use product, Tribute Solo 32 DF Herbicide, is presented in Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium.*

4.0 Impact on the Environment

Refer to Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium*, for a detailed assessment of the environmental impact of iodosulfuron-methyl-sodium.

The required information on the *n*-octanol–water partitioning data for three major transformation products as presented in Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium*, was submitted and found to be satisfactory to the PMRA.

Following is the environmental assessment for the currently registered use pattern.

4.1 Fate and Behaviour in the Environment

The *n*-octanol–water partition coefficient of the iodosulfuron-methyl-sodium major transformation products (AE F059411, AE 0000119 and AE 0034855) indicates that these compounds have limited potential for bioaccumulation/bioconcentration in biological organisms.

4.2 Effects on Non-Target Species

To estimate risk of potential adverse effects on non-target species, a quotient method is used. The risk quotient (RQ) is calculated by dividing the exposure estimate by a value representing the most sensitive toxic endpoint. Risk quotients are initially calculated for a screening-level assessment in order to obtain higher estimates of risk. The screening-level assessment is a realistic worst-case scenario. A safety factor is applied to the aquatic toxicity endpoint to account for interspecies sensitivity as well as protection goals. The PMRA uses a safety factor of two for the acute lethal concentration to 50% (LC_{50}) / effect concentration to 50% (EC_{50} for invertebrates, algae and plants, and 10 for all other aquatic organisms. Risk quotients for chronic effects are calculated using the no observed effect concentration (NOEC) from chronic toxicity studies. Negligible risk is predicted if the RQ is less than the trigger value of one. If the trigger values are exceeded under the realistic worst-case scenario, then a refinement of the assessment is necessary to evaluate how frequently impacts might be expected in the range of conditions that occur in the field. A refined assessment takes into consideration more realistic exposure scenarios (e.g. drift to non-target habitats and runoff to water bodies) and may consider different toxicity endpoints.

Due to changes in the methods of determining risk, the risk assessment in Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium,* was re-examined. The results are as follows.

4.2.1 Effects on Terrestrial Organisms

For terrestrial vertebrates, iodosulfuron-methyl-sodium did not cause mortality or clinical signs of toxicity on an acute (gavage) or reproductive basis. Iodosulfuron-methyl-sodium was found to cause minor weight loss during short-term dietary studies (no observed effect level [NOEL] 67–401 mg/kg bw/d for rats and mice). However, risk quotients calculated under a realistic worst-case scenario indicate that iodosulfuron-methyl-sodium presents a negligible risk to wild mammals and birds following acute, short-term or long-term exposure; all risk quotients were less than one (Appendix I, Table 6).

For terrestrial invertebrates, iodosulfuron-methyl-sodium (technical and formulated product) was not toxic in acute dose-response studies, with LC_{50} values exceeding the highest dose (limit) tested. Mortality was observed in only two test species, a ground-dwelling predator and a parasitic wasp, beginning at 12 g EP/ha (most sensitive lethal rate to 50% [LR_{50}] = 14.9 g EP/ha). Risk quotients calculated under realistic worst-case scenarios indicate that iodosulfuron-methyl-sodium presents a negligible risk to terrestrial invertebrates following acute or short-term exposure; all risk quotients were less than one (Appendix I, Table 6).

For terrestrial plants, seedling emergence and vegetative vigour were examined and Tribute Solo 32 DF Herbicide affected seedling emergence and vegetative vigour. The most sensitive endpoint was for the seedling emergence dry weight of 14.1 g EP/ha. Risk quotients calculated for seedling emergence exceeded one. Therefore, buffer zone calculations were conducted.

A refined assessment considered that the most likely scenario of exposure to non-target plants is through drift. A buffer zone of one metre was calculated.

4.2.2 Effects on Aquatic Organisms

On an acute basis, iodosulfuron-methyl-sodium has an LC_{50} value of >86.9 mg a.i./L (NOEC of 28.1 mg a.i./L) for *Daphnia magna* , > 88 mg a.i./L (NOEC of 88 mg a.i./L) for rainbow trout and >92 mg a.i./L (NOEC of 92 mg a.i./L) for bluegill sunfish. The end-use product Tribute Solo 32 DF Herbicide has an LC_{50} value of >100 mg EP/L (NOEC of 100 mg EP/L) for *Daphnia magna*, 2.6 mg EP/L (NOEC of 1.0 mg EP/L) for rainbow trout and 2.8 mg EP/L (NOEC of 1.0 mg EP/L) for bluegill sunfish. Observable effects were reported following long-term exposure of invertebrates (reduced number of offspring at 0.02 mg EP/L). The toxicity of iodosulfuron-methyl-sodium to green and blue-green algae was variable (EC_{50} values range from 0.041 to >81.5 mg a.i./L). Risk quotients calculated under a realistic worst-case scenario indicate that iodosulfuron-methyl-sodium and Tribute Solo 32 DF Herbicide present negligible risks to invertebrates and fish and algae following short-term or long-term exposure; risk quotients were less than one (Appendix I, Table 6).

Iodosulfuron-methyl-sodium has an EC_{50} of 0.00083 mg a.i./L (NOEC 0.00039 mg a.i./L) for the aquatic vascular plant, which was the most sensitive aquatic organism tested (Appendix I, Table 6). The EC_{50} of Tribute Solo 32 DF Herbicide is 0.0025 mg EP/L (NOEC 0.001 mg EP/L). The risk quotient calculated under a realistic worst-case scenario exceeded the trigger value of one (Appendix I, Table 6). Risk quotients calculated for vascular plants exceeded one. Therefore, buffer zone calculations were conducted.

A refined assessment considered that the most likely scenario of exposure to aquatic plants is through drift and runoff. A buffer zone of one metre was calculated.

5.0 Value

5.1 Effectiveness Against Pests

Data were generated from 60 small-plot field trials conducted over a 2-year period at several locations in Ontario, Quebec, Manitoba and northern United States border states under conventional tillage practices. For each trial, an appropriate experimental design was used and an appropriate set of treatments was included to address the pest claims. Treatments were conducted at the labeled rates and a reduced application rate in order to confirm that the requested rates are the lowest to provide effective and consistent control on a weed-specific basis.

Tribute Solo 32 DF Herbicide was granted conditional registration with one of the conditions being that the lowest effective rate for common ragweed be established. The registrant has since decided not to support the claim of common ragweed control and has removed it from the Tribute Solo 32 DF Herbicide label. The registration condition has now been adequately addressed from a value perspective and no further data are required.

Refer to Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium,* for a detailed value assessment of Tribute Solo 32 DF Herbicide.

6.0 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

During the review process, iodosulfuron-methyl-sodium was assessed in accordance with the Pest Management Regulatory Agency (PMRA) Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of iodosulfuron-methyl-sodium were also considered, including major transformation products formed in the environment, microcontaminants in the technical product and formulants in the end-use product, Tribute Solo 32 DF Herbicide. The PMRA has reached the following conclusions:

- Iodosulfuron-methyl-sodium does not meet the Track 1 criteria for persistence in soil, persistence in water, persistence in sediment or bioaccumulation. The half-lives in soil, ranging from 0.8 to 21.8 days under laboratory conditions, are below the criterion of ≥182 days. The half-lives in water, ranging from 12.5 to 19 days in laboratory conditions, are below the criterion of ≥182 days. A half-life value in sediment was not determined; however, the low whole system half-lives, ranging from 13.5 to 23.3 days in laboratory conditions, are below the criterion of ≥365 days. Its log *n*-octanol–water partition coefficient of -1.22 to 1.96 is below the criterion of ≥5. Iodosulfuron-methyl-sodium does not meet all four Track 1 criteria; therefore, it is not classified as a Track 1 substance.

- The transformation product metsulfuron-methyl (AE F075736) formed in soil and water does not meet the Track 1 criteria for persistence in soil, persistence in water or bioaccumulation. Its half-life values of 20 to 99 days in soil are below the criterion of ≥182 days. Its half-life values of 34.4 to 55.2 days in water are below the criterion of ≥182 days. Its log *n*-octanol–water partition coefficient of -1.7 is below the criterion of ≥5. Metsulfuron-methyl does not meet all Track 1 criteria; therefore, it is not classified as a Track 1 substance.

- The transformation product AE F161778 formed in soil does not meet the Track 1 criterion for persistence in soil, persistence in water or bioaccumulation. The half-life values of 9.4 to 21 days in soil are below the criterion of ≥182 days. Its half-life values of 2.9 to 21.3 days in water are below the criterion of ≥182 days. The log *n*-octanol–water partition coefficient is unknown. AE F161778 does not meet all Track 1 criteria; therefore, it is not classified as a Track 1 substance.

- The transformation product AE F059411 formed in soil and water does meet the Track 1 criterion for persistence in soil. The half-life values of 119 to 269 days in soil meet the criterion of ≥182 days. However, they do not meet the criteria for persistence in water or bioaccumulation. The half-life values of 87.6 days in water are below the criterion of ≥182 days. The log *n*-octanol–water partition coefficient of 1.26 is below the criterion of ≥5. AE F059411 and does not meet all Track 1 criteria; therefore, it is not classified as a Track 1 substance.

- The transformation product AE 0000119 formed in water does meet the Track 1 criterion for bioaccumulation. The log *n*-octanol–water partition coefficient of 0.89 is below the criterion of ≥5. AE 0000119 does not meet all Track 1 criteria; therefore, it is not classified as a Track 1 substance.

- Technical grade iodosulfuron-methyl-sodium does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

- The end-use product, Tribute Solo 32 DF Herbicide, does not contain any formulants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

Therefore, the use of iodosulfuron-methyl-sodium is not expected to result in the entry of Track 1 substances into the environment.

7.0 Summary

7.1 Human Health and Safety

The toxicological database is adequate to define the majority of the toxic effects that may result from human exposure to iodosulfuron-methyl-sodium. In subchronic and chronic studies conducted in laboratory animals, some treatment-related effects on the liver, kidney and blood parameters were noted. There was no evidence of genotoxicity or oncogenicity. There was no effect on reproduction, but effects on the developing fetus were noted at doses much higher than the dose producing the most sensitive effects in the database. Iodosulfuron-methyl-sodium is not considered a neurotoxicant.

Refer to Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium*, for a detailed assessment of the occupational and bystander database for iodosulfuron-methyl-sodium and the end-use product, Tribute Solo 32 DF Herbicide.

7.2 Environmental Risk

Iodosulfuron-methyl-sodium and its major transformation products present negligible risk to wild mammals, birds, plants, earthworms, bees and most other arthropods, aquatic invertebrates, fish, aquatic plants and algae. The end-use product presented a risk to terrestrial and aquatic plants. Therefore, a buffer zone of one metre is required to protect both terrestrial and aquatic areas.

7.3 Value

Tribute Solo 32 DF Herbicide had been granted conditional registration with one of the conditions being that the lowest effective rate for common ragweed be established. The registrant has since decided not to support the claim of common ragweed control, and this claim has therefore been removed from the Tribute Solo 32 DF Herbicide label. The condition of registration has now been adequately addressed from a value perspective, and no further data are required.

Refer to Regulatory Note REG2004-04, *Iodosulfuron-methyl-sodium*, for a detailed assessment of the value of end-use product Tribute Solo 32 DF Herbicide.

8.0 Proposed Regulatory Decision

Health Canada's Pest Management Regulatory Agency, under the authority of the *Pest Control Products Act*, is proposing full registration for the sale and use of the technical grade active ingredient iodosulfuron-methyl-sodium and end-use product Tribute Solo 32 DF Herbicide to control certain broadleaf and grassy weeds in field corn. An evaluation of current scientific data from the applicant and scientific reports has resulted in the determination that, under the proposed conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

°C	degrees Celsius
µg	microgram
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
ALAT	alanine aminotransferase
ALS	acetolactate synthase
ASAT	aspartate aminotransferase
bw	body weight
bwg	body weight gain
CD	cesarian derived
cm	centimetre
C_{max}	maximal plasma concentration
CPK	creatine phosphokinase
d	day
DF	dry flowable
DNA	deoxyribonucleic acid
E	reduction in beneficial capacity
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EEC	estimated environmental concentration
EP	end-use product
F	female
F_2	second generation offspring
g	gram
GD	gestation day
GSD	geometrical standard deviation
ha	hectare
HDT	highest dose tested
HCT	hematocrit
HGB	hemoglobin
HPLC	high performance liquid chromatography
ILV	independent laboratory validation
kg	kilogram
K_{ow}	*n*-octanol–water partition coefficient
L	litre
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
LOEC	lowest observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate to 50%
m	metre

M	male
M:E	myeloid to erythroid
MAS	maximum average score
mg	milligram
MIS	maximum irritation score
mL	millilitre
MMAD	mass median aerodynamic diameter
MRL	maximum residue limit
MS	mass spectrometry
MTD	maximum tolerated dose
MWHC	maximum water holding capacity
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
Pa	pascal
pH	-log 10 hydrogen ion concentration
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RAC	raw agricultural commodity
RBC	red blood cell
ROC	residues of concern
ROMD	repeat oral mid dose
RQ	risk quotient
SF	safety factor
SOHD	single oral high dose
SOLD	single oral low dose
TRR	total radioactive residue
TS	test substance
UAN	urea ammonium nitrate
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
WDG	water dispersible granule
WP	wettable powder
wt	weight
w/v	weight/volume ratio

Appendix I Tables and Figures

Table 1 Toxicology Summary Table

METABOLISM (RATS) - Iodosulfuron-Methyl-Sodium

Absorption: rapidly and extensively absorbed following oral administration, greater than 93% of AD absorbed following SOLD, greater than 70% of AD absorbed following SOHD and greater than 79% of AD absorbed following ROMD (100 mg/kg bw); C_{max} achieved within 3.6-6.0 h following SOLD (10 mg/kg bw) and within 7.3–7.6 h following SOHD (500 mg/kg bw); a comparison of the area under the curve following oral and IV low dose indicates a calculated absorption rate or bioavailability of approx. 86 and 63% of AD for males and females, respectively.
Distribution: highest residues levels observed in plasma and whole blood; however, mean recovery of radioactivity in tissues/carcass at 72 h following dosing was less than 0.5% of AD for all dose groups, indicating little potential for accumulation.
Metabolism: majority of AD excreted as unchanged parent compound, approximately 48.7–86.3% of AD in urine and approximately 1.1–11.1% of AD in feces; major metabolites were identified as AE F145740 (approx. 0.9–4.5% of AD; 4-iodo-2-[3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)ureidosulfonyl] benzoic acid), AE F148741 (approx. 1.5-8.2% of AD; methyl 2-[3-(4-hydroxy-6-methyl-1,3,5-triazin-2-yl)ureidosulfonyl]-4-iodobenzoate) and AE F168532; (approx. 0.3–6.6% of AD; methyl 2-[3-(4-hydroxymethyl-6-methoxy-1,3,5-triazin-2-yl)ureidosulfonyl]-4-iodobenzoate); each of these metabolites was present in both urine and feces; remaining metabolites each accounted for less than 0.6% of AD.
Excretion: major route of excretion was via urine with majority of AD being eliminated within 24 h; generally complete within 72 h; biphasic elimination showing fast initial elimination followed by slower terminal phase; following SOLD, there were no sex-related differences in the pattern of excretion with approx. 93.9-97.6% of AD being recovered in urine and approx. 4.3–7.3% being recovered in feces; following SOHD, urinary excretion was reduced and there were slight sex-related differences; following SOHD, urinary excretion accounted for approx. 69.1–71.5% of AD in males and approx. 78.4–85.5% of AD in females; fecal excretion accounted for approx. 24.5–26.5% of AD in males and approx. 14.9–17.0% of AD in females; radioactivity was not detected in exhaled air or organic volatiles.

Absorption, plasma kinetics, distribution and elimination in dogs were comparable to those in rats. Overall the studies show no significant difference in the metabolic profile between the rat and dog.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL & LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
ACUTE STUDIES - Iodosulfuron-Methyl-Sodium			
Oral - rat	Hoe: WISKf(SPF71) Wistar rats 5 animals/sex **Dose levels**: 1600, 2000 and 3150 mg/kg bw	**LD_{50}** Males = 2947 mg/kg bw Females = 2448 mg/kg bw Combined = 2678 mg/kg bw	Mortality observed in 4/10 animals at 2000 mg/kg bw and 6/10 animals at 3150 mg/kg bw; deaths between days 1–4; numerous treatment-related clinical observations; necropsy findings included feed mash and test compound found in the stomach, yellowish mucous in intestinal tract and general autolysis; no changes in bw gains in either sex. **LOW TOXICITY**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL & LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Dermal - rat	Hoe: WISKf(SPF71) Wistar rats 5 animals/sex **Dose level**: 2000 mg/kg bw	**LD_{50}** greater than 2000 mg/kg bw for both sexes	No mortality; no treatment-related clinical signs, necropsy findings or changes in bw in either sex; signs of skin irritation (erythema; dry, rough skin with fine and coarse scales) observed on days 2–3, but not present by days 5–7. **LOW TOXICITY**
Inhalation (4-hour nose-only) - rat	Hoe: WISKf(SPF71) Wistar rats 5 animals/sex **Dose level**: Analytical: 2.81 mg/L air Nominal: 2-3 mg/L air MMAD: 2.62-3.04 µm GSD: 2.04 - 2.11 µm	**LC_{50}** greater than 2.81 mg/L air for both sexes	No mortality; no treatment-related changes in bw in either sex. Impaired breathing, red encrusted noses and narrowed palpebral fissures noted during exposure, resolved one day after exposure. **LOW TOXICITY**
Eye irritation - rabbit	New Zealand albino rabbits 3 females **Dose level**: 0.1 g	MIS: 32.3/110 at 1 h MAS (for 24, 48 and 72 h): 16.7/110.	At 1 h, conjunctival redness (grade 1–2) observed in 3/3 animals, conjunctival chemosis (grade 1–3) in 3/3 animals, and conjunctival discharge (grade 1–2) in 3/3 animals, continued to be observed in one animal at 72 h; completely resolved by d 7. **MODERATELY IRRITATING**
Dermal irritation - rabbit	New Zealand White rabbits 3 females **Dose level**: 0.5 g	MIS: 0.33/8 at 1 h MAS (for 24, 48 and 72 h): 0.11/8	Initially, one animal exhibited slight erythema (grade 3), completely resolved by 48 h. None of the test animals exhibited edema. **MINIMALLY IRRITATING**
Dermal sensitization (Guinea pig maximization method)	Pirbright -White guinea pigs 20 females in test group and 10 females in control group **Dose level**: 0.5 mL of 50% w/v mixture of TS in isotonic saline for both dermal induction and challenge treatments	No signs of dermal irritation were observed in any treated or control animals at 24 or 48 h following dermal challenge treatment.	**NOT A DERMAL SENSITIZER**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL & LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
ACUTE STUDIES - Tribute Solo 32 DF Herbicide			
Oral	5 Hsd:Sprague-Dawley (CD) rats/sex/dose **Dose level:** 2000, 2600 (F), 3600 (M), 5000 mg/kg bw	LD_{50} equal to 3479 mg/kg bw in females	80% mortality at 5000 mg/kg bw by 48 h; piloerection, hunched posture, abnormal gait, ungroomed appearance and lethargy observed at all dose levels, resolved by day 9. **LOW TOXICITY**
Dermal	5 Hsd:Sprague-Dawley (CD) rats/sex **Dose level:** 5000 mg/kg bw	LD_{50} greater than 5000 mg/kg bw	No mortality and no gross necropsy findings or changes in bw; local irritation, resolved by day 8; edema resolved by day 4. **LOW TOXICITY**
Inhalation (4 h nose-only)	5 Sprague-Dawley (CD) rats/sex **Dose level:** 4.69 mg/L (analytical)	LD_{50} greater than 4.69 mg/L	1 male and 1 female died; wet fur, respiratory abnormalities, hunched posture, resolved by day 4. Necropsy findings include enlarged lungs with dark foci (1 animal), or red lungs with dark liver (2 animals); no changes in bw. **LOW TOXICITY**
Eye irritation	3 male New Zealand White rabbits **Dose level:** 0.1 mL	MIS: 16.33/110 at 1 h MAS (24, 48, 72 h): 7.44/110	**MILDLY IRRITATING**
Skin irritation	3 male New Zealand White rabbits **Dose level:** 0.5 mL	MIS: 3.33/8 at 1 h MAS (24, 48, 72 h): 0.56/8	**MODERATELY IRRITATING**
Dermal sensitivity - Buehler method	Female Dunkin-Hartley guinea pigs (20 in test group, 10 in control group) **Dose level:** 0.5 mL of 70% TS for induction and 25% TS in sterile water for challenge	Positive	**POTENTIAL SKIN SENSITIZER**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL & LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
SHORT-TERM TOXICITY - Iodosulfuron-Methyl-Sodium			
90-day dietary - mouse	10 [Crl:CD-1(ICR)BR] mice/sex/dose **Dose levels**: 0, 700, 2100 or 7000 ppm (equal to 0/0, 119/139, 332/401 and 1311/1332 mg/kg bw/d in M/F)	**NOAEL**: Males: 700 ppm (119 mg/kg bw/d) Females: 2100 ppm (401 mg/kg bw/d) **LOAEL**: Males: 2100 ppm (332 mg/kg bw/d) Females: 7000 ppm (1332 mg/kg bw/d)	*2100 ppm: increased liver wt (M); centrilobular hepatocellular enlargement (M); lipofuscin deposition possibly due to degradation of subcellular organelles in cytoplasm (M); centrilobular fat deposition (M). 7000 ppm: lower bw/bwg (M); increased ALP (M); increased liver wt (F); cream areas/foci in liver (M/F); centrilobular hepatocellular enlargement (F); vacuolation of centrilobular hepatocytes due to fat deposition (M/F); focal necrosis (M/F) **Control wk 13 bw:** M: 41.4 g F: 30.5 g **Control wk 13 daily food consumption**: M: 6.2 g/animal F: 4.8 g/animal
90-day dietary - rat	10 Sprague-Dawley [Crl:COBS CD (SD) BR] rats/sex/dose **Dose levels**: 0, 200, 1000, 5000 or 10 000 ppm (equal to 0/0, 13.8/15.4, 67/74, 347/388 and 686/790 mg/kg bw/d for M/F)	**NOAEL**: 1000 ppm (67/74 mg/kg bw/d for M/F) **LOAEL**: 5000 ppm (347/388 mg/kg bw/d for M/F)	5000 ppm: lower bw/bwg (both sexes) 10 000 ppm: lower bw/bwg (both sexes) **Control wk 13 bw:** M: 513 g F: 316 g **Control wk 13 daily food consumption:** M: 27 g/animal F: 19 g/animal

STUDY	SPECIES, STRAIN AND DOSES	NOAEL & LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
90-day dietary - dog	4 dogs (Beagle)/sex/dose **Dose levels**: 0, 200, 1200 or 7200 ppm (equal to 0/0, 8.1/8.4, 49/51 and 301/317 for M/F)	**NOAEL**: 200 ppm (8.1/8.4 mg/kg bw/d in M/F) **LOAEL**: 1200 ppm (49/51 mg/kg bw/d in M/F)	*1200 ppm: decreased RBC, HGB and HCT (M) and percent late normoblasts (M/F); generalized hematopoietic hyperplasia bone marrow (F); decreased eosinophils (M/F); increased immature granulocytes bone marrow smear (F); increased ASAT, ALAT and CPK activity (M). 7200 ppm: Conjunctivitis (M/F); decreased bw, bwg and food efficiency (M/F); decreased RBC, HGB and HCT (F), erythroblasts (M/F), proerythroblasts (F) and increased myeloid/erythroid ratio (M/F), generalized hematopoietic hyperplasia in bone marrow (M) and extramedullary hematopoiesis in liver and spleen (M/F); decreased basophils (M), myeloblasts (F) and lymphocytes (F) and increased immature granulocytes in bone marrow smear (M); increased ALAT, ASAT and CPK activity (F); decreased total protein, albumin and A/G ratio (M); decreased creatinine (M/F); increased liver, spleen and/or and kidney wt (M/F); pigmentation Kupffer cells (M/F); slight centrilobular congestion (M); subcapsular tubular necrosis with cyst formation (M), interstitial nephritis (F) and hyaline droplets (F) in kidney; atrophy lymphoid tissue in spleen (M). In the absence of any indication of peripheral blood loss via hemolysis or hemorrhaging, hematological and histopathological findings indicative of anaemia noted in males at 1200 ppm and in both sexes at 7200 ppm may be due to interference of the test substance with cell maturation in hematopoietic tissue.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL & LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
12-month dietary - dog	6 purebred Beagle dogs/sex/dose **Dose levels**: 0, 30, 200 or 1200 ppm (equal to 0/0, 1.03/1.08, 7.37/7.25 and 41.8/43.7 mg/kg bw/d for M/F)	**NOAEL**: Males: 1200 ppm (41.8 mg/kg bw/d) Females: 200 ppm (7.25 mg/kg bw/d) **LOAEL**: Males: not determined Females: 1200 ppm (43.7 mg/kg bw/d)	1200 ppm: increased incidence of peripheral swelling of spleen (F); generalized hematopoietic hyperplasia bone marrow (F); subcapsular sinusoidal congestion and capsular fibrosis of the spleen (F)
CHRONIC TOXICITY AND ONCOGENICITY - Iodosulfuron-Methyl-Sodium			
80-week dietary - mouse	50-60 Sprague-Dawley CD-1 mice/sex/dose **Dose levels**: 0, 35, 350 or 1750 ppm (equal to 0/0, 5.15/5.72, 54.2/57.6 and 279/277 mg/kg bw/d for M/F)	**NOAEL**: 350 ppm (54.2/57.6 mg/kg bw/d for M/F) **LOAEL**: 1750 ppm (279/277 mg/kg bw/d for M/F)	1750 ppm: increased liver wt (M/F); centrilobular mononuclear infiltration (M/F), centrilobular hepatocyte enlargement (M/F), pigmentation of centrilobular hepatocytes (M) and centrilobular fat deposition (M). No evidence to indicate any carcinogenic potential of iodosulfuron-methyl-sodium at any dose level up to and including 1750 ppm, the HDT. MTD was not achieved in this study, but there was a negative carcinogenicity outcome in the rat and mutagenicity battery was also negative. Higher dose levels of iodosulfuron-methyl-sodium are not expected to provide additional information relevant to risk assessment.
2-year dietary - rat	70 Sprague-Dawley Crl:CD rats/sex/dose **Dose levels**: 0, 70, 700 or 7000 ppm (equal to 0/0, 2.96/3.91, 29.7/39.1 and 331/452 mg/kg bw/d for M/F)	**NOAEL**: 700 ppm (29.7/39.1 mg/kg bw/d for M/F) **LOAEL**: 7000 ppm (331/452 mg/kg bw/d for M/F)	7000 ppm: lower bw, bwg and food efficiency (M/F); lower food consumption (M); increased incidence of "wasted external appearance" (M/F). No evidence to indicate any carcinogenic potential of iodosulfuron-methyl-sodium at any dose level up to and including 7000 ppm, the HDT. Dosing considered adequate based on treatment-related decrease (greater than 10%) in body weight/body weight gain in both sexes at 7000 ppm (HDT).

STUDY	SPECIES, STRAIN AND DOSES	NOAEL & LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
REPRODUCTION AND DEVELOPMENTAL TOXICITY - Iodosulfuron-Methyl-Sodium			
Multi-generation - rats	25 Hoe: WISKf(SPF71) rats/sex/dose **Dose levels**: 0, 50, 500 or 5000 ppm (equal to 0/0, 3.43/3.90, 34.2/39.7 and 346/390 mg/kg bw/d)	**Parental**: NOAEL: 5000 ppm (346/390 mg/kg bw/d in M/F) LOAEL: not determined **Offspring:** NOAEL: 500 ppm (34.2/39.7 mg/kg bw/d for M/F) LOAEL: 5000 ppm (346/390 mg/kg bw/d for M/F) **Reproductive:** NOAEL: 5000 ppm (346/390 mg/kg bw/d for M/F) LOAEL: not determined	**Parental**: There were no adverse treatment-related effects in either generation. **Offspring**: 5000 ppm: decreased pup survival and decreased mean litter size in F_2 pups on lactation days 0 and 4. **Reproductive**: There were no adverse treatment-related effects in either generation. Neonates appear to be both qualitatively and quantitatively more sensitive than parental animals.
Develop-mental toxicity - rat	23 mated female Wistar [Hoe: WISKf(SPF71)] rats/dose **Dose leve**l: 0, 100, 315 or 1000 mg/kg bw/d	**Maternal**: NOAEL: 315 mg/kg bw/d LOAEL: 1000 mg/kg bw/d **Developmental**: NOAEL: 315 mg/kg bw/d LOAEL: 1000 mg/kg bw/d	**Maternal**: 1000 mg/kg bw/d: increased salivation during GD 8–17 **Developmental**: 1000 mg/kg bw/d: increased incidences of poor ossification/non-ossification of sacral vertebral arch, individual skull bones, sternebrae, metacarpal 5 in forepaw and phalanx III of 1st to 5th toes of hind paw; these findings generally within historical control range. **Teratogenicity**: No evidence of any treatment-related irreversible structural changes at any dose level up to and including 1000 mg/kg bw/d (limit dose); therefore, under the conditions of this study, iodosulfuron-methyl-sodium was not teratogenic.

Develop-mental toxicity - rabbit	15 adult female Chbb: HM(SPF) Kleinrusse (Himalayan) rabbits/dose **Dose levels**: 0, 25, 100 or 400 mg/kg bw/d	**Maternal**: NOAEL: 400 mg/kg bw/d LOAEL: not determined **Developmental**: NOAEL: 400 mg/kg bw/d LOAEL: not determined	**Maternal**: No adverse treatment-related findings. **Developmental**: No adverse treatment-related findings. . **Teratogenicity**: No evidence of any treatment-related irreversible structural changes at 400 mg/kg bw/d (HDT).
STUDY	**SPECIES and STRAIN or CELL TYPE**	**CONCENTRATIONS or DOSES**	**RESULTS**
GENOTOXICITY - Iodosulfuron-Methyl-Sodium			
Bacterial reverse gene mutation assay (in vitro)	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; *E. coli* WP2 *uvr*A	0, 4, 20, 100, 500, 2500, or 5000 µg/plate with/without S9 metabolic activation.	**NEGATIVE**
Gene mutations in mammalian cells in vitro	Chinese hamster lung V79 fibroblasts (at the HGPRT locus)	0, 100, 300, 600, 1200, 1600, 2000 or 2649 µg/mL without S9 metabolic activation. 0, 300, 600, 1200 or 2649 µg/mL with S9 metabolic activation.	**NEGATIVE**
In vitro chromosomal aberration assay	Chinese hamster lung V79 fibroblasts	0, 500, 1500 or 2649 µg/mL with S9 metabolic activation. 0, 100, 250 or 500 µg/mL without S9 metabolic activation.	**NEGATIVE**
Micronucleus assay (in vivo)	5 NMRI mice/sex/dose/sampling time (12, 24 and 48 h)	0, 200, 1000 or 2000 mg/kg bw	**NEGATIVE**
Unscheduled DNA synthesis in vitro	Primary rat hepatocytes (male Wistar rat)	**Initial assay**: 0, 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, 10, 30, 100, 300, 1000 or 3000 µg/mL **Confirmatory assay**: 0, 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, 10, 30, 100, 300, 1000, 3000 or 5000 µg/mL	**NEGATIVE**
ACUTE STUDIES - Metabolites of Iodosulfuron-Methyl-Sodium			

STUDY	SPECIES, STRAIN AND DOSES	NOAEL & LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Acute oral - rat AE F114368	5 Sprague-Dawley rats/sex **Dose level**: 2000 mg/kg bw	**LD_{50}**: greater than 2000 mg/kg bw for both sexes	No mortality; no treatment-related clinical signs, necropsy findings or changes in body weight. **LOW TOXICITY**
Acute oral - rat AE F143133	5 Sprague-Dawley rats/sex **Dose level**: 2000 mg/kg bw	**LD_{50}**: greater than 2000 mg/kg bw for both sexes	No mortality; no treatment-related necropsy findings or changes in body weight; clinical signs included decreased spontaneous activity, squatting posture, stilted/uncoordinated gait and irregular respiration, resolved by day 3. **LOW TOXICITY**
Acute oral - rat AE C627337	5 Sprague-Dawley rats/sex **Dose level**: 2000 mg/kg bw	**LD_{50}**: greater than 2000 mg/kg bw for both sexes	No mortality; no treatment-related clinical signs, necropsy findings or changes in body weight. **LOW TOXICITY**
Acute oral - rat AE C627339	5 Sprague-Dawley rats/sex **Dose level**: 2000 mg/kg bw	LD_{50}: greater than 2000 mg/kg bw for both sexes	No mortality; no treatment-related necropsy findings or changes in body weight; clinical signs included hypoactivity, irregular respiration, uncoordinated gait and increased salivation, resolved by day 3. **LOW TOXICITY**
Acute oral - rats 2-amino-4-methoxy-6-methyl-S-triazine	5 Sprague-Dawley rats/sex/dose **Dose levels**: 2000, 2500, 2750 or 3000 mg/kg bw	**LD_{50} (95% confidence interval)**: Males: 3247.2 mg/kg bw (1156.5–9117.7) Females: 2533.9 mg/kg bw (1885.5–3399.9) Combined: 2767.6 mg/kg bw (2031.1–3771.1)	Mortality observed in 4/10, 3/10, 4/10 and 7/10 animals at 2000, 2500, 2750 and 3000 mg/kg bw/d, respectively; all deaths occurred between days 1–5; clinical signs observed at all dose levels, persisted in some animals throughout the study; most animals lost weight during first week of study but regained loss by day 14; no gross lesions in animals sacrificed at scheduled termination; animals dying during study exhibited necropsy findings in lungs, spleen, liver, stomach, intestines and kidneys. **LOW TOXICITY**
Acute dermal - rats AE F114844	5 Sprague-Dawley rats/sex **Dose level**: 2000 mg/kg bw	**LD_{50}**: greater than 2000 mg/kg bw	No mortality; no treatment-related clinical signs, necropsy findings or changes in body weight. **LOW TOXICITY**

STUDY	SPECIES and STRAIN or CELL TYPE	CONCENTRATIONS or DOSES	RESULTS
MUTAGENICITY STUDIES - Metabolites of Iodosulfuron-Methyl-Sodium			
Bacterial reverse gene mutation assay (in vitro) AE F059411	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; *E. coli* WP2 *uvr*A	0, 50, 160, 500, 1600 or 5000 µg/plate with/without S9 metabolic activation	**NEGATIVE**
Bacterial reverse gene mutation assay (in vitro) AE C627337	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; *E. coli* WP2 *uvr*A	0, 50, 160, 500, 1600 or 5000 µg/plate with/without S9 metabolic activation	**NEGATIVE**
Bacterial reverse gene mutation assay (in vitro) AE F114368	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; *E. coli* WP2 *uvr*A	0, 50, 160, 500, 1600 or 5000 µg/plate with and without S9 metabolic activation	**NEGATIVE**
Bacterial reverse gene mutation assay (in vitro) AE F114844	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; *E. Coli* WP2 *uvr*A	**Initial assay**: 0, 50, 160, 500, 1600 or 5000 µg/plate with/without S9 metabolic activation **Confirmatory assay**: *S. typhimurium* strains at 0, 1.6, 5, 16, 50, 160 or 500 µg/plate with S9 metabolic activation and 0, 5, 16, 50, 160, 500 or 1600 µg/plate without S9 metabolic activation; *E coli* at 0, 50, 160, 500, 1600 or 5000 µg/plate with/without S9 metabolic activation	**NEGATIVE**
Bacterial reverse gene mutation assay (in vitro) AE F114133	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; *E. Coli* WP2 *uvr*A	0, 50, 160, 500, 1600 or 5000 µg/plate with/without S9 metabolic activation	**NEGATIVE**

STUDY	SPECIES and STRAIN or CELL TYPE	CONCENTRATIONS or DOSES	RESULTS
Bacterial reverse gene mutation assay (in vitro) AE F114368	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; *E. Coli* WP2 *uvr*A	0, 50, 160, 500, 1600 or 5000 µg/plate with/without S9 metabolic activation	**NEGATIVE**

Table 2 Integrated Food Residue Chemistry Summary

DIRECTIONS FOR USE OF IODOSULFURON-METHYL-SODIUM			
Crop	**Formulation/Type**	**Method/Timing**	**Rates**
Field corn	Tribute Solo 32 DF Herbicide	1–8 leaf stage or 5–6 visible collars (the leaf is counted once the next leaf is visible in the whorl).	1 application of 1 g or 2 g iodosulfuron-methyl-sodium/ha + 1.0% v/v Hasten + 2.5L/ha of 28% UAN

ANALYTICAL METHODOLOGY		
Parameters	**Plant Matrices**	
Method ID	BY/02/99	
Type	Data gathering and enforcement purposes (LC-MS only)	
Analytes	Iodosulfuron-methyl-sodium(AE F115008); metsulfuron-methyl (AE F075736)	
Instrumentation	HPLC-UV (corn grain), HPLC-MS (corn grain and forage)	
LOQ	0.025 ppm (corn grain); 0.05 ppm (corn forage and fodder)	
Standards	External bracketing standards	
ILV	Method BYROOR001 for method No. BY/02/99 (LC-MS only)	
Multiresidue method	The multiresidue methods are not suitable for the analysis of iodosulfuron-methyl-sodium (AE F115008) or the metabolite metsulfuron-methyl (AE F075736).	
NATURE OF THE RESIDUE IN PLANTS		
Crop	Wheat (Yecora or Ralle variety)	
Radiolabel	2-^{14}C-triazinyl	phenyl-UL-^{14}C
Test site	Plant containers in an outdoor vegetation area.	Plant steel chambers in a climatic chamber.
Treatment	Foliar by spray.	
Rate	1 application at 20 g a.i./ha (10-fold), including the safener mefenpyr-diethyl at 1:3 ratio.	
EP	Wettable powder (WP)	

Preharvest interval	87 days	77 days
Major metabolites (>10% of the TRR)	Forage: iodosulfuron-methyl-sodium Hay: iodosulfuron-methyl-sodium, AE F145741, AE 0031838 Straw: iodosulfuron-methyl-sodium, metsulfuron-methyl Grain: AE 0031838	Forage, hay, straw: iodosulfuron-methyl-sodium
	Although metabolites other than the parent were identified as greater than 10% of the TRR, the absolute TRR values (ppm) were low.	
Residue of concern	Iodosulfuron-methyl-sodium	

CONFINED ROTATIONAL CROP STUDY - SOYBEAN, WHEAT, SUGARBEET (AMERICAN STUDY)	
Formulation used for trial	A 70WDG, water dispersible granule containing the safener isoxadifen-ethyl and radiolabelled [2-triazinyl-^{14}C]iodosulfuron-methyl-sodium
Application rate and timing	Soybeans and sugarbeets were planted 7 and 14 days after soil was treated at 5.4 g a.i./ha (threefold); wheat was planted 65 days after soil was treated at 8.1 g a.i./ha (fourfold).
Succeeding crops	
Soybean forage, seeds **Wheat forage, grain and straw** **Sugarbeet tops and roots**	At 7 and 14 days plantback, TRRs were 0.003 ppm. No further analysis. At 65 days plantback, TRRs were <0.001-0.007 ppm. No further analysis. At 60 days plantback, TRRs were 0.001 ppm. No further analysis. Therefore, proposed rotational crop plantback interval of 10 months is adequate.
Residue of Concern	Iodosulfuron-methyl-sodium
CONFINED ROTATIONAL CROP STUDY - WHEAT, SPINACH, CARROT (GERMAN STUDY)	
Formulation used for trial	A WP20, wettable powder containing radiolabelled [2-triazinyl-^{14}C]iodosulfuron-methyl-sodium
Application rate and timing	[2-triazinyl-^{14}C]iodosulfuron-methyl-sodium was applied to bare soil at 20 g a.i./ha (10-fold), and spinach, carrots and wheat were sown after 29 days, 120 days and 365 days.

Succeeding crops	
Wheat grain, chaff and straw **Spinach** **Carrot roots and foliage**	TRRs were less than 0.01 ppm at all plantback intervals, with the exception of straw. Only straw was further analyzed. Triazine-containing metabolites were identified at 7 to 14% of the TRRs. TRRs were less than 0.01 ppm at all plantback intervals. TRRs were less than 0.01 ppm at all plantback intervals for carrot roots; TRRs were greater than 0.01 ppm in carrot tops at 120 and 365 plantback intervals. Since the application rate is exaggerated (10-fold) and only livestock feed commodities have TRRs greater than 0.01 ppm, the proposed rotational crop plantback interval of 10 months is adequate.
Residue of concern	Iodosulfuron-methyl-sodium

NATURE OF THE RESIDUE IN LIVESTOCK			
Species	**Radiolabel**	**Dose Level**	**Sacrifice**
Dairy cow **(British Friesian)**	[phenyl-^{14}C]iodosulfuron-methyl-sodium	Dosed orally for 7 consecutive days, 14.23 ppm (0.29 mg/kg bw/day).	Interval from last dose to sacrifice, 22 hours.
71% of the administered dose was excreted in urine and 21% in feces; with approximately 8% remaining in tissues, organs and milk.			
Laying hen **(*Gallus gallus domesticus*)**	[phenyl-^{14}C]iodosulfuron-methyl-sodium	Dosed orally for 14 consecutive days, 10 ppm (1.47 mg/kg bw/day).	Interval from last dose to sacrifice, 22 hours.
92% of the administered dose was excreted in urine and feces; with approximately 8% remaining in tissues, organs and eggs.			

	Cow	**Hen**
Major metabolites (>10% of the TRR)	Omental fat, kidney: iodosulfuron-methyl-sodium Renal fat: none identified Liver: iodosulfuron-methyl-sodium, AE F114368 Milk: AE C627337	Egg yolk, liver, skin: iodosulfuron-methyl-sodium Egg white: iodosulfuron-methyl-sodium, AE 145741
ROC	Iodosulfuron-methyl-sodium	

FREEZER STORAGE STABILITY
Iodosulfuron-methyl-sodium is stable in freezer storage at -18°C in wheat grain (24 months), forage (26 months) and straw (26 months). These data support the available corn field trial and processing studies.

CROP FIELD TRIALS - CORN WDG TREATMENT	
Twenty-one field corn trials were conducted in Zones 1 (2 trials), 2 (1 trial), 5 (16 trials) and 6 (2 trials) in the United States. Residues of iodosulfuron-methyl-sodium and the metabolite metsulfuron-methyl were less than the reported LOQs of 0.025 ppm in corn grain and 0.05 ppm in corn forage and stover when applied at total application rate of 7.2–9.3 g a.i./ha (threefold to fivefold).	
PROPOSED MAXIMUM RESIDUE LIMITS	
Field corn	0.025 ppm
PROCESSED FOOD AND FEED	
The data indicate that residues of iodosulfuron-methyl-sodium and the metabolite metsulfuron-methyl were below the respective method LOQs (less than 0.025 ppm) in/on samples of the RAC, field corn grain, harvested 100 days following 2 applications (broadcast spray and drop nozzle), with a 3-day retreatment interval, of iodosulfuron-methyl-sodium and isoxadifen-ethyl at 23 g a.i./ha followed by 9.9 g a.i./ha for a total rate of 32.9 g a.i./ha. No concentration factor needed.	
LIVESTOCK FEEDING	
Based on data from the ruminant and poultry metabolism studies, there is no reasonable expectation that finite residues of iodosulfuron-methyl-sodium will occur in livestock commodities (DIR98-02, *Residue Chemistry Guidelines*, Section 2). Therefore, livestock feeding studies and MRLs for livestock commodities are not required at this time.	

Table 3 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
CROPS (N = 1)	**Iodosulfuron-methyl-sodium**
	Wheat
ROC FOR MONITORING AND ENFORCEMENT	Iodosulfuron-methyl-sodium
ROC FOR RISK ASSESSMENT	Iodosulfuron-methyl-sodium
METABOLIC PROFILE IN DIVERSE CROPS	Only one crop was examined.
ANIMAL STUDIES	
ANIMALS (N = 2)	Dairy cow, hen
ROC FOR MONITORING AND ENFORCEMENT	Iodosulfuron-methyl-sodium
ROC FOR RISK ASSESSMENT	Iodosulfuron-methyl-sodium
METABOLIC PROFILE IN LIVESTOCK	Similar
FAT SOLUBLE RESIDUE	No

DIETARY RISK from food and water			
Chronic non-cancer dietary risk ADI = 0.073 mg/kg bw/day **EEC (chronic and acute) = 0.172 µg a.i./L (90th percentile)**	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Food (MRLs)	**Food + EEC**
	All infants <1 yr old	0.07	0.07
	Children 1 to 2 yrs	0.1	0.1
	Children 3 to 5 yrs	0.1	0.1
	Children 6 to 12 yrs	0.1	0.1
	Youth 13 to 19 yrs	0.07	0.07
	Adults 20 to 49 yrs	0.03	0.03
	Adults 50+ yrs	0.03	0.03
	Females 13 to 49 yrs	0.03	0.03
	Total population	0.03	0.07

Table 4 Fate and Behaviour in the Environment

Study Type	Test Substance	Iodosulfuron-methyl-sodium	Major Transformation Products
Soil			
Phototransformation	Iodosulfuron-methyl-sodium	Half-life Dark: stable Irradiated: 9.1 d	AE 0002166 was a major transformation product.
Aerobic metabolism	Iodosulfuron-methyl-sodium 0.13 mg/kg soil	Half-life 0.8–3.3 d (30-50% MWHC) 10–21.8 d (25% MWHC) 15.4 d (10°C)	AE F075736 , AE F059411, AE F161778, and three unidentified compounds (M2, U1 and U2) were major transformation products.
	AE F075736	Half-life = 20–78 d (30-50% MWHC) Half-life = 65–99 d (25% MWHC)	—

Study Type	Test Substance	Iodosulfuron-methyl-sodium	Major Transformation Products
	AE F161778	Half-life = 9.4–21 d (30-50% MWHC) Half-life = 27–35 d (25% MWHC)	—
Adsorption/ desorption	Iodosulfuron-methyl-sodium	Adsorption K_{oc}: 15.5–22.6 mL/g	Very high mobility
	AE F075736	Adsorption K_{oc}: 2.9–15.1 mL/g	Very high mobility
	AE F059411	Adsorption K_{oc}: 21.3–74.4 mL/g	High to very high mobility
Field dissipation	AE F115008 00 WG20 A1 (20% iodosulfuron-methyl-sodium)	Half-life = 4 d	Non-persistent Parent compound and transformation products were detected in the top 0–15cm soil layer AE F075736 and AE F059411 were major transformation products.
Aquatic systems			
Hydrolysis	Iodosulfuron-methyl-sodium	Half-life pH 4 = 2.5 d pH 5 = 18.4 d pH 6 = 197 d pH 7 > 365 d pH 9 = 167 d (Arrhenius equation was used to estimate half-lives for 25°C)	AE F149760, AE F114368 and AE F145741 were major transformation products (30–50°C).
Phototransformation	Iodosulfuron-methyl-sodium	Half-life Dark: stable Irradiated: 9–10.2 d	Low potential for phototransformation in water AE 0002166 was a major transformation product.

Study Type	Test Substance	Iodosulfuron-methyl-sodium	Major Transformation Products
Aerobic metabolism	Iodosulfuron-methyl-sodium	Whole system Half-life: 13.5–23.3 d Water Half-life: 12.5–19 days	AE F075736, AE F059411, AE 0000119, AE 0014966 and AE 0034855 were major transformation products.
	AE F075736	Whole system Half-life: 34.4–55.2 d	—
	AE F161778	Whole system Half-life: 2.9–21.3 d	—
	AE 0014966	Whole system Half-life: 5.8–20.8 d	—
	AE F059411	Whole system Half-life: 87.6 d	—
Anaerobic metabolism	Iodosulfuron-methyl-sodium	Whole system Half-life: 14.-3-28.1 d	AE F075736 was a major transformation product.

Table 5 Toxicity to Non-Target Species

Organism	Study Type	Species	Test Substance	Toxicity Data	Toxicity Classification
Terrestrial Organisms					
Mammals	Acute	*Rattus norvegicus* (rat)	Iodosulfuron-methyl-sodium	LD_{50} = 2678 mg/kg bw (male & female)	Practically non-toxic
			Tribute Solo 32 DF Herbicide	LD_{50} = 3479 mg EP/kg bw	Practically non-toxic

Organism	Study Type	Species	Test Substance	Toxicity Data	Toxicity Classification
	Short-term	*Rattus norvegicus* (rat)	Iodosulfuron-methyl-sodium	NOAEL (90-day): 67 mg/kg bw/d (male) 74 mg/kg bw/d (female)	—
		Mus musculus (mouse)	Iodosulfuron-methyl-sodium	NOAEL (90-day): 119 mg/kg bw/d (male) 401 mg/kg bw/d (female)	—
	Long-term (reproduction)	*Rattus norvegicus* (rat)	Iodosulfuron-methyl-sodium	NOAEL: 346 mg/kg bw/d (male) 390 mg/kg bw/d (female)	—
Birds	Acute	*Colinus virginianus* (bobwhite quail)	Iodosulfuron-methyl-sodium	LD_{50} > 1744 mg/kg bw NOEL = 1744 mg/kg bw LOEL > 1744 mg/kg bw Mortality	Slightly toxic
	Short-term	*Colinus virginianus* (bobwhite quail)	Iodosulfuron-methyl-sodium	LC_{50} > 4358 mg/kg diet NOEC = 4358 mg/kg diet LOEC > 4358 mg/kg diet Mortality	Slightly toxic
		Anas platyrhynchus (mallard duck)	Iodosulfuron-methyl-sodium	LC_{50} > 4510 mg/kg diet NOEC = 4510 mg/kg diet LOEC > 4510 mg/kg diet Mortality	Slightly toxic
	Long-term (reproduction)	*Colinus virginianus* (bobwhite quail)	Iodosulfuron-methyl-sodium	NOEC = 980 mg/kg diet LOEC > 980 mg/kg diet Mortality and reproduction	—

Organism	Study Type	Species	Test Substance	Toxicity Data	Toxicity Classification
		Anas platyrhynchus (mallard duck)	Iodosulfuron-methyl-sodium	NOEC = 905 mg/kg diet LOEC > 905 mg/kg diet Mortality and reproduction	—
		Cotumux japonica (Japanese quail)	Iodosulfuron-methyl-sodium	NOEC = 984 mg/kg diet LOEC > 984 mg/kg diet Mortality and reproduction	—
Bee	Acute oral	*Apis mellifera* (honey bee)	Iodosulfuron-methyl-sodium	LD_{50} > 81.4 mg/bee NOEC = 22.7 mg/bee LOEC = 81.4 mg/bee Mortality	Relatively non-toxic
			Tribute Solo 32 DF Herbicide	LD_{50} > 22.9 mg EP/bee NOEC = 22.9 mg EP/bee	Relatively non-toxic
	Acute contact	*Apis mellifera* (honey bee)	Iodosulfuron-methyl-sodium	LD_{50} > 150 mg/bee NOEC = 100 mg/bee LOEC = 125 mg/bee Mortality	Relatively non-toxic
			Tribute Solo 32 DF Herbicide	LD_{50} > 159 mg EP/bee NOEC = 159 mg EP/bee	Relatively non-toxic
Other arthropods	Acute	*Aphidius rhopalosiphi* (aphid)	Tribute Solo 32 DF Herbicide	98–100% (E^c)	Moderately harmful[a, b] at 12–15%, 1.5×, 3× application rate
		Typhlodromus pyri (mite)	Tribute Solo 32 DF Herbicide	7–26% (E^c)	Harmless[a, b] at 12–15%, 1.5×, 3x application rate

Organism	Study Type	Species	Test Substance	Toxicity Data	Toxicity Classification
		Chrysoperla carnea (green lacewing)	Tribute Solo 32 DF Herbicide	7.5–22% (E[c])	Harmless[a, b] at 12–15%, 1.5×, 3× application rate
		Poecilus cupreus (ground beetle)	Tribute Solo 32 DF Herbicide	4% (E[c])	Harmless[a, b] at 1.5×, 3× application rate
		Pardosa spp. (wolf spider)	Tribute Solo 32 DF Herbicide	4–21% (E[c])	Harmless[a, b] at 12–15%, 1.5×, 3× application rate
		Aleochara bilineata (beetle)	Tribute Solo 32 DF Herbicide	32–42% (E[c])	Slightly harmful[a, b] at 12–15%, 1.5×, 3× application rate
Earthworm	Short-term	*Eisenia fetida* (earthworm)	Iodosulfuron-methyl-sodium technical herbicide	LC_{50} > 1000 mg/kg soil NOEC = 1000 mg/kg soil LOEC >1000 mg/kg soil	—
			AE F075736 (92.2%)	LC_{50} > 1000 mg/kg soil NOEC = 320 mg/kg soil LOEC = 560 mg/kg soil Weight	—
			AE F059411 (99.6%)	LC_{50} > 1000 mg/kg soil NOEC = 1000 mg/kg soil LOEC > 1000 mg/kg soil	—
			Tribute Solo 32 DF Herbicide	LC_{50} > 1000 mg EP/kg soil NOEC = 320 mg EP/kg soil Weight	—

Organism	Study Type	Species	Test Substance	Toxicity Data	Toxicity Classification
Vascular plants	Seedling emergence	*Lactuca sativa* (lettuce)	Tribute Solo 32 DF Herbicide	EC_{25} = 14.1 g EP/ha NOEC < 3.8 g	—
	Vegetative vigour	*Cucumis sativus* (cucumber)	Tribute Solo 32 DF Herbicide	EC_{25} = 16.1 g EP/ha NOEC = 32 g EP/ha	—
Freshwater Organisms					
Invertebrates	Acute	*Daphnia magna*	Iodosulfuron-methyl-sodium	LC_{50} > 86.9 mg a.i./L NOEC = 28.1 mg a.i./L Immobility	Slightly toxic
			Tribute Solo 32 DF Herbicide	LC_{50} > 100 mg EP/L NOEC = 100 mg EP/L Immobility	Practically non-toxic
	Long-term (reproduction)	*Daphnia magna*	Iodosulfuron-methyl-sodium	LC_{50} > 49.8 mg a.i./L NOEC = 9.1 mg a.i./L LOEC = 15.9 mg a.i./L Number offspring per female	—
			Tribute Solo 32 DF Herbicide	LC_{50} = 0.064 mg EP/L NOEC = 0.02 mg EP/L Number offspring per female	—
Fish	Acute	*Oncorhynchus mykiss* (rainbow trout)	Iodosulfuron-methyl-sodium	LC_{50} > 88 mg a.i./L NOEC = 88 mg a.i./L Mortality	Slightly toxic

Organism	Study Type	Species	Test Substance	Toxicity Data	Toxicity Classification
			Tribute Solo 32 DF Herbicide	LC_{50} = 2.6 mg EP/L NOEC = 1.0 mg EP/L Mortality	Moderately toxic
		Lepomis macrochirus (bluegill sunfish)	Iodosulfuron-methyl-sodium	LC_{50} > 92mg a.i./L NOEC = 92 mg a.i./L Mortality	Slightly toxic
			Tribute Solo 32 DF Herbicide	LC_{50} = 2.8 mg EP/L NOEC = 1.0 mg EP/L Mortality	Moderately toxic
Algae	Short-term	*Pseudokirchneriella subcapitata* (green algae)	Iodosulfuron-methyl-sodium	EC_{50} = 0.041 mg a.i./L NOEC = 0.014 mg a.i./L Biomass inhibition	—
			AE F075736	EC_{50} = 0.12 mg/L NOEC = 0.018 mg/L Biomass inhibition	—
			AE F059411	EC_{50} > 101 mg/L NOEC = 101 mg/L Biomass inhibition	—
			Tribute Solo 32 DF Herbicide	EC_{50} = 0.74 mg EP/L NOEC ≤ 0.4 mg EP/L Biomass inhibition	—

Organism	Study Type	Species	Test Substance	Toxicity Data	Toxicity Classification
		Anabaena flos-aquae (blue-green algae)	Iodosulfuron-methyl-sodium	EC_{50} = 1.4 mg a.i./L NOEC = 0.63 mg a.i./L Biomass inhibition	—
		Navicula pelliculosa (diatom)	Iodosulfuron-methyl-sodium	EC_{50} > 81.5 mg a.i./L NOEC = 81.5 mg a.i./L Biomass inhibition	—
Vascular plant	Short-term	*Lemna gibba* (duck weed)	Iodosulfuron-methyl-sodium	EC_{50} = 0.00083 mg a.i./L LOEC = 0.00063 mg a.i./L NOEC = 0.00039 mg a.i./L Biomass and growth rate inhibition	—
			AE F059411	EC_{50} = 101 mg/L NOEC = 57 mg/L LOEC = 101 mg/L Biomass inhibition	—
			Tribute Solo 32 DF Herbicide	EC_{50} = 0.0025 mg EP/L LOEC = 0.002 mg EP/L NOEC = 0.001 mg EP/L Biomass inhibition	—

[a] Classification by Hassen et al. (1994) for laboratory tests conducted with inert substrates: beneficial capacity <30% harmless; 30–79% slightly harmful; 80–99% moderately harmful; >99% harmful.

[b] For toxicity studies with beneficial insects, Tribute Solo 32 DF was applied at 12–15, 150, or 300 g EP/ha equivalent to 12–15% (drift) to the field boundary, 1.5× (150%) and 3× (300%) the proposed maximum field application rate in Canada (100 g EP/ha).

[c] E = reduction in beneficial capacity.

Table 6 Screening Level Risk Assessment on Non-target Species

Organism	Study Type	Test Substance	Toxicity	Exposure	Units	RQ[c]
Terrestrial Vertebrates—all food obtained from treated field without dissipation of active substance						
Mammals	Acute	Iodosulfuron-methyl-sodium	LD_{50} = 2678 (male & female)	0.17	mg a.i./kg bw[a]	<0.00006
		Tribute Solo 32 DF Herbicide	LD_{50} = 3479	8.65	mg EP/kg bw[a]	0.002
	Short-term	Iodosulfuron-methyl-sodium	NOEC = 67	1.01	mg a.i./kg diet	0.015
	Long-term (reproduction)	Iodosulfuron-methyl-sodium	NOEC = 346	1.01	mg a.i./kg diet	0.003
Birds	Acute	Iodosulfuron-methyl-sodium	NOEL = 1744	0.026	mg a.i./kg bw[b]	0.00001
	Short-term	Iodosulfuron-methyl-sodium	NOEC = 4358	0.35	mg a.i./kg diet	0.00008
	Long-term (reproduction)	Iodosulfuron-methyl-sodium	NOEC = 905	0.07	mg a.i./kg diet	0.00008

Organism	Study Type	Test Substance	Toxicity	Exposure	Units	RQ[c]
Terrestrial Invertebrates—contact exposure to treated surfaces (arthropods) or exposure to treated soil of 15 cm depth (earthworms)						
Bee	Acute oral	Iodosulfuron-methyl-sodium	LD_{50} > 91200	2	g a.i./ha	<0.00002[c]
Other arthropods	Acute contact	Tribute Solo 32 DF Herbicide	LR_{50} = 14.9	2	g EP/ha	0.13
Earthworm	Acute	Iodosulfuron-methyl-sodium	NOEC = 1000	0.89	mg a.i./kg soil	0.0009
		Tribute Solo 32 DF Herbicide	NOEC = 320	0.044	mg EP/kg soil	0.00001
Terrestrial Vascular Plants—exposure to direct overspray						
Vascular plant	Seedling emergence	Tribute Solo 32 DF Herbicide	ER_{25} = 14.1	100	g EP/ha	7.1
	Vegetative vigour	Tribute Solo 32 DF Herbicide	ER_{25} = 16.1	100	g EP/ha	6.2
Freshwater Organisms—exposure to water body of 80 cm depth directly oversprayed						
Invertebrates	Acute	Iodosulfuron-methyl-sodium	½ EC_{50} = 43	0.0003	mg a.i./L	0.000007
		Tribute Solo 32 DF Herbicide	½ EC_{50} = 50	0.013	mg EP/L	0.00026
	Long-term (reproduction)	Iodosulfuron-methyl-sodium	NOEC = 9.1	0.0003	mg a.i./L	0.00003
		Tribute Solo 32 DF Herbicide	NOEC = 0.02	0.013	mg EP/L	0.7
Fish	Short-term	Iodosulfuron-methyl-sodium	1/10 LC_{50} = 8.8	0	mg a.i./L	0.00003

Organism	Study Type	Test Substance	Toxicity	Exposure	Units	RQ[c]
		Tribute Solo 32 DF Herbicide	1/10 LC_{50} = 0.26	0.013	mg EP/L	0.05
Algae	Short-term	Iodosulfuron-methyl-sodium	½ EC_{50} = 0.0021	0.0003	mg a.i./L	0.14
		Tribute Solo 32 DF Herbicide	½ EC_{50} = 0.37	0.013	mg EP/L	0.035
Vascular plant	Short-term	Iodosulfuron-methyl-sodium	½ EC_{50} = 0.0004	0.0003	mg a.i./L	0.75
		Tribute Solo 32 DF Herbicide	½ EC_{50} = 0.0013	0.013	mg EP/L	10

[a] Calculated using standardized values of 0.060 kg/day for rat daily food intake rate and 0.35 kg for rat body weight (USEPA 1988).

[b] Calculated using daily food intake rate of 0.015 kg/day and body weight of 0.20 kg from bobwhite quail acute oral toxicity study.

[c] Risk quotient = exposure/toxicity, trigger for a refined assessment is >50 for bees, >2 for other arthropods and >1 for all other organisms.

Appendix II Supplemental Maximum Residue Limit Information - International Situation and Trade Implications

There is only one specified Canadian maximum residue limit (MRL) (field corn grain), which differs from the tolerance established in the United States www.access.gpo.gov/nara/cfr/waisidx_04/40cfr180_04.html.
(Note: If applicable, also compare with Codex MRLs at www.mrldatabase.com)

Table 1 Differences Between Canadian MRLs and Other Jurisdictions

Commodity	Canada (ppm)	United States (ppm)	Codex* (ppm)
Corn, field, grain	**0.025**	**0.03**	**Not reviewed by Codex**

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

References

A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

1.0 The Active Ingredient, Its Properties and Uses

PMRA 1260246 Analytical Profile of Five Typical Production Batches, Code AE F115008, Iodosulfuron-methyl-sodium (Technical Grade Active Ingredient), Aventis, Study identification PA01/071, March 20, 2002, 46 pages, DACO 2.13.3.

2.0 Toxicology

PMRA 855991 Iodosulfuron-Methyl-Sodium. Toxicology-PMRA Registration Requests and Bayer CropScience Waiver requests. Bayer CropScience Inc. Report No.: AE F115008-2004. 21 pages. GLP is N/S. Publication status is N/S., AE F115008-2004, DACO: 4.3.4,4.4.2,4.5.12,4.5.3

3.0 Impact on Human and Animal Health

PMRA 1053449 Attachment 1: Response to DACO 5.8 Clarification. Blindformulierung mit AE F107892. Response to Level C Deficiency letter. Date of submission unknown., DACO: 5.8

4.0 Impact on the Environment

PMRA 948720 Estimation of octanol-water partiton coefficient (log Kow) of AE F059411, AE 000119, and AE 0034855. Report Date 10 November 2004. Report Number B004818.

PMRA 1064396 Estimation of octanol-water partition coefficient (log Kow) for iodosulfuron (AE F115008) using KOWWIN (Vers. 1.6). Report Date 9 August 2005. Report Number B004818 (Addendum)

5.0 Value

No additional references.