Proposed Re-evaluation Decision PRVD2021-02

Isoxaflutole and Its Associated End-use Products

Consultation Document

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Proposed re-evaluation decision for isoxaflutole and associated end-use products

Under the authority of the *Pest Control Products Act,* all registered pesticides must be re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports and other regulatory agencies, as well as comments received during public consultations. Health Canada applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Isoxaflutole is a broad spectrum herbicide registered for use in field corn and soybeans in Eastern Canada and British Columbia and for use in seed corn in Eastern Canada only. Currently registered products containing isoxaflutole can be found in the Pesticide Label Search and in Appendix I.

This document presents the proposed re-evaluation decision for isoxaflutole, including the proposed risk mitigation measures to protect human health and the environment, as well as the science evaluation on which the proposed decision is based. All products containing isoxaflutole that are registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period,[1] during which the public including the pesticide manufacturers and stakeholders may submit written comments and additional information to PMRA Publications. The final re-evaluation decision will be published after taking into consideration the comments and information received during the consultation period.

Proposed re-evaluation decision for isoxaflutole

Under the authority of the *Pest Control Products Act* and based on an evaluation of available scientific information, Health Canada is proposing continued registration of all uses of isoxaflutole and associated end-use products registered for sale and use in Canada.

The human health risk assessment indicated that, dietary and occupational (mixing/loading/application, and postapplication) risks were shown to be acceptable when isoxaflutole is used according to proposed conditions of registration which includes a new mitigation measure of a restricted-entry interval. Statements to update labels based on current policies and language are proposed. To meet current labelling standards and to reduce bystander exposure, an updated spray drift advisory label statement is proposed for all end-use products.

The environmental risk assessment found that potential risks to the environment from isoxaflutole were shown to be acceptable when used according to the proposed conditions of registration, which includes new mitigation measures such as precautionary label statements and spray buffer zones.

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

Isoxaflutole has value as an herbicide due to its broad-spectrum of activity, ability to manage certain resistant weeds, and as a resistance management tool.

Risk Mitigation Measures

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment and must be followed by law. The proposed label amendments including any updated label statements as a result of the re-evaluation of isoxaflutole, are summarized below. Refer to Appendix VII for details.

Human Health

Label improvements:

As a result of the re-evaluation of isoxaflutole, Health Canada is proposing additional revisions to the isoxaflutole labels to update label statements to current policies and language.

To protect bystanders, a statement indicating to apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal is proposed.

Risk mitigation:

To protect workers entering treated sites, a restricted-entry interval (REI) of 12 hours is proposed.

Environment

Risk mitigation:

To protect the environment, the following risk mitigation measures are proposed:

- Standard label statements to inform users of the potential toxic effects of isoxaflutole to aquatic organisms and terrestrial plants.
- Spray buffer zones for the protection of aquatic and terrestrial habitats.
- A leaching advisory statement.
- Precautionary label statements to reduce the potential for runoff of isoxaflutole to adjacent aquatic habitats for sites with characteristics that may be conducive to runoff and when heavy rain is forecast.

Value

Risk mitigation:

A warning statement of potential adverse effects on sugar beet crops from carryover of isoxaflutole.

International context

Isoxaflutole is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the United States, the European Union and Australia. As of 15 October 2020, no decision by an OECD member country to prohibit all uses of isoxaflutole for health or environmental reasons has been identified.

Next steps

Upon publication of this proposed re-evaluation decision, the public, including the registrants and stakeholders are encouraged to submit additional information that could be used to refine risk assessments during the 90-day public consultation period.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document,[2] which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with Health Canada's responses.

Refer to Appendix I for details on specific products impacted by this proposed decision.

Additional scientific information

No additional scientific data are required at this time.

[2] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

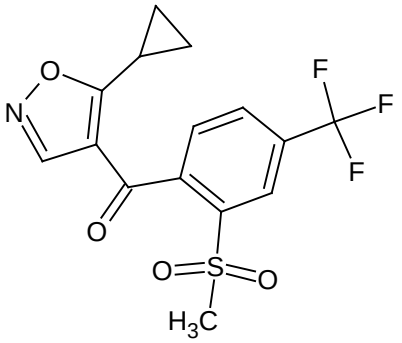
Science Evaluation

1.0 Introduction

Isoxaflutole is a broad-spectrum herbicide that is registered for use in field corn and soybeans in Eastern Canada and British Columbia and for use in seed corn in Eastern Canada only. Applications are made by ground equipment to all crops, either as a surface preplant or pre-emergence treatment. It can also be applied post-emergence only to field corn before the 3-leaf stage. Products are formulated as wettable granules or suspensions. Appendix II lists all the uses for which isoxaflutole is presently registered. All uses are supported by the registrants and were therefore considered in the health and environmental risk assessments of isoxaflutole.

2.0 Technical Grade Active Ingredient

2.1 Identity

Common name		Isoxaflutole
Function		Herbicide
Chemical Family		Isoxazole
Chemical name		
	1 International Union of Pure and Applied Chemistry (IUPAC)	(5-cyclopropyl-1,2-oxazol-4-yl)(α,α,α-trifluoro-2-mesyl-p-tolyl)methanone
	2 Chemical Abstracts Service (CAS)	(5-cyclopropyl-4-isoxazolyl)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methanone
CAS Registry Number		14112-29-0
Molecular Formula		$C_{15}H_{12}F_3NO_4S$
Structural Formula		
Molecular Weight		359.3

Purity of the Technical Grade Active Ingredient	98%
Registration Numbers	26141; 33596

2.2 Physical and chemical properties

Property	Result
Vapour pressure at 25°C	0.001 mPa
Ultraviolet (UV) / visible spectrum	No significant absorbance observed at $\lambda > 350$ nm in acidic, neutral or basic mediums.
Solubility in water at 20–25°C	6.2 mg/L (pH 5.5)
n-Octanol/water partition coefficient	log K_{ow}= 2.34
Dissociation constant	Not applicable. No dissociable moiety.

3.0 Human health assessment

3.1 Toxicology summary

Isoxaflutole is an isoxazole herbicide, which inhibits the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD) in mammals and plants. A detailed review of the toxicological database for isoxaflutole was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. A number of supplementary mechanistic studies were also submitted to support proposed modes of action. The studies were carried out in accordance with accepted international testing protocols and Good Laboratory Practices. Information from the published scientific literature was also considered in the toxicology assessment. The scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with isoxaflutole.

In rat toxicokinetic studies, ^{14}C-phenyl-radiolabelled isoxaflutole was rapidly and extensively absorbed following administration of single or repeated gavage doses. The peak blood concentration occurred within one hour following either single low- or high-dose administration. Tissue distribution of radioactivity was similar in males and females.

Residual radioactivity levels in tissues seven days postdosing were low after administration of a single high-dose, with the highest tissue concentrations in blood and plasma, followed by the liver and kidneys of males, and in the liver, kidneys, lungs and heart of females. Following single or repeated low doses, the highest tissue concentrations were in the liver and kidneys.

Isoxaflutole was extensively metabolized, with no differences noted between male and female animals. The major metabolite in both urine and feces was the diketonitrile RPA 202248, which accounted for ≥70% of the administered dose (AD) when residues in urine and feces were combined. Unchanged isoxaflutole was detected in only minor amounts in urine and fecal extracts from the single high-dose group during the first 24 hours postdosing. Seven or nine other metabolites were detected in the urine and feces, respectively. Of these, RPA 203328, which is also an environmental transformation product, was also detected in minor amounts in both the urine and feces from the low-dose groups.

Elimination was dose-dependent, with the majority of the AD excreted in the first 24 and 48 hours following low- and high-dose administration, respectively. Following administration of a single or repeat low-dose, the primary route of excretion was urinary, while the fecal route predominated following administration of a single high-dose. The identity of select isoxaflutole metabolites is presented in Appendix III, Table 3.

Isoxaflutole was of low acute toxicity via the oral and inhalation routes in rats and via the dermal route in rats and rabbits. It was non-irritating to minimally irritating to rabbit eyes, non-irritating to rabbit skin and was not a dermal sensitizer in guinea pigs following assessment by both the Maximization and modified Buehler methods.

Following short- and long-term dietary exposure to isoxaflutole, the main target organ was the liver in mice, rats and dogs. Liver effects included increased organ weight, altered serum enzyme activities, as well as histopathological changes including hepatocytic hypertrophy, hepatocyte fatty vacuolation, and necrosis. Other notable findings in long-term dietary studies included enlarged thyroid and thyroid follicular hyperplasia in rats, as well as hematological changes in mice and dogs suggestive of regenerative hemolytic anaemia. There was evidence of increased toxicity with increased duration of dosing. Clinical chemistry changes and liver toxicity, including hepatocyte hypertrophy and necrosis in rats, mice and dogs, were observed at lower dose levels in longer-term versus short-term studies.

Ocular changes were observed in repeat-dose oral studies in rats consisting of opacity, inflammation, keratitis, vascularization and epithelial changes. Mechanistic studies suggest that the observed ocular lesions in rats are linked to the inhibition of 4-hydroxyphenylpyruvate dioxygenase (HPPD) by isoxaflutole. This enzyme is involved in the normal catabolism of tyrosine and its inhibition results in an increase in plasma tyrosine levels (tyrosinaemia). A direct correlation between tyrosinaemia and ocular toxicity has been demonstrated in the published literature in various species. Following prolonged tyrosinaemia, tyrosine crystals accumulate in the corneal epithelium leading to corneal opacity and subsequent keratitis. Studies have shown that subsequent to HPPD inhibition, the extent of the tyrosinaemia is controlled by another catabolic enzyme, tyrosine aminotransferase (TAT), which catalyses the production of 4-hydroxyphenylpyruvic acid (HPPA) from tyrosine. HPPA and its related phenolic form are then eliminated by the kidneys. The available mode of action (MOA) data show that mice have a

greater capacity than rats to utilize the TAT metabolic route following isoxaflutole administration, which limits the development of tyrosinaemia and thus ocular lesions in this species. In an in vitro study with nitisinone, another HPPD inhibitor (PMRA# 2713629), the metabolism of tyrosine under untreated and HPPD-inhibited conditions was investigated in hepatocyte preparations from rats, mice, rabbits, dogs and humans. The TAT metabolic pathway in humans and mice was shown to have a similar metabolic capacity, while this pathway in the rabbit, dog and rat had much less capacity. Thus, with respect to the development of ocular lesions resulting from HPPD inhibition, the mouse is a better quantitative model than the rat for human risk assessment of tyrosine-induced eye lesions. The absence of ocular lesions noted in studies conducted with isoxaflutole in mice alleviates the concern for this endpoint in the human health risk assessment. Moreover, the HPPD inhibitor nitisinone is used as an effective therapeutic agent in humans to treat patients suffering from rare genetic diseases of tyrosine catabolism. Rarely, ocular effects are seen in these patients due to high plasma tyrosine levels; however, these effects are transient and can be readily reversed upon adherence to a restricted protein diet.

In a short-term dermal toxicity study in rats, no significant systemic toxicity or signs of dermal irritation were noted following exposure to isoxaflutole up to the limit dose of testing. A repeated-dose inhalation toxicity study was not available.

In a standard battery of in vitro and in vivo genotoxicity studies, isoxaflutole was not genotoxic.

In an 18-month dietary oncogenicity study in mice, significant liver toxicity (elevated serum enzyme activities, increased weight, histopathological changes) was noted. Statistically significant increases in the incidence of hepatocellular adenomas, as well as the combined incidence of hepatocellular adenomas and carcinomas were observed in both sexes at the highest dose level. A statistically significant increase in the incidence of hepatocellular carcinoma was also noted in high-dose males. Additionally, a reduced time to tumour formation was noted in these animals. At the high dose level, incidences of hepatocellular adenoma and hepatocellular carcinoma also exceeded historical control (HC) ranges in both sexes. While the incidence of hepatocellular carcinoma in males at the mid-dose was slightly above HC range, the combined incidence of adenomas/carcinomas was similar to that in concurrent control animals and therefore did not support a treatment-related effect.

In a rat two-year dietary chronic toxicity/carcinogenicity study, histopathological findings in the liver (hepatocellular hypertrophy) and thyroid (enlarged thyroid and follicular hyperplasia) were observed. At the high-dose level, large decreases in bodyweight were observed in both sexes at study termination. In male rats, statistically significantly increased incidences of hepatocellular adenomas, hepatocellular carcinomas, combined hepatocellular adenomas and carcinomas, as well as thyroid follicular cell adenomas, were noted at the high-dose level. A slight increase in the incidence of thyroid follicular cell adenoma at the mid-dose level did not reach statistical significance, but was considered treatment-related, given that it exceeded both the concurrent control and HC range. In female rats, statistically significantly increased incidences of hepatocellular adenomas, hepatocellular carcinomas, and combined hepatocellular adenomas and carcinomas were observed at the high-dose level. Additionally, the incidences of endometrial adenoma, endometrial carcinoma and combined endometrial adenoma and carcinoma were above the HC range in these animals. Both the hepatocellular and endometrial tumours observed

in high-dose females were considered treatment-related; however, these effects occurred at a dose that exceeded the maximum tolerated dose (MTD) in females based on excessive bodyweight and bodyweight gain decrements observed within the first year of dosing, and as such, were not considered relevant for human health risk assessment.

Mechanistic studies were provided to support a nuclear receptor-mediated MOA for liver tumour formation in rats and mice based on constitutive androstane receptor (CAR) and pregnane X receptor (PXR) activation. Activation of CAR/PXR produces alterations in gene transcription and activation of specific metabolic enzymes, which result in a transient increase in hepatocellular proliferation, formation of altered hepatic foci and, ultimately, liver tumours. In a series of mechanistic studies in rats and mice, it was demonstrated that isoxaflutole induced hepatic CYP450 enzymes via CAR and/or PXR. In mice and rats, increased hepatocyte hypertrophy and proliferation were noted after short-term dietary exposure. In a short-term dietary study in rats, which included a recovery group, hepatocellular proliferation was reversible. The increase in hepatocyte proliferation in rats and mice was shown to be specific to CAR/PXR activation using genetically modified CAR/PXR double knockout animals. Furthermore, in in vitro hepatocyte assays, isoxaflutole induced hepatic CYP450 enzymes and hepatocyte proliferation in mouse and rat but not in human hepatocyte cultures. One uncertainty with the proposed MOA was the lack of histopathological evidence of pre-neoplastic foci, despite an increased incidence of hepatocellular adenomas and carcinomas in the long-term studies.

Mechanistic studies were also provided to support a non-genotoxic MOA for the thyroid follicular cell tumours observed in rats. The proposed MOA involves perturbation of thyroid hormone homeostasis via reduction of circulating thyroid hormone as a result of microsomal enzyme induction in the liver through activation of CAR/PXR. Prolonged stimulation of the thyroid leads to follicular cell hypertrophy, hyperplasia, and eventually follicular cell adenomas and carcinomas. The mechanistic studies showed that in rats, short-term oral administration of isoxaflutole up-regulated sulfotransferase and UDP glucuronosyltransferase (UGT) transcripts and enzymatic activity in the liver. These enzymes are known to play a role in T4 metabolism. Short-term oral administration of isoxaflutole in rats also resulted in increased systemic clearance of 125I-thyroxine, with a concomitant decrease in T4 levels and decreased 125I-T4 terminal half-life. Plasma thyroid-stimulating hormone (TSH) levels and pituitary TSHb transcript levels were increased. Continued perturbation of thyroid hormone levels lead to increased thyroid weight, thyroid follicular cell hypertrophy and hyperplasia. Dose and temporal concordance for these key events were observed in the rat two-year chronic dietary toxicity/carcinogenicity study and, to some extent, in the dietary short-term mechanistic studies. CAR/PXR double knockout rats were generally refractory to the thyroid effects induced by isoxaflutole in wildtype animals, thus illustrating a direct link between CAR/PXR activity and the thyroid changes observed.

Overall, the data support the plausibility of the proposed MOAs for liver and thyroid tumours, although some residual uncertainties with regards to some of the key events remain. However, the weight of evidence for the proposed MOAs was considered sufficient to support a threshold approach to cancer risk assessment for the liver and thyroid tumours.

In a dietary two-generation reproductive toxicity study in rats, reproductive toxicity occurred at the highest dose level tested, consisting of an increased incidence of stillbirths in the F1 generation and decreased litter weight at birth. In the offspring, increased mortality during postnatal (PND) 0-4 in the F1 generation and decreased pup bodyweight in the F1 and F2 generations was observed at the mid-dose level in the presence of liver toxicity in parental animals. Decreased viability, increased number of pups with no milk present in the stomach, and an increased number of pups with under-developed renal papilla in both the F1 and F2 generations, were noted at the highest dose level. The mortality during the early postnatal period in F1 pups at the mid-dose level (decreased viability index), in the presence of slight parental toxicity, was considered a serious effect. However, the level of concern for this finding was tempered by the absence of an effect on pup viability in F2 pups, as well as in F1 offspring in a supplemental dietary one-generation reproductive toxicity study in rats where parental animals were dosed at similar levels.

In the developmental toxicity studies in rats and rabbits, there was evidence of increased sensitivity of the young. In a rat gavage developmental toxicity study, reduced fetal bodyweights, ossification delays and skeletal variations were observed at a dose level that did not produce maternal toxicity. In dams, systemic toxicity was limited to decreased bodyweight gain and food consumption during treatment, and increased salivation postdosing at the highest dose level. In a rabbit gavage developmental toxicity study, fetal variations, including increased incidence of 27^{th} pre-sacral vertebrae and 13^{th} pair of ribs, were noted in the absence of maternal toxicity. At higher dose levels, effects in maternal animals included decreased bodyweight, bodyweight gain and food consumption, as well as increased post-implantation loss (increased incidence of late resorptions). There was no evidence of treatment-related malformations in either species.

The potential for isoxaflutole to produce neurotoxic effects following acute and repeated exposure was investigated in rats. There was no evidence of selective neurotoxicity in either the acute gavage neurotoxicity or the 90-day dietary neurotoxicity study. While the non-guideline gavage developmental neurotoxicity study (DNT) in rats lacked brain morphometric data, the available information did not provide any indication that isoxaflutole was a developmental neurotoxicant. In this study, decreased pup survival, decreased brain weight, and decreased bodyweight and bodyweight gain were noted in offspring at dose levels that caused decreased bodyweight, bodyweight gain and food consumption in maternal animals.

In the dietary two-year chronic study in rats, increased incidence of progressive axonal/myelin degeneration and cholesterol cleft/granuloma of the sciatic nerve occurred and was associated with an increased incidence of focal degeneration and chronic inflammation of the thigh muscle. These effects were statistically significant in mid-dose males and in high-dose animals of both sexes. As a result of these effects, the movement and gait were affected.

Hepatorenal tyrosinemia (type I) in humans (PMRA# 2997190, 2997200) is linked to extensive clinical manifestations, including acute and chronic liver and kidney disease, and neurological manifestation of peripheral and autonomic nervous system, evidenced by pain with extensor hypertonia/opisthotonic posturing, muscle weakness, paresthesias, motor paralysis, vomiting, diarrhea, and paralytic ileus. Electrophysiologic studies and neuromuscular biopsies in human tyrosinemia patients showed axonal degeneration and secondary demyelination, neuropathological effects similar to those in rats treated with isoxaflutole. Vacuolation of the

cerebral white matter was also a consistent finding at autopsy in humans, but was not noted in rats. The observed neurological effects (such as muscle weakness/paralysis, and abnormal/limited gait) and neuropathology (demyelination and axonal degeneration) in rats and humans are a secondary effect of tyrosinemia. As noted earlier, rats are much more sensitive to the induction of tyrosinemia than humans.

In a 28-day dietary immunotoxicity study in rats, decreased bodyweight gain and a slight decrease in thymus weight were noted. Although the study was considered supplemental due to methodological limitations, it did not provide any evidence that isoxaflutole was immunotoxic when the antibody response to sheep-red blood cells was assessed using an enzyme-linked immunosorbent assay.

Several studies were available for two isoxaflutole mammalian metabolites. Metabolites RPA 202248 and RPA 203328 were of low acute oral toxicity in rats and non-genotoxic in bacterial gene mutation assays. In addition, for RPA 203328 there were no treatment-related toxicological findings in short-term dietary studies in rats up to the limit dose of testing and, no evidence of developmental toxicity in rats at doses causing decreased bodyweight and food consumption in maternal animals. On the basis of the available data, RPA 203328 is considered to be less toxic than the parent isoxaflutole.

The toxicology reference values for use in the human health risk assessment are summarized in Appendix III, Table 1. Results of the toxicology studies conducted on laboratory animals with isoxaflutole are summarized in Appendix III, Table 2. The identity of select isoxaflutole metabolites is presented in Appendix III, Table 3.

3.1.1 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies, including gavage developmental toxicity studies in rats and rabbits, and a dietary two-generation reproductive toxicity study in rats. A supplemental dietary one-generation reproductive toxicity study in rats and an acceptable non-guideline DNT study in rats were also available.

With respect to potential prenatal and postnatal toxicity, there was an indication of increased susceptibility of the young compared to parental animals in the developmental toxicity studies.

In the rat developmental toxicity study, decreased fetal weight, as well as skeletal variations and ossification delays were observed at a dose level that did not cause adverse effects in maternal animals. In the rabbit developmental toxicity study, minor developmental effects consisting of fetal skeletal variations and ossification delays were observed in the absence of maternal toxicity. At higher dose levels, post-implantation loss (increased incidence of late resorptions) was observed in the presence of other signs of maternal toxicity in rabbits. In the DNT study in rats, decreased pup survival and decreased brain weight at PND 11 in both sexes and PND 72 in males were observed in offspring at a maternally toxic dose level.

In the rat dietary two-generation reproductive toxicity study, decreased viability index starting at the mid-dose level during the early postnatal period in the F1 generation was considered a serious effect. However, the level of concern for this finding was tempered by the presence of slight maternal toxicity and large dose spacing between the NOAEL and LOAEL values (10-fold). Additionally, the effect on pup viability occurred only at much higher dose levels in the F2 generation of the reproductive toxicity study (24-fold higher), as well as in a supplemental one-generation dietary reproductive toxicity study (27-fold higher), and in a non-guideline gavage DNT study in rats (14-fold higher). Significant maternal toxicity was also observed at the high-dose levels where these effects occurred in each of these studies.

Overall, the database is adequate for determining the potential sensitivity of the young and effects on the young are well characterized. The effects noted in the developmental toxicity studies in the absence of maternal toxicity were not considered serious in nature. Although there were serious effects in the young in both the rat DNT study and rabbit developmental toxicity study, these effects (mortality and post-implantation loss, respectively) occurred at high dose levels (higher than the developmental LOAEL in the case of the rabbit developmental toxicity study), as well as in the presence of maternal toxicity. In addition, the reference values selected for risk assessment are protective of these effects. Therefore, based on the above, the 10-fold PCPA factor was reduced to onefold.

3.2 Dietary exposure and risk assessment

In a dietary exposure assessment, Health Canada determines how much of a pesticide residue, including residues in meat and milk, may be ingested with the daily diet. Exposure to isoxaflutole and RPA 202248 from potentially treated imported foods is also included in the assessment. These dietary assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

Health Canada considers limiting use of a pesticide when risk exceeds 100% of the reference dose. The PMRA's Science Policy Notice SPN2003-03, *Assessing Exposure from Pesticide in Foods, A User's Guide*, presents detailed acute and chronic risk assessments procedures.

The residue definition for enforcement in Canada is the following:

- Isoxaflutole ((5-cyclopropyl-4-isoxazoly)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methanone) and the metabolite RPA 202248 (1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropylpropane) for all plant and animal commodities. No change to the existing residue definition for plant commodities or animal commodities is proposed.

The residue definition for risk assessment in Canada is the following:

- Isoxaflutole and the metabolite RPA 202248 for all plant and animal commodities. No change to the existing residue definition for plant commodities or animal commodities is proposed.

Residue estimates used in the dietary risk assessment may be based conservatively (using upper bound estimates) on the maximum residue limits (MRLs) or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency (CFIA) National Chemical Residue Monitoring Program and the United States Department of Agriculture's Pesticide Data Program (USDA's PDP). Theoretical and experimental processing factors as well as specific information regarding the percent of crops treated may also be incorporated to the greatest extent possible.

Sufficient information was available to adequately assess the dietary exposure and risk from isoxaflutole and RPA 202248. Chronic dietary (food and drinking water) exposure and risk assessments for isoxaflutole were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 2.14), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998.

The chronic exposure estimates are considered to be refined but retained a certain level of conservatism due to the use of MRLs/American tolerances and anticipated residues (from crop field trials).

3.2.1 Determination of acute reference dose (ARfD)

Establishment of an acute reference dose is not required, as an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies. Therefore, an acute risk assessment is not required.

3.2.2 Determination of acceptable daily intake (ADI) for isoxaflutole

To estimate risk following repeated dietary exposure to isoxaflutole, the results from the two-year dietary chronic toxicity/carcinogenicity study in rats and the dietary two-generation reproductive toxicity study in rats were considered co-critical. The NOAEL of 2 mg/kg bw/day from the two-year chronic toxicity/carcinogenicity study was established based on increased liver weight and increased incidence of histopathological findings in the liver and bile duct in

both sexes, as well as effects on the kidney, thyroid and sciatic nerve in males at a LOAEL of 20 mg/kg bw/day. In the two-generation reproductive toxicity study in rats, a NOAEL of 1.8 mg/kg bw/day was established based on effects at the LOAEL of 17/18 mg/kg bw/day (♂/♀), which included liver toxicity in parental animals, decreased pup body weight, and decreased viability index in F_1 offspring.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* hazard characterization section, the PCPA factor was reduced to onefold. Thus, the composite assessment factor (CAF) is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2 \text{ mg/kg bw/day}}{100} = 0.02 \text{ mg/kg bw/day of isoxaflutole}$$

3.2.3 Chronic dietary exposure and risk assessment

The chronic dietary risk from food and drinking water was calculated using the average consumption of different foods and water, and the average residue values on those foods and water. The estimated exposure to isoxaflutole and the metabolite RPA 202248 was then compared to the ADI. When the estimated exposure is less than the ADI, the chronic dietary exposure is acceptable.

The chronic assessment was conducted using anticipated residues (from crop field trials), and MRLs/tolerances for commodities for which no anticipated residues were available. Experimental processing factors were used when available and theoretical processing factors were used when experimental processing factors were not available. Drinking water contribution to the exposure was accounted for by direct incorporation of the chronic estimated environmental concentration (EEC) value obtained from modelling (see Section 3.3) into DEEM. The chronic dietary (food and drinking water) exposure estimates were less than the ADI for the general population and all subpopulations (< 10% of the ADI). On this basis, a dietary exposure from food and drinking water, is considered acceptable under current conditions of use.

3.3 Exposure from drinking water

Residues of isoxaflutole and its metabolite RPA 202248 in potential drinking water sources were estimated from modelling. Estimated environmental concentrations (EECs) in surface water were calculated using the PRZM/EXAMS models on standard Level 1 scenarios (EEC = 6.1 µg a.i./L), a small reservoir. EECs in groundwater were calculated using the PRZM-GW model (EEC value = 3.5 µg a.i./L). All scenarios were run using 50-year weather data and were calculated using conservative inputs with respect to application rate and timing, and geographic scenario.

3.4 Occupational and non-occupational exposure and risk assessment

Occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

3.4.1 Toxicological endpoints for occupational exposure

3.4.1.1 Short- and intermediate-term dermal and inhalation

For short- and intermediate-term occupational exposures via the dermal and inhalation routes, the NOAEL of 1.8 mg/kg bw/day from the two-generation reproductive toxicity study was selected for risk assessment. Parental liver toxicity, as well as offspring toxicity in the form of decreased bodyweight and decreased viability in the F1 generation was observed. Worker populations could include pregnant or lactating women and therefore, these endpoints were considered appropriate for the occupational risk assessment. The use of the 21-day dermal toxicity study was not considered for the short- and intermediate-term dermal scenarios, as the dermal toxicity study did not assess an endpoint of concern in the database (pup viability in the rat reproductive toxicity study). With regard to the selection of reference values for inhalation risk assessment, a repeat-dose inhalation toxicity study was not available and thus, use of a NOAEL from an oral study was considered appropriate.

The target MOE for these scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.1.2 Cancer risk assessment

The weight of evidence for the proposed MOAs for liver and thyroid tumours was considered sufficient to support a threshold approach to cancer risk assessment (see Section 3.1). The selected reference values provide a sufficient margin to these tumour types. Increased incidences of endometrial and liver tumours were also observed in female rats in the chronic toxicity/carcinogenicity study; however, these occurred at an exceedingly toxic dose level and were not considered relevant to the human health risk assessment.

3.4.1.3 Dermal absorption

A dermal absorption study was on file (PMRA# 1409079) and was re-examined to ensure that current policies and practices were met. An updated dermal absorption value of 15% was considered appropriate to estimate the dermal absorption for isoxaflutole for typical pesticide application and postapplication scenarios.

3.4.2 Non-occupational exposure and risk assessment

Non-occupational (residential) risk assessment involves estimating risks to the general population, including youth and children, during or after pesticide application.

Isoxaflutole is not registered for residential use in Canada. Therefore, residential exposure is not expected. The use of isoxaflutole could however result in potential bystander exposure through spray drift during commercial applications. The potential for bystander exposure is considered to be minimal.

The standard spray drift advisory label statement is not currently included on all end-use product labels. Thus, to meet current labelling standards and to reduce bystander exposure, a new spray drift advisory label statement is proposed for all end-use product labels (refer to Appendix VII).

3.4.3 Occupational exposure and risk assessment

There is potential for exposure to isoxaflutole in occupational scenarios to workers handling commercial-class isoxaflutole products during the application processes as well as to workers entering treated areas.

3.4.3.1 Occupational applicator exposure and risk assessment

For commercial-class products, there are potential exposures for mixers, loaders, and applicators (M/L/A). Based on typical use patterns, the major scenarios identified were:

- Open mixing/loading of liquids
- Open mixing/loading of water dispersable granules (dry flowables)
- Groundboom application of liquids

Based on the number of applications and the timing of application, workers applying isoxaflutole would have a short-term (<30 days) duration of exposure.

The exposure estimates for mixer/loaders and applicators are based on the following personal protective equipment (PPE):

Baseline PPE - long pants, long-sleeved shirt and chemical-resistant gloves

Dermal and inhalation exposures for occupational applicators were estimated using data from the Agricultural Handler Exposure Task Force (AHETF).

Inhalation exposures were based on light inhalation rates (17 L/min).

The calculated MOEs for agricultural applicators exceed the target MOE and risks were shown to be acceptable. The results of the risk assessment are summarized in Appendix IV, Table 1.

3.4.3.2 Occupational postapplication exposure and risk assessment

The postapplication occupational risk assessment considered exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact (for example, scouting). Based on the registered use pattern, there is potential for short-term (<30 days) postapplication exposure to isoxaflutole residues for workers.

Potential dermal exposure to postapplication workers was estimated using updated activity-specific transfer coefficients (TCs) from the Agricultural Re-entry Task Force (ARTF) to estimate postapplication exposure resulting from contact with treated foliage at various times after application. A TC is a factor that relates worker exposure to dislodgeable residues. TCs are specific to a given crop and activity combination, for example, hand harvesting apples or scouting late season corn, and reflect standard clothing worn by adult workers.

Dislodgeable foliar residues (DFR) refer to the amount of residue that can be dislodged or transferred from a surface, such as the leaves of a plant. There were no chemical-specific DFR studies submitted to the PMRA for the re-evaluation of isoxaflutole; therefore, the following standards were used:

- A standard peak value of 25% of the application rate with a dissipation rate of 10% per day

Exposure would be predominantly dermal for workers performing postapplication activities in crops treated with a foliar spray. Based on the vapour pressure of isoxaflutole, inhalation exposure is likely to be negligible provided that the minimum 12 hour restricted-entry interval is followed.

For agricultural workers entering a treated site, REIs are calculated to determine the minimum length of time required before workers can enter after application to perform tasks involving hand labour. An REI is the duration of time that must elapse before residues decline to a point where risks are shown to be acceptable for postapplication worker activities (in the case of isoxaflutole, performance of a specific activity that results in exposures above the target MOE of 100).

The calculated MOEs for postapplication exposure in agricultural sites were shown to be acceptable for all uses provided a 12 hour REI is followed. The results of the risk assessment are summarized in Appendix IV, Table 2.

3.5 Aggregate exposure and risk assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation).

Aggregate exposure from food and drinking water is considered acceptable under the current conditions of use for all subpopulations (refer to Section 3.2). As discussed in Section 3.4.2, isoxaflutole is not registered for residential use in Canada. Given the limited potential for bystander exposure, aggregate exposure and risks are considered acceptable for currently registered uses of isoxaflutole.

3.6 Cumulative risk assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Isoxaflutole belongs to a class of herbicides that inhibit the liver enzyme HPPD. Other Canadian registered herbicides in this class include pyrasulfotole, topramezone, tolpyralate, bicyclopyrone, mesotrione and tembotrione.

Inhibition of HPPD can result in elevated blood tyrosine levels, or tembotrione. HPPD-inhibiting herbicides induce various toxicological effects in laboratory animals including ocular toxicity, and liver and kidney effects. No clear common mechanism for toxicity has been confirmed on which to base a cumulative risk assessment for the liver and kidney effects.

The observed ocular toxicity in rats following exposure to HPPD inhibition is highly correlated with elevation of the blood tyrosine levels. Marked species differences have been noted in the ocular effects associated with inhibition of HPPD due to differences in the capacity of the tyrosine clearance metabolic pathway. Overall, the weight of evidence suggests that exposure to low level environmental residues of HPPD inhibiting herbicides are unlikely to result in the high blood levels of tyrosine and ocular toxicity in humans, due to an efficient human metabolic process to handle excess tyrosine. Therefore, a cumulative health risk assessment with other HPPD inhibitors in relation to ocular toxicity is not required.

Isoxaflutole shares a common metabolite, RPA 203328, with pyrasulfotole, another HPPD inhibitor that is a registered pesticide in Canada. RPA 203328 is a minor metabolite and is not included in the residue definition for either isoxaflutole or pyrasulfotole. The results from the available toxicology studies conducted with RPA 203328 also indicate that this metabolite is of equal or lower toxicity than isoxaflutole. Therefore, there are no concerns regarding the cumulative health effects pertaining to this metabolite at this time.

3.7 Health incident reports

Human and animal incident reports

As of 2 October 2020, one human incident and one incident, involving a human and domestic animals had been submitted to the PMRA. Both incidents occurred in the United States and involved the application of a product containing isoxaflutole and another active ingredient to neighbouring fields. In the human incident, the individual reportedly had seizures. In the incident involving a human and domestic animals, the person had pulmonary oedema and shortness of breath, and chickens, two dogs and a cat experienced respiratory, neurological and/or systemic effects; in addition, death was reported in chickens. Based on the information in both of the reports, the nature of the exposure to the pesticide could not be determined. It was unknown where the individuals or animals were located when the spraying took place, where the field was

in proximity to the yard, whether there was drift of the product after application and an unknown route of exposure. Therefore, it was concluded that there was insufficient information to assess an association with the pesticide in each of these incidents.

Best practice statements currently appear on all Canadian labels for registered isoxaflutole products that direct the applicator not to apply the product either in a way that will contact workers or other persons, directly or through drift. Based on the overall low number of human and domestic animal incidents, the lack of information in the reported American incidents, and the presence of best practice statements on all Canadian isoxaflutole product labels aimed at minimizing potential exposure to the pesticide, no additional mitigation measures are proposed based on the incident reports.

4.0 Environmental assessment

4.1 Fate and behaviour in the environment

A summary of the physico-chemical properties and environmental fate data for isoxaflutole and its transformation products is presented in Appendix V, Tables 1 to 3. Isoxaflutole is not very soluble in water and has a low potential to volatilize from water surfaces and moist soil. The octanol/water partition coefficient for isoxaflutole (log K_{ow} of 2.32) indicates that it is not expected to bioaccumulate. Hydrolysis and direct photolysis are the principle mechanisms of transformation of isoxaflutole under environmentally relevant conditions, however, direct photolysis of isoxaflutole is limited in soil.

Isoxaflutole transforms rapidly in soil (aerobic soil DT_{50} = 0.3 to 5.2 days). The two major transformation products formed in aerobic soil (RPA 202248 and RPA 203328) are both more persistent than the parent.

Isoxaflutole is not persistent in water/sediment systems and dissipates rapidly (DT_{50} up to 0.7 days), with two major transformation products being produced (RPA 202248 and RPA 205834), both of which are more presistent than the parent. Isoxaflutole is not expected to partition to sediment.

Isoxaflutole and its transformation products are not persistent in soil under Canadian field conditions. Isoxaflutole and its transformation products were found only in the top 15-cm soil layer. Laboratory based adsorption/desorption studies indicate that isoxaflutole is moderately to very highly mobile in soil. A soil column leaching study found the transformation products RPA 202248 and RPA 203328 in the leachate and indicated mobility of isoxaflutole and its transformation products changes in relation to the organic matter content of the soil. Overall, there is a potential for transformation products of isoxaflutole to leach downward through soil to groundwater. An advisory statement will be required on the product labels.

Based on the vapour pressure and Henry’s law constant, isoxaflutole is not expected to volatilize to air from moist soil or water and entry of isoxaflutole into the atmosphere is expected to be extremely low.

4.2 Environmental risk characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level). EECs are reported in Table 4. Summaries of toxicity data for both terrestrial and aquatic non-target organisms to isoxaflutole and its transformation products are presented in Appendix V, Tables 5 and 6.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the RQ is then compared to the level of concern (LOC). If the screening level RQ is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

Representative use patterns for isoxaflutole were considered in the environmental risk assessment and were selected to provide conservative exposure scenarios. The risk of isoxaflutole and its related end-use products to non-target organisms was assessed based upon the maximum annual application rate of 105 g a.i./ha for all crops, which is applied as a single spray application (see Appendix V, Table 4).

A risk assessment of isoxaflutole and its transformation products, RPA 204428, RPA 203328 and RPA 205834, was conducted for freshwater and marine aquatic organisms based on available toxicity data. For acute toxicity studies, uncertainty factors of 2 and 10 are used for aquatic plants and invertebrates, and fish species, respectively, when calculating RQs. An uncertainty factor of one is applied to chronic NOEC endpoints. RQs for isoxaflutole and its transformation products were calculated based on the highest maximum seasonal application rate for all uses.

A summary of the toxicity data for non-target organisms is presented in Appendix V, Table 6. The screening level RQs for isoxaflutole and its transformation products, RPA 202248, RPA 203328 and RPA 205834, and the spray drift refined level RQs are summarized in Appendix V, Tables 12 to 14.

4.2.1 Terrestrial and Aquatic Risk Assessments

Results of the risk assessment are presented in Appendix V, Tables 7 to Table 14. To calculate the EECs for the transformation products, the application rate for isoxaflutole was multiplied by the ratio of the molecular weight of the transformation product and the parent, isoxaflutole. This is a conservative estimate and assumes that isoxaflutole completely transforms to that transformation product. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following use of isoxaflutole as an herbicide. Toxicity data was also available for some of the transformation products and was used in the terrestrial risk assessment.

Isoxaflutole and its major transformation products, RPA 202248, RPA 203328 and RPA 205834, are not expected to pose risks of concern to earthworms, pollinators, birds, mammals, aquatic invertebrates and fish. Potential risks of concern were identified at the screening level for non-target terrestrial and aquatic plants and marine invertebrates.

The effect of isoxaflutole to non-target terrestrial plants was determined through seedling emergence and vegetative vigour assays using ten plant species. A species sensitivity distribution (SSD) was determined for the effects of isoxaflutole on non-target terrestrial plants using the data for the ten plant species. Risk to non-target terrestrial plants was determined by comparing the HD_5 value to the direct on-field and off-field exposure from drift. The RQs for on-field (RQ = 434) and off-field (RQ = 26) risk exceeded the LOC, therefore, terrestrial spray buffer zones will be required to mitigate risks to non-target plants.

Aquatic risks were further characterised by estimating aquatic exposure due to runoff and spray drift separately. Isoxaflutole is applied only once per season and it dissipates rapidly in soil and water. The acute and chronic exposure of aquatic systems through runoff is expected to be low. In addition, the available studies show that the transformation products are less toxic than isoxaflutole. Screening level RQ values for isoxaflutole for the most sensitive aquatic organisms are ≤ 13 and RQ values based on exposure due to runoff are expected to be lower. Due to the small potential risks identified at the screening level, refinement of the risk assessment using water modelling was not deemed necessary. Standard precautionary label statements are proposed. To mitigate risks from spray drift, aquatic spray buffer zones and standard label statements for runoff are expected to mitigate potential exposure to aquatic systems.

4.2.2 Environmental Incident Reports

As of April 2020, no environmental incidents had been reported to the PMRA for isoxaflutole. The U.S. EPA Ecological Incident Information System (EIIS), which was last updated on October 5, 2015, contains approximately 500 incidents of crop injury related to isoxaflutole (most from direct treatment). In the absence of mitigative measures, damage to non-target plants is not unexpected as isoxaflutole is an herbicide and seedling emergence and vegetative vigour

studies indicate that some plants are quite sensitive. Based on the results of the risk assessment, terrestrial buffer zones have been established to mitigate the risk to non-target plants adjacent to sites of application.

In addition, one bee incident and one incident involving tree damage were reported in the USEPA EIIS. Details about these incidents were insufficient to establish causality (that is, if they were directly related to exposure to isoxaflutole). Therefore, these incidents did not impact the risk assessment.

4.3 Toxic Substances Management Policy Considerations

In accordance with the PMRA Regulatory Directive DIR99-03[3], the assessment of isoxaflutole against Track 1 criteria of Toxic Substances Management Policy (TSMP) under Canadian Environmental Protection Act was conducted. Health Canada has reached the conclusions that:

- Isoxaflutole does not meet all Track 1 criteria, and is not considered a Track 1 substance (refer to Appendix V, Table 15)
- Isoxaflutole does not form any transformation products that meet all Track 1 criteria.

4.3.1 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*[4]. The list is used as described in the Health Canada's Science Policy Note SPN2020-01[5] and is based on existing policies and regulations including the Toxic Substances Management Policy[6] and Formulants Policy[7], and taking into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations under the Canadian Environmental Protection Act*, 1999 (substances designated under the Montreal Protocol).

Health Canada has reached the conclusion that isoxaflutole and its end-use products do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

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3 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

4 SI/2005-114, last amended on June 24, 2020. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

5 PMRA's Science Policy Note SPN2020-01, *Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under paragraph 43(5)(b) of the Pest Control Products Act

6 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

7 DIR2006-02, *Formulants Policy and Implementation Guidance Document*

5.0 Value Assessment

Isoxaflutole controls or suppresses a broad spectrum of annual grasses and broadleaf weeds, including weeds that are ALS (acetolactate synthase) resistant, triazine resistant, and glyphosate resistant. As such, there is value for the broad-spectrum activity of the active ingredient, its ability to control weeds that other herbicides have become resistant to, and for resistance management purposes.

List of Abbreviations

abs	absolute
AD	administered dose
ADI	acceptable daily intake
A/G	albumin/globulin
AHETF	Agricultural Handlers Exposure Task Force
a.i.	active ingredient
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate aminotransferase
ATP	adenosine triphosphate
ATPD	Area treated per day
BrdU	bromodeoxyuridine
BROD	CYP3A-dependent 7-benzyloxyresorufin oxidation
bw	body weight
bwg	bodyweight gain
d	day(s)
CAF	composite assessment factor
CAR	constitutive androstane receptor
CHO	Chinese hamster ovary cell
cm^2	Centimeters squared per hour
C_{max}	maximum plasmatic concentration
CR	Chemical Resistant
CYP	cytochrome P
DA	Dermal absorption
DAT	days after treatment
DFR	Dislodgeable foliar residue
DIR	Regulatory Directive
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
dw	dry weight
EC_{50}	exposure concentration to 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
EGF	epidermal growth factor
EIIS	Ecological Incident Information System
ELS	early life stage
ER_{50}	application rate resulting in 50% reduction in the observed parameter
EPHX	epoxide hydroxylase
EROD	7-ethoxy-resorufin O-deethylation
EU	European Union
F_1	first generation
F_2	second generation

fc	food consumption
fe	food efficiency
g	gram(s)
GD	gestation day
GLP	good laboratory practice
ha	Hectare
hr(s)	hour(s)
HC	historical control
HC5	hazardous concentration to 5% of species
HD5	hazardous dose or rate to 5% of species
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HPAA	4-hydroxyphenyl acetic acid
HPLA	4-hydroxyphenyl lactic acid
HPPA	4-Hydroxyphenylpyruvic acid
HPPD	4-hydroxyphenylpyruvate dioxygenase
kg	kilogram(s)
KO	knockout
K_{oc}	organic carbon-water partition coefficient
K_{ow}	octanol-water partition coefficient
L	litre(s)
LAH	lauric acid hydroxylase
LC_{50}	lethal concentration required to kill 50% of the test group
LD	lactation day
LD_{50}	lethal dose required to kill 50% of the test group
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOEC	lowest observed effect concentration
LOEL	lowest observed effect level
LR_{50}	lethal rate 50%
max	maximum
µg	microgram
mg	milligram(s)
mL	millilitre
MAS	maximum average score for 24, 48 and 72 hours
MIS	maximum irritation score
M/L/A	Mixer/Loader/Applicator
mm Hg	Millimeters of mercury
MOA	mode of action
MOE	margin of exposure
MROD	7-methoxyresorufin O-demethylation
MTD	maximum tolerated dose
NA	not applicable
NAFTA	North American Free Trade Agreement
NAT	N-acetyl-tyrosine
NER	non-extractable residues
NTBC	2-(2-nitro-4-trifluoromethylbenzoyl)-cyclohexane-1,3-dione
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration

NOEL	no observed effect level
OC	organic carbon
P	parental generation
PB	phenobarbital
PCPA	*Pest Control Product Act*
PCV	packed cell volume
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	Personal Protective Equipment
PXR	pregnane X receptor
RBC	red blood cell
REI	Restricted Entry Interval
rel	relative
RQ	risk quotient
SC	suspension concentrate
SRBC	sheep red blood cells
SSD	species sensitivity distribution
SULT	sulfotransferase
TAT	tyrosine aminotransferase
T_4	thyroxine
T_3	triiodothyronine
TC	Transfer co-efficient
TSH	thyroid stimulating hormone
T_{max}	time to reach maximum plasmatic concentration
TP	transformation product
TSMP	Toxic Substances Management Policy
UDP	uridine diphosphate
µg	microgram
TP	transformation product
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
USGS	United States Geological Survey
≥	equal or greater than
>	greater than
ºC	degree(s) Celsius
%	percent
WBC	white blood cells
WDG	Water dispersible granule
wk(s)	week(s)
WT	wildtype
wt	weight
♂	males
♀	females
↑	increased
↓	decreased

Appendix I Registered Products Containing Isoxaflutole in Canada[1]

Table 1 Products Containing Isoxaflutole Subject to Proposed Label Amendments

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
26141	Technical Grade Active Ingredient	BAYER CROPSCIENCE INC.	ISOXAFLUTOLE TECHNICAL	SOLID	98.0%
26142	Commercial	BAYER CROPSCIENCE INC.	CONVERGE 75 WDG HERBICIDE	WETTABLE GRANULES	75.0%
27446	Commercial	BAYER CROPSCIENCE INC.	CONVERGE PRO	SUSPENSION	480 g/L
29071	Commercial	BAYER CROPSCIENCE INC.	CONVERGE FLEXX HERBICIDE	SUSPENSION	240 g/L
32553	Commercial	BASF CANADA INC.	BALANCE BEAN HERBICIDE	SUSPENSION	480 g/L
33249	Commercial	BASF CANADA INC.	BALANCE BEAN MTZ	SUSPENSION	105 g/L
33596	Technical Grade Active Ingredient	BASF CANADA INC.	BASF ISOXAFLUTOLE TECHNICAL HERBICIDE	SOLID	98.0%

[1]as of 15 October 2020, excluding discontinued products or products with a submission for discontinuation

Appendix II Registered Commercial Class Uses of Isoxaflutole[1, 2]

Site	Listed Weeds	Formulation	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate		Maximum Number of Applications per year	Minimum Interval Between Applications (Days)
					per CROP CYCLE (g a.i./ha)	per YEAR (g a.i./ha)		
Use-site category 13 – Terrestrial Feed Crops								
Field corn (Eastern Canada and British Columbia only)	**Early Season Control of:** barnyard grass, common lamb's quarters*, smooth and large crabgrass, common ragweed* **, seedling dandelion, eastern black nightshade*, green foxtail***, seedling plantain, redroot pigweed*, annual sowthistle, spiny annual sowthistle, tall waterhemp, velvetleaf, wild mustard, witchgrass, wormseed mustard, common waterhemp*, **	Suspension	Ground equipment	53	53	105	1	NA
	Season Long Control of: common lamb's quarters*, smooth and large crabgrass, common ragweed*, **, seedling dandelion, eastern black nightshade*, seedling plantain, redroot pigweed*, annual sowthistle, spiny annual sowthistle, tall waterhemp**, velvetleaf, wild mustard, witchgrass, wormseed mustard, barnyard grass, green foxtail, common waterhemp*, **	Suspension	Ground equipment	105	105	105	1	NA
	Season Long Control: common lamb's quarters*, common ragweed*, eastern black nightshade, seedling dandelion, smooth and large crabgrass, velvetleaf, redroot pigweed*, tall waterhemp*, seedling plantain, witchgrass, wild and wormseed mustard, barnyard grass and green foxtail	Wettable granules	Ground equipment	105	105	105	1	NA
Seed corn (Eastern Canada only)	**Early Season Control of:** barnyard grass, common lamb's quarters*, smooth and large crabgrass, common ragweed*, seedling dandelion, eastern black nightshade, green foxtail***, seedling	Suspension	Ground equipment	53	53	105	1	NA

Site	Listed Weeds	Formulation	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate		Maximum Number of Applications per year	Minimum Interval Between Applications (Days)
					per CROP CYCLE (g a.i./ha)	per YEAR (g a.i./ha)		
	plantain, redroot pigweed*, annual sowthistle, spiny annual sowthistle, tall waterhemp, velvetleaf, wild mustard, witchgrass, wormseed mustard, fall panicum, lady's thumb, proso millet, wild buckwheat, yellow foxtail							
	Season Long Control of: common lamb's quarters*, smooth and large crabgrass, common ragweed*, seedling dandelion, eastern black nightshade, seedling plantain, redroot pigweed*, annual sowthistle, spiny annual sowthistle, tall waterhemp, velvetleaf, wild mustard, witchgrass, wormseed mustard, barnyard grass, green foxtail, fall panicum, lady's thumb, proso millet, wild buckwheat, yellow foxtail	Suspension	Ground equipment	105	105	105	1	NA
Isoxaflutole tolerant soybean (Eastern Canada and British Columbia only)	**Early Season Control of:** common lamb's quarters*, redroot pigweed*, common ragweed*, **, velvetleaf, wild mustard, wormseed mustard, eastern black nightshade*, green foxtail***, common waterhemp*, **, seedling plantain, seedling dandelion, witchgrass, smooth and large crabgrass, annual sowthistle, spiny annual sowthistle, barnyard grass, yellow foxtail, lady's thumb, wild buckwheat	Suspension	Ground equipment	53	53	105	1	NA

Site	Listed Weeds	Formulation	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate		Maximum Number of Applications per year	Minimum Interval Between Applications (Days)
					per CROP CYCLE (g a.i./ha)	per YEAR (g a.i./ha)		
	Season Long Control of: common lamb's quarters*, redroot pigweed*, common ragweed*, **, velvetleaf, wild mustard, wormseed mustard, eastern black nightshade*, green foxtail, common waterhemp* **, seedling plantain, seedling dandelion, witchgrass, smooth and large crabgrass, annual sowthistle, spiny annual sowthistle, barnyard grass, lady's thumb, Canada fleabane**, ****, yellow foxtail, giant ragweed**, ****, wild buckwheat	Suspension	Ground equipment	105	105	105	1	NA

[1]As of 2020-06-01, excluding discontinued products or products with a submission for discontinuation. Note that since the initiation of this re-evaluation, two new products (Reg. No's. 32553 and 33249) have been registered, but fall within the currently registered use pattern.

[2]All information is derived from registered product labels.

*Includes triazine and ALS resistant biotypes.

**Includes glyphosate resistant biotypes.

***Early season suppression only.

****Up to 10 cm in diameter/height.

Appendix III Toxicity profile and reference values for health risk assessment

Table 1 Isoxaflutole toxicology reference values for use in health risk assessment

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute Dietary	No endpoint of concern attributable to an acute exposure was identified; therefore, an ARfD was not established.		
Repeated Dietary	Co-critical studies: Two-year dietary chronic/carcinogenicity toxicity study in rat and two-generation dietary reproductive toxicity study in rat	NOAEL = 2 mg/kg bw/day Histopathological findings in the liver (♂/♀); histopathological findings in the thyroid, kidney and sciatic nerve (♂) NOAEL = 1.8 mg/kg bw/day Liver toxicity (parents), ↓ pup bw, ↓ viability index in F_1 pups	100
	ADI = 0.02 mg/kg bw/day		
Short-and intermediate-term dermal and inhalation[2,3]	Two-generation reproductive toxicity study	NOAEL = 1.8 mg/kg bw/day Liver toxicity (parents), ↓ pup bw, ↓ viability index in F_1 pups	100
Cancer	An increased incidence of hepatocellular tumours was observed in both sexes in rats and mice, as well as an increased incidence of thyroid follicular cell tumours in ♂ rats. MOAs addressing these tumours were considered sufficient to support a threshold approach to the cancer risk assessment. The reference values selected for non-cancer risk assessment are protective of these findings.		

[1]CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments.
[2]Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.
[3]Since an oral NOAEL was selected, a dermal absorption factor of 15% was used in a route-to-route extrapolation.

Table 2 Toxicity profile of technical isoxaflutole

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted).

Study Type/Animal/PMRA#	Study Results
Toxicokinetic Studies	
Absorption, Distribution, Metabolism and Excretion Sprague-Dawley Rat PMRA# 1175635	Dosing: Rats received either a single oral low dose (1 mg/kg bw), a repeat oral low dose (1 mg/kg bw/day for 14 days (unlabelled) followed by a single oral gavage dose of 1 mg/kg bw), or a single oral high dose (100 mg/kg bw) of [^{14}C]-phenyl-labelled isoxaflutole. **Absorption:** Absorption was rapid in both sexes at low and high oral doses. Maximal mean whole body concentration was achieved within 1 hr and C_{max} was directly proportional to dose. Higher maximum concentration was achieved in ♂ compared to ♀; however, T_{max} was shorter for ♀ regardless of dose level.

Study Type/Animal/PMRA#	Study Results
	Decreased absorption relative to the dose administered was observed in both sexes at the high-dose level. **Distribution:** Recovery of radioactivity in the tissues 7 days postdosing was low (1.4–4.3% of AD) indicating little potential for retention. Tissue distribution of radioactivity between the sexes was similar. In the high-dose group, the highest levels were found in the blood and plasma and to a lesser extent in the liver and kidneys of ♂ and in the liver, kidneys, lungs and heart of ♀. In the single and repeat low-dose groups, higher tissue concentrations were found in the liver and kidneys. **Metabolism and Excretion:** Isoxaflutole was rapidly and extensively metabolized. Nine metabolites were detected in the urine and eleven in the feces. There were no sex differences in metabolism. The major metabolite in both urine and feces of all dose groups was RPA 202248 (70–85% of AD). The minor metabolite RPA 203328 (0.6–3.6% of AD) was detected in urine and feces. Isoxaflutole was detected at low levels in urine and fecal extracts in the single high-dose group during the first 24 hrs (5.6–8.3% of AD). Data suggest that only Phase I reactions occurred. There was no indication of any metabolites resulting from Phase II reactions as the test substance and/or its metabolites were not eliminated as glucuronides and/or as sulphate conjugates. Elimination was rapid and dose dependent. Mean total recovery was 99%. Urinary elimination was predominant in the single and repeat low dose groups (68–74% of AD) while excretion via the feces was about 25% of AD. The major route of elimination in the high-dose group was the feces (55–63% of AD). The difference in elimination route between the low and high dose groups may reflect a proportionally lower absorption in the high-dose group, with a consequent direct fecal elimination of non-absorbed parent compound. The absorption, distribution, metabolism and excretion were not influenced by repeated oral administration.
In vitro metabolism Wistar rat and human liver microsomes PMRA# 2713620	The in vitro metabolism of [^{14}C]-phenyl-labelled isoxaflutole when incubated with rat or human liver microsomes was very similar. In both species, the metabolite Iso-2 was predominant and accounted for 98.8% and 100% of the radioactivity following metabolism in rat and human microsomes respectively**.** The identity of the Iso-2 metabolite was not confirmed in this study and therefore, no parallel can be drawn with the available in vivo metabolism study. **Supplemental-Non guideline study**
Acute Toxicity Studies	
Acute Oral Toxicity (Limit test) Sprague-Dawley Rat PMRA# 1175619	LD_{50} > 5000 mg/kg bw No deaths or clinical signs of toxicity. **Low acute oral toxicity**
Acute Oral Toxicity (Limit test) Wistar Female Rat PMRA# N/A	LD_{50} > 2000 mg/kg bw No deaths or clinical signs of toxicity. **Low acute oral toxicity**

Study Type/Animal/PMRA#	Study Results
Acute Dermal Toxicity (Limit test) Wistar Rat PMRA# N/A	LD_{50} > 2000 mg/kg bw No deaths or clinical signs of toxicity. **Low acute dermal toxicity**
Acute Dermal Toxicity (Limit test) New Zealand White Rabbit PMRA# 1175620	LD_{50} > 2000 mg/kg bw No deaths or clinical signs of toxicity. 2 ♂ and 1 ♀ exhibited very slight erythema one day postdosing. This reaction persisted in 1 ♂ for an additional 24 hrs. **Low acute dermal toxicity**
Acute Inhalation Toxicity (Whole body) Sprague-Dawley Rat PMRA# 1175621	LC_{50} > 5.23 mg/L All animals exhibited partially closed eyes and accumulated test material on their fur during testing. There was no mortality or adverse clinical signs. **Low acute inhalation toxicity**
Primary Eye Irritation New Zealand White Rabbit PMRA# 1175622	MIS = 5.83 at 1 hr MAS: 0 All eye irritation resolved by 24 hrs. **Non-irritating to the eyes**
Primary Eye Irritation New Zealand White Rabbit PMRA# 2920239	**Supplemental-Study not on file** All animals showed slight redness of the conjunctivae in the treated eye at 1 hr. The conjunctival redness in two animals persisted through 24 hrs after treatment **Minimally irritating**
Dermal Irritation New Zealand White Rabbit PMRA# 1175604	MIS = 0.17/8 at 1 hr MAS = 0 Very slight erythema was noted in one animal 1 hr after patch removal. All animals were free from dermal irritation within 24 hrs. **Non-irritating to the skin**
Dermal Irritation Female New Zealand White Rabbit PMRA# 2920239	**Non-irritating to the skin**
Dermal Sensitization – Maximization Test Dunkin-Hartley Guinea Pig PMRA# 1175606	No dermal reactions observed at 24 or 48 hrs postchallenge. **Not a dermal sensitizer**

Study Type/Animal/PMRA#	Study Results
Dermal Sensitization – (Buehler Test) Female Hartley Guinea Pig PMRA# 2920239	**Not a dermal sensitizer**
Short-Term Toxicity Studies	
28-day oral toxicity (dietary) CD1-Mouse PMRA# 1175607	**Supplemental: Range-finding, non-GLP study** **≥ 29/35 mg/kg bw/d:** ↓ creatinine, ↑ liver wt (♂/♀); ↓ bilirubin, ↑ incidence of periportal microvacuolation in the liver (slight) **(♂)** **≥ 121/143 mg/kg bw/d:** ↑ centrilobular hypertrophy (♂/♀); ↑ incidence of liver enlargement (♂); ↑ ALT (♀) **≥ 475/534 mg/kg bw/d:** ↑ ALT, ↑ AST, ↑ incidence of hepatocellular necrosis with inflammatory cell infiltrate (♂); ↑ incidence of liver enlargement (♀) **1140/1347 mg/kg bw/d**:↑ increased extra medullary hematopoiesis in the spleen, ↑ white striation in the liver, ↑ total protein (♂/♀); ↑ brown pigment deposition within liver macrophage (♂); ↑ incidence of hepatocellular necrosis with inflammatory cell infiltrate, ↑ incidence of adrenal x-zone cell vacuolation (♀)
90-day oral toxicity (dietary) CD1 Mouse PMRA# 1175608	**Supplemental: Range-finding study** **≥ 7.6/8.7 mg/kg bw/d:** ↑ liver wt (♂) **≥ 170/181 mg/kg bw/d:** ↑ incidence of periacinar hepatocytic hypertrophy (♂) **324/376 mg/kg bw/d:** ↑ ALT, AST (♂/♀); ↑ yellow staining on ventral surface, ↑ ALP, ↑ incidence of pale and enlarged liver (♂); ↑ creatine phosphokinase, creatinine, ↑ liver wt, ↑ incidence of periacinar hepatocytic hypertrophy (♀)
6 wk oral toxicity with 7 wks recovery period (dietary) CD Rat PMRA# 1175610	**Supplemental: non-guideline study with methodological limitations** **≥ 25 mg/kg bw/d:** ↑ incidence of opaque eyes, focal corneal opacity (not dose-related), ↓ ALP, AST, glucose (♂) **≥ 100 mg/kg bw/d:** ↓ urinary pH, ↓ WBC (♂); ↑ incidence of opaque eyes, focal corneal opacity (not dose-related), ↓ ALP (♀) **≥ 402 mg/kg bw/d:** ↓ bw (wk 6), ↓ bwg, ↓ fe during treatment. (♂/♀) **999/990 mg/kg bw/d:** ↓ fc during treatment (♀) Histopathological examination of the cornea was limited to 10 animals (5/sex) total. Findings observed for a few of these animals included epithelia thickening and vacuolization, sub-epithelial fibroblastic reaction and active stromal vascularization. Some evidence of recovery after 7 wks. As a result of ↑ bwg during the recovery period, there was no significant change in bw at the end of the study period. There were no histopathological findings in the liver after the recovery period. Clinical and ophthalmoscopic examination suggested that the corneal lesions were reversible; however, histopathological results suggest that long-term administration resulted in generalized thickening of the corneal epithelium. Sub-epithelial fibroblastic reaction and vascularization of the stroma were detected.

Study Type/Animal/PMRA#	Study Results
	Note: control animals were sacrificed after 17 weeks, 4 weeks later than treated groups. Therefore, organ weights cannot adequately be compared
90-day oral toxicity (dietary) CD Rat PMRA# 1175611	**NOAEL = 3/10 mg/kg bw/d (♂/♀)** **≥ 3 mg/kg bw/d:** ↑ plasma tyrosine levels; ↓ WBC (♂) (non-adverse) **≥ 10 mg/kg bw/d:** ↑ incidence of opaque eyes, corneal opacity and corneal lesions, ↓ lymphocytes, ↓ AST, ↑ histopathological findings in the cornea, ↑ periacinar hepatocytic hypertrophy (slight at this dose level) (♂) **99 mg/kg bw/d:** ↓ urinary pH, ↑ liver wt (♂/♀); ↑ incidence of dull eyes, ↓ platelets, ↑ urinary specific gravity, ↑ kidney wt (♂); ↑ incidence of opaque eyes, corneal opacity and corneal lesions, ↑ cholesterol, ↑ histopathological findings in the cornea, ↑ renal corticomedullary mineralization (♀)
8-week oral toxicity (capsule/dietary) Beagle Dog PMRA# 1175612	**Supplemental: non-guideline study** One animal/sex was dosed at 1000 mg/kg bw/d for 39 days by capsule. Following a 7-day period with no treatment, animals were dosed via the diet at ~ 1000 mg/kg bw/d for 2 wks Corneal opacity was noted in the ♀; however, it is unclear if this change was treatment-related. ↑ urinary volume during the period of dietary administration compared to the period of capsule administration **1000 mg/kg bw/d:** ↑ rel liver wt, ↑ ALP during treatment periods (♂/♀); congestion in the liver with minimal centrilobular rarefaction of hepatocytes and occasional medullary foci of mineralization in the kidney (♀).
One-year oral toxicity (dietary) Beagle Dog PMRA# 1175613	**NOAEL = 45 mg/kg bw/d (♂/♀)** **≥ 8.6/8.4 mg/kg bw/d:** ↑ liver wt (♂/♀) (non-adverse) **≥ 45/45 mg/kg bw/d:** ↑ urinary ketones (wk 26 only) (♂/♀); ↑ kidney wt, ↑ thymus involution (♂) (non-adverse) **≥ 453/498 mg/kg bw/d:** thin appearance, pale gums, ↓ terminal bw, ↓ bwg, fe, ↓ albumin, ↓ total protein, ↓ albumin globulin ratio, ↑ 5' nucleotidase, ↑ALP, ↑ALT, ↑ urinary total reducing substance and ketones, ↑ incidence of gelatinous gallbladder foci, friable liver surface (this dose only in ♂), ↑ hepatocellular swelling, ↑ prominent hematopoiesis in the sternum and femur, ↑ thyroid follicular cell hypertrophy (♂/♀); ↑ spleen wt, ↑ rel thyroid wt, ↑ incidence of pale mucous membranes and/or gums, ↑ pale mottling of outer spleen surface, ↑ centrilobular necrosis and fibrosis. (♂); ↓ hematocrit, ↓ hemoglobin, ↓ RBCs from Wk 26 onwards, ↑ incidence of clumping and margination of centrilobular staining and vacuolated hepatocytes, ↑ thymus involution. (♀) **1265/1254 mg/kg bw/d:** all ♂ sacrificed after 26 wks due to apparent anaemia suspected from pale gums, ↓ hematocrit, hemoglobin and RBCs wk 13 onwards (confirmed anemia), ↑ reticulocyte, ↓ PCV, evidence of polychromasia, hypochromasia and anisocytosis on wk 26, ↑ ALT, ↑ incidence of dark thyroid, ↑ incidence of dilated centrilobular sinusoids and centrilobular glycogen depletion, ↑ extramedullary hematopoiesis in the liver and spleen, ↓ spermatogenesis, multinucleated cells in testes tubules and spermatids in majority of tubules in epididymides, ↑ round spermatids in epididymides, overall, terminal examination suggested intravascular hemolysis in these animals (♂); ↑ kidney wt, ↑ incidence of

Study Type/Animal/PMRA#	Study Results
	pale mucous membranes and/or gums, ↑ incidence of pale mottling of outer spleen surface, ↓ corpora lutea (♀)
21-day dermal toxicity CD Rat PMRA# 1175609	**NOAEL ≥ 1000 mg/kg bw/d** **1000 mg/kg bw/d:** ↑ liver wt (non-adverse)
Chronic Toxicity/Oncogenicity Studies	
18-month oncogenicity (dietary) CD-1 Mouse PMRA# 1175623 1175624	**NOAEL = 3.2/4.0 mg/kg bw/d (♂/♀)** **Non-neoplastic effects:** **≥ 64/78 mg/kg bw/d:** ↓ terminal bw, ↓ overall bwg (♂/♀); ↑ yellow/urine staining, ↑ hepatocyte necrosis at termination, ↑ periacinar hepatocytic hypertrophy at interim sacrifice (♂) **977/1161 mg/kg bw/d:** ↓ bw (wk 4 onwards ♂; wk 13 onwards ♀), ↓ fe during the first 14 wks, ↑ liver wt from wk 26 onwards, ↑ liver masses, ↑ extramedullary hematopoiesis in the spleen, ↑ amyloidosis in the duodenum, ileum, jejunum, kidneys, heart, thyroid and lymph nodes at termination, ↑ pigment laden Kupffer cells,↑ erythrocyte in hepatocytes, ↑ liver basophilic foci, ↑ periacinar hepatocytic hypertrophy (wk 26 and termination) (♂/♀); ↑ adrenal wt (wk 52 and 78), ↑ area of change in the liver and abdominal distension, ↑chronic myocarditis, ↑ pigment laden hepatocytes,↑ liver cell ploidy (♂); ↑ adrenal wt, ↑ pigment laden lymph node macrophage, ↑ necrosis of individual hepatocytes (wk 26 onwards), ↑ periacinar hepatocytic fatty vacuolation (♀) **Neoplastic effects:** **977/1161 mg/kg bw/d:** ↑ incidence of combined hepatocellular adenoma and carcinoma, ↑ incidence of fatal tumours, ↑ incidence of hepatocellular carcinoma, ↓ time to first liver carcinoma appearance (♂/♀) **Hepatic adenoma:** Overall incidence in ♂ receiving 0, 3.2, 64, 977 mg/kg bw/d was: 17%, 19%, 9/52, **52%*** respectively [HC range 3.8–23.1%]. Overall incidence in ♀ receiving 0, 4, 78, 1161 mg/kg bw/d was: 0%, 2%, 2%, **29%*** respectively [HC range = 0–2%] **Hepatic carcinoma** Overall incidence in ♂ receiving 0, 3.2, 64, 977 mg/kg bw/d was: 8%, 10%, 15%, **33%*** respectively [HC range = 1.9–11.5%]. Overall incidence in ♀ receiving 0, 4, 78, 1161 mg/kg bw/d was: 0%, 0%, 0%, **7.6%*** respectively [HC range = 0–2%] **Hepatic adenoma/carcinoma combined** Overall incidence in ♂ receiving 0, 3.2, 64, 977 mg/kg bw/d was: 25%, 29%, 27%, **73%*** respectively Overall incidence in ♀ receiving 0, 4, 78, 1161 mg/kg bw/d was: 0%, 2%, 2%, **35%*** respectively * statistically significant (by pair-wise comparison) $p<0.05$ **Evidence of Carcinogenicity**

Two-year chronic toxicity/ carcinogenicity (dietary) Crl: CD Rat PMRA# 1175625, 1175626, 1175627, 2713643, 2713644, 2836476	**NOAEL = 2 mg/kg bw/d (♂/♀)** Interim sacrifice at 52 wks. Additional group treated for 52 wks and allowed to recover for 8 wks prior to sacrifice. **Non-neoplastic effects:** **≥ 0.5 mg/kg bw/d:** ↑ corneal keratitis (♂) (non-adverse) **≥ 20 mg/kg bw/d:** ↑ incidence of periacinar hepatocytic hypertrophy, ↑ portal tract changes in bile duct, ↑ liver wt (♂/♀); ↑ corneal lesion (opacity, vascularization), ↑ incidence of opaque eyes, ↑ thyroid wt, ↓WBC and lymphocytes wks 24 and 52 (non-adverse), ↑ incidence of enlarged thyroid, ↑ increase thickening of the eye epithelium (decedent and termination combined), ↑ liver focal cystic degeneration, ↑ mid-zonal foamy hepatocyte site, ↑ incidence of enlarged thyroid with masses, ↑ cystic thyroid follicular hyperplasia, ↑ incidence of progressive nephropathy, ↑ axonal/myelin degeneration and cholesterol cleft/granuloma of the sciatic nerve and associated focal degeneration and chronic inflammation of the thigh muscle (♂) **500 mg/kg bw/d:**↑ thin appearance, abnormal gait and limited used of limbs from wk 91 onwards, ↑ urine staining, ↑ brown staining on tail, ↓ bw, ↓ bwg, ↓ fe for the first 14 weeks, ↓ AST wk 6–50, ↑ total protein,↑α-1 globulin, ↓ urinary pH, ↑ urinary specific gravity and reducing substance, ↑ kidney and heart wt, ↓ thymus wt, ↑ incidence of area of change in lungs, swollen liver and liver masses, ↑ incidence of macrophage accumulation in the lungs (♂/♀); ↑ cholesterol, ↑ thyroid wt (interim and termination), ↑ incidence of area of change in the liver, ↑ incidence of opaque eyes (decedent), ↑ incidence of dark thyroid and thyroid nodules , ↑ progressive nephropathy. (♂); ↑ hunched posture, ↑ ungroomed coat from wk 32 onwards, ↓ fc (slight), ↓ ALP and ALT (slight), ↑ urinary ketone bodies (wks 50 and 77), ↑ uterus/cervix wt, ↑ incidence of cystic thyroid follicular hyperplasia, ↑ incidence of focal degeneration and chronic inflammation of the thigh muscle, ↑ incidence on endometrial polyp. (♀) **Interim at 52 weeks:** **≥ 2 mg/kg bw/d:** ↑ total cholesterol (♀) **≥ 20 mg/kg bw/d:** ↑ liver wt, ↑ incidence of swollen liver, ↑ periacinar hepatocytic hypertrophy, ↑mid-zonal foamy hepatocytes (♂) **500 mg/kg bw/d:** ↑ thin appearance, opaque eyes, brown staining on tail, ↓ terminal bw (♂: -14%, ♀: - 27%), ↓ bwg (♂: -18%, ♀: - 43%), ↑ corneal opacity, vascularization and ghost vessels, ↓ AST, ↑ total protein, ↑ α-1 globulin, β-globulin, ↓ A/G ratio, ↓ urinary pH, ↑ urinary specific gravity, ↑ incidence of urinary reducing substance, ↑ pigment laden hepatocytes. (♂/♀); ↑ cholesterol, ↑ thyroid wt, ↑ keratitis, superficial exfoliation of epithelial cells, epithelial thickening and sub-epithelial fibroblastic reaction in cornea, ↑ vascularisation of corneal stroma (♂); ↑ ungroomed coat from wk 32 onwards, ↓ ALP, ALT, ↑ urinary ketone bodies, ↑ liver wt, ↑ rel thyroid wt, ↑ periacinar hepatocytic hypertrophy, ↑ mid-zonal foamy hepatocytes, ↑ incidence of endometrial polyp (♀) **Treated for 52 wks followed by 8 wks of recovery:** **≥ 2 mg/kg bw/d:** ↑ total cholesterol (♀) **≥ 20 mg/kg bw/d:** no significant change in liver wt, ↓ histopathological findings in the liver (♂)

	500 mg/kg bw/d: ↓ number of animal with opaque eyes, ↓ bw, ↑ bwg, regression of corneal lesions (↓ number of animals with corneal opacity and vascularization, ↑ ghost vessels), no treatment-related urinalysis findings. (♂/♀); no treatment-related clinical chemistry findings, no significant change in thyroid wt, ↓ number of animals with keratitis, superficial exfoliation of epithelial cells, epithelial thickening and sub-epithelial fibroblastic reaction in the cornea (♂); No increase in un-groomed coat observed, ↓ albumin, ↑ α-1 globulin, β-globulin, ↓ A/G ratio, ↑ thyroid wt, no change in liver wt, ↑ incidence of area of change in lungs, ↓ histopathological findings in the liver (♀) **Neoplastic effects:** **Hepatic adenoma:** Overall incidence in ♂ receiving 0, 0.5, 2, 20, 500 mg/kg bw/d was: 2.7%, 4%, 6.7%, 8%, **18.7% **** respectively [HC range = 0–10%], ↓ tumour latency at the high-dose level. Overall incidence in ♀ receiving 0, 0.5, 2, 20, 500 mg/kg bw/d was: 5.3%, 2.7%, 1.3%, **39.2%**** respectively [HC range = 0–3.6%] **Hepatic carcinoma** Overall incidence in ♂ receiving 0, 0.5,2, 20, 500 mg/kg bw/d was: 6.7%, 1.4%,5.3%, 2/75, **22.7%**** respectively [HC range = 0–3.6%], Overall incidence in ♀ receiving 0, 0.5, 2, 20, 500 mg/kg bw/d was: 0%, 0%, 1.3%, 0%, **32.2%**** respectively [HC range = 0–3.6%] **Hepatic adenoma/carcinoma combined** Overall incidence in ♂ receiving 0, 0.5, 2, 20, 500 mg/kg bw/d was: 8.3%, 5.3%, 12%, 10.7%, **41.3%***** respectively Overall incidence in ♀ receiving 0, 0.5, 2, 20, 500 mg/kg bw/d was: 5.3%, 2.7%, 2.7%, 0%, **32.2%**** respectively **Thyroid follicular cell adenoma** Overall incidence in ♂ receiving 0, 0.5, 2, 20, 500 mg/kg bw/d was: 4.1%, 1.3%, 6.8%, 9.3%, **20%**** respectively [HC range = 0–6.4%] Overall incidence in ♀ receiving 0, 0.5, 2, 20, 500 mg/kg bw/d was: 1.4%, 0/73, 1.4%, 5.5%, 4.1% respectively [HC range = 0–2.0%] **Thyroid follicular cell adenoma/carcinoma combined:** Overall incidence in ♂ receiving 0, 0.5, 2, 20, 500 mg/kg bw/d was: 3/74 (4.1%), 2/72 (1.3%), 7/74 (9.5%), 8/75 (10.7%), **18/75 (20%)**** respectively [HC mean (♂) = 3.04%; range = 0–6.4%] Overall incidence in ♀ receiving 0, 0.5, 2, 20, 500 mg/kg bw/d was: 1.4%, 1.4%, 2.7%, 5.5%, **6.8%**** respectively **Endometrial adenomas and carcinomas (combined)** Overall incidence at 0, 0.5, 2, 20, 500 mg/kg bw/d was 0, 0, 0, 0, **5 (2** adenomas (2.7%) and 3 carcinomas (6.6%)) respectively [HC range 0–1.7%, for adenoma, 0-2% for carcinoma] **** statistically significant at p < 0.01 (pair-wise)** ***** statistically significant at p < 0.001 (pair-wise)** **Evidence of Carcinogenicity**

Study Type/Animal/PMRA#	Study Results
Developmental/Reproductive Toxicity Studies	
Pilot one-generation reproductive toxicity (dietary) CRL:CD Rat PMRA# 1175629	**Supplemental: Dose range-finding study** **≥ 20 mg/kg bw/d:** ↓ bw in P animals throughout treatment, ↓ overall bwg (♂) **500 mg/kg bw/d:** ↓ bw in F_1 animals postlactation, ↑ corneal keratitis from LD 35–49 onwards in F_1 (♂/♀)**;** ↓ fc during premating (slight) **(**♂**);** ↓ bw in P ♀ throughout treatment, ↓ overall bwg, ↓ fc during lactation (slight), ↑ corneal keratitis wk 13 in P (♀) **Reproductive Toxicity** **500 mg/kg bw/d:** ↓ pups/litter, ↓ litter wt at birth (slight) **Offspring Toxicity** **500 mg/kg bw/d:** ↓ mean bw in F_1, ↓ overall bwg, ↓ viability index, ↑ pups dying PND 0–4
Two-generation reproductive toxicity (dietary) CRL:CD Rat PMRA# 1175630 1175631 2713645	**Parental Toxicity** **Parental NOAEL = 1.8/1.8 mg/kg bw/d (**♂/♀**)** **≥ 17/18 mg/kg bw/d:** ↑ liver wt in P animals, ↑ incidence of centrilobular hepatocellular hypertrophy in P and F_1 (♂/♀); ↑ hepatocellular vacuolation in P and F1 (♂); ↓ bw in F_1 generation during early lactation (♀) **414/434 mg/kg bw/d:** ↓ bw in P and F_1 animals throughout the study, ↓ bwg in P and F_1 animals throughout the study, ↑ chronic corneal keratitis in F_1 and F_2 postweaning, ↑ liver wt in F_1 adults, ↑ incidence of mottled liver and large renal pelvis in P and F_1 adults, ↑ incidence of subacute corneal inflammation in P and F_1 adults (♂/♀); ↓ fc in P and F_1 premating (♂); ↓ fc in P and F_1 premating, gestation and lactation, ↑ ovarian cyst in F_1, ↑ incidence of pup with no milk in stomach (♀) **Reproductive Toxicity** **Reproductive NOAEL = 18 mg/kg bw/d (**♂/♀**)** **434 mg/kg bw/d:** ↑ stillborn pups in F_1, ↓ litter weight at birth in both F_1 and F_2 **Offspring Toxicity** **Offspring NOAEL = 1.8 mg/kg bw/day** **≥ 18 mg/kg bw/d:** ↓ pup bw, ↓ PND 4 viability index in F_1, ↑ number of pups dying between PND 0-4 in F_1 **434 mg/kg bw/d:** In F_1 and F_2: ↑ cannibalized pup between PND 0–4, ↑ number of pups dying between PND 0–4, ↑ incidence of pup with no milk in stomach and with under developed renal papilla on PND 4, In F_2: ↓ viability index, ↑ incidence of chronic keratitis, ↑ incidence of eye inflammation, retinal bleeding (♂/♀); ↑ incidence of large renal pelvis in weanlings (♀) **Serious effect in the presence of maternal toxicity**
Developmental Toxicity (gavage) Sprague-Dawley Rat	**Maternal NOAEL = 100 mg/kg bw/d** **Maternal Toxicity:** **500 mg/kg bw/d:** ↑ salivation postdosing, ↓ bwg during treatment, ↓ fc during and post-treatment

Study Type/Animal/PMRA#	Study Results
PMRA# 1175632, 2713622	**Developmental NOAEL = 10 mg/kg bw/d** **Developmental Toxicity:** **≥ 100 mg/kg bw/d:** ↓ fetal wt/litter, ↑ incidence of small fetuses, ↑ incidence of incomplete sternebra, ↑ incomplete ossification of three sternebra, ↓ ossification of metacarpals/metatarsals, ↑ occurrence of 14th ribs **500 mg/kg bw/d:** ↑ incidence of subcutaneous hemorrhage, and oedema, ↓ incidence of 13 rib pairs, ↑ incomplete ossification of caudal vertebra, 1st thoracic vertebral centrum and metacarpals/metatarsal, ↑ incidence of pale rimmed placenta, ↑ incidence of asymmetric pelvis (slight) **Sensitivity of the young** **No evidence of malformations**
Developmental Toxicity (gavage) New Zealand White Rabbit PMRA# 1175633 PMRA# 2713623 2830346	**Maternal Toxicity:** **Maternal NOAEL = 20 mg/kg bw/d** **100 mg/kg bw/d:** ↓ fecal output, ↓ bw on GD 18, ↓ bwg, ↓ fc, ↑ resorption (late), ↑ post-implantation loss **Developmental** **NOAEL = 5 mg/kg bw/d** **Developmental Toxicity:** **≥ 20 mg/kg bw/d**: ↑ incidence of 27th pre-sacral vertebrae, ↑ incidence of 13 pairs of ribs, ↓ ossification of heads of long bones **100 mg/kg bw/d:** ↓ live fetus litter, ↑ resorption (late), ↑ post-implantation loss, ↑ incidence of incomplete ossification of pubic bones, ↑ incidence of medium anterior fontanelle, ↑ incidence of rudimentary ribs, ↑ incidence of un-erupted incisors **Sensitivity of the young** **No evidence of malformations**
Genotoxicity Studies	
Bacterial Reverse Mutation Assay Salmonella typhimurium TA98, TA100, TA1535, TA 1537, TA1538 PMRA# 1175644	**Negative with or without metabolic activation**
In vitro cell gene mutation test L5178Y TK$^{+/-}$ Mouse Lymphoma Cells PMRA# 1175650	**Negative with or without metabolic activation**
Point Mutation Assay V79 Chinese Hamster Embryonic Lung Cells PMRA# 1175651	**Negative with or without metabolic activation**

Study Type/Animal/PMRA#	Study Results
In vitro chromosomal aberration assay Human Peripheral Lymphocytes PMRA# 1175653	**Negative with or without metabolic activation**
In vitro chromosomal aberration assay Human Peripheral Lymphocytes PMRA# 1175654	**Negative with or without metabolic activation**
Micronucleus Test - Gavage CD1-Mouse Bone Marrow Cells PMRA# 1175655	**5000 mg/kg bw:** 1 mouse (sex not specified) showed piloerection and hunched posture immediate before scheduled sacrifice, 24 hrs after dosing. **Negative**
In vivo/in vitro unscheduled DNA synthesis Sprague-Dawley Rat PMRA# 2713642	**Negative for unscheduled DNA synthesis**
Neurotoxicity Studies	
Acute Neurotoxicity (gavage) Albino Rat PMRA# 1175637, 2713646	**NOAEL = 2000 mg/kg bw** ≥ **500 mg/kg bw**: ↓ bwg (♂) (non-adverse) **2000 mg/kg bw**: ↓ bwg (♀) (non-adverse) **No evidence of selective neurotoxicity**
90-day Neurotoxicity (Dietary) Albino Rat PMRA# 1175638, 2713646	**NOAEL = 25/750 mg/kg bw/d (♂/♀)** ≥ **250 mg/kg bw/d:** ↓ bw, ↓ bwg (♂) **750 mg/kg bw/d:** One ♂ sacrificed moribund (♂); ↓ bwg (♀) (non-adverse) **No evidence of selective neurotoxicity**
Developmental Neurotoxicity (gavage) Crl:CD Rat PMRA# 2713619	**Acceptable non-guideline due to the lack of brain morphometric analyses** **Maternal Toxicity:** **NOAEL = 25 mg/kg bw/d** **250 mg/kg bw/d:** ↓ bw, ↓ bwg, ↓ fc **Offspring Toxicity:** **NOAEL = 25 mg/kg bw/d** **250 mg/kg bw/d:** ↓ pup survival, ↓ bw, ↓ bwg, ↓ abs brain wt at PND 11(♂/♀); slight delay in balanopreputial separation, ↓ abs brain wt PND 72 (♂) **No evidence of selective neurotoxicity**

Study Type/Animal/PMRA#	Study Results
Immunotoxicity Studies	
28-day immunotoxicity (dietary) Sprague-Dawley Rat PMRA# 2713618	**Supplemental due to poor stability of the test compound and high variability in the SRBC assay.** **279 mg/kg bw/d:** ↓ bwg, ↓ thymus wt (equivocal) (♂)
Special Studies (non-guideline): Ocular Toxicity/Tyrosinaemia	
14-day biochemical investigation of free plasma amino acid levels (dietary) CD Mouse PMRA# 1175643	Supplementation of the diet with isoxaflutole did not result in a significant change in free amino acid levels. Effects on tyrosine concentrations were assessed in a separate study.
14-day biochemical investigation of free plasma amino acid levels (dietary) CD Rat PMRA# 1175645	Supplementation of the diet with isoxaflutole did not result in a significant change in free amino acid levels. Effects on tyrosine concentrations were assessed in a separate study.
14-day biochemical investigation of plasma tyrosine levels (dietary) CD Mouse PMRA# 1175643	Doses: 0, 23, 91, 364, 900 mg/kg bw/d Tyrosine levels ↑ fivefold as compared to controls with no evidence of dose-response.
14-day biochemical investigation of plasma tyrosine levels (dietary) CD Rat PMRA# 1175645	Doses: 0, 10, 100, 400 mg/kg bw/d Tyrosine levels ↑ threefold as compared to controls with no evidence of dose-response.
Qualitative comparison of Tyrosine Metabolism (gavage) ♂ CD Rat ♂ CD-1 Mouse PMRA# 1175672	Dosing: A single dose of isoxaflutole (10 mg/kg bw) was administered. One hour after, ^{14}C-tyrosine was administered (500 mg/kg bw) **Excretion:** Urinary excretion was the predominant route of elimination of tyrosine in mice (mice: 46.79% AD; rats: 15.70% AD), with the majority of the radioactivity being excreted in first 12 hrs. A significant portion of radioactivity was eliminated in expired air in rats as CO_2 (rat: 17.04% AD, mice 6.47% AD) in the 48 hrs following administration. Excretion in expired air occurred at a constant rate in mice, while in rats, excretion was highest at the later sampling intervals. **Metabolism:** In urine, higher amounts of 4-hydroxyphenyl lactic acid (HPLA) and 4-hydroxyphenyl acetic acid (HPAA) were observed in mice as compared to rats. Some metabolites were eliminated as glucuronides and/or sulphates in urine, but

Study Type/Animal/PMRA#	Study Results
	HPLA and HPAA were not observed as conjugates. This study demonstrated species related qualitative and quantitative differences in the excretion of tyrosine in rats and mice following single dose administration of isoxaflutole.
One-Week Tyrosine Tolerance (gavage) ♂ CD Rat PMRA# 1175674	Dosing: A single dose of isoxaflutole or NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-cyclohexane-1, 3-dione) (10 mg/kg bw) was administered followed by ^{14}C-Tyrosine (500 mg/kg bw) on Days 1, 2, 3 and 8 postdosing. Pre-treatment of rats with isoxaflutole or NTBC increased the urinary excretion of tyrosine metabolites: NAT (N-acetyl-tyrosine), 4-HPAA and 4-HPLA. The effect of isoxaflutole was reversible after 48 hours while effects from NTBC were still evident 8 days after termination of exposure.
Short-term effect of tyrosine supplementation (dietary) CD rat Brown Norway Rat CD1 Mouse PMRA# 1175675	Animals were administered either basal diet or diet supplemented with 2 or 5% tyrosine for 14 days. Plasma tyrosine levels were increased following tyrosine supplementation in both strains of rats but not in mice. CD rats appear to be more sensitive than Brown Norway rats to the increase in tyrosine levels. Slight corneal opacities was observed in ♂ Brown Norway rats while slight to very severe corneal opacity was noted in ♂ CD rats.
In vitro enzyme inhibition assay CD ♂ Rat liver PMRA# 1175657	In this study, the ability of NTBC, isoxaflutole and RPA 202248 to inhibit the conversion of HPPA to homogentisate by HPPD in vitro was determined. Rat liver HPPD was inhibited by RPA 202248, NTBC but not isoxaflutole NTBC I_{50} = 59 nM RPA 202248 I_{50} = 131 nM
Effect of NTBC and L-Tyrosine supplementation on blood tyrosine levels (gavage) ♀ Sprague-Dawley Rat PMRA# 2713626	Dosing: Animals were administered NTBC for 18 days by gavage. Diets were supplemented with 2% L-tyrosine from day 15-19. Blood samples were collected on day 15 and 19. **≥10 µg/kg bw/d NTBC+ tyrosine supplementation:** ↑ blood tyrosine levels, ↑ incidence of white area in the eyes
Developmental Toxicity Sprague-Dawley Rat PMRA# 2713628/1189892	Dosing: 0, NTBC (10 µg/kg bw/d), NTBC (10 µg/kg bw/d) + L-tyrosine (dietary supplementation) **Maternal** **L-tyrosine:** ↓ bwg, ↑ tyrosine blood levels **NTBC**: ↓ bwg, ↑ mottled kidneys, ↑ tyrosine blood levels **NTBC+L-tyrosine**: ↓ bwg, ↓ fc, ↑ mottled kidneys, ↑ opaque eyes ↑ tyrosine blood levels. **Offspring** **NTBC+L-tyrosine**: ↓ fetal wt, ↑ incidence of skeletal variation (delayed and incomplete ossification)

Study Type/Animal/PMRA#	Study Results
Effect of NTBC on cellular level of tyrosine and HPLA in vitro rat (Wistar), Dog (Beagle), rabbit (New Zealand White), mouse (CD-1) and human LiverbeadsTM PMRA# 2716329/1189897	Rat, dog, rabbit Liverbeads™: minimal HPLA detected after incubation with NTBC; deficient alternate tyrosine metabolic pathway Mouse and human Liverbeads™: HPLA detected, level increased with time of incubation with NTBC; efficient alternate tyrosine metabolic pathway Conclusions: No clear evidence of increased tyrosine levels due to inhibition of HPPD by NTBC. This demonstrates the presence of an efficient alternate tyrosine metabolic pathway in mouse and human hepatocytes but not in rat, dog, or rabbit hepatocytes.
Short-term effect of tyrosianemia on organs (gavage/dietary) Wistar Rat PMRA# 2713627	Dosing: 0, 20000 ppm L-tyrosine (dietary), 20000 ppm L-tyrosine (dietary)+NTBC 10 µg/kg bw/d (gavage) for 28 days **L-tyrosine group:** ↑ plasma tyrosine **NTBC:** ↑ plasma tyrosine on day 28 and termination **NTBC +L-tyrosine**: minimal to slight bilateral ocular opacity, diffuse interstitial mixed cell inflammation in the pancreas, ↑ focal/multifocal acinar degeneration and apoptosis in the pancreas, colloid alteration of thyroid follicles
Mechanistic Studies: Tumour MOA - Supplemental	
2 or 13-week Oral Toxicity (dietary) Sprague-Dawley Rat PMRA# 2713625	**After 2 weeks:** **≥ 200 mg/kg bw/d:** ↑ liver wt, ↑ BrdU labelling index **After 13 weeks:** **≥ 50 mg/kg bw/d:** ↓ fc **≥ 200 mg/kg bw/d:** ↓ bw, ↑ liver wt, ↑ BrdU labelling index **After 14-day recovery:** Reversal of hepatocellular proliferation. Partial recovery of bw effects in the 13-week treatment group.
7-Day Oral Toxicity (dietary) Sprague-Dawley (WT) and PXR KO/CAR KO Rat PMRA# 2737967	**WT:** **513/429 mg/kg bw/d:** ↓ bw, ↓ bwg, ↓ fc, ↑ liver wt, ↑ hepatocellular hypertrophy and mitosis, ↓ liver glycogen ↑ thyroid follicular hypertrophy, ↑ liver BrdU labelling index, ↓ direct bilirubin, ↓ total and free T4, ↑ total P450, ↑ PROD, BROD and BQ activity, ↑ CYP2B1, CYP2B2, CYP3a1, UGT2B1, UGT1a6, EPHX and GSTM4 transcripts in the liver (♂/♀); ↓ total and free T_3, ↑ TSH, ↓ LAH and ↑ T_4-UGT activity, ↓ CYP4A1, SULT2A2, ↑ TSH beta transcript in the pituitary (♂) **PXR KO/CAR KO** **425/460 mg/kg bw/d** ↓ bw, ↓ bwg, ↓ fc, ↓ EROD, ↓ BROD, ↑ UGT1A6, ↓ total and free T_4, ↓ T_3 (♂/♀);↓ liver glycogen, ↑ liver BrdU labelling index (slight), ↓ total CP450, ↑ BQ, ↑SULT2A2 (♂). Proliferation in the liver of PXR/CAR double KO was significantly less than the proliferation observed in WT animals. Additionally, changes in T_4 and T_3 concentration in PXR/CAR double KO did not correlate with changes in plasma TSH levels or increases in TSHb transcripts in the pituitary.
Enzyme levels and DNA synthesis (In vitro) Primary human hepatocytes	**≥ 1 µM:** ↑ PROD, ↑ BROD (no dose-response) (♂); ↑ BQ (♀) **≥ 30 µM:** ↑BQ (♂); ↑ BROD (no dose-response) (♀)

Study Type/Animal/PMRA#	Study Results
PMRA# 2737968, 2737966	**≥ 300 µM:** ↓ ATP levels indicating cytotoxicity, ↓ DNA synthesis **Positive controls:** **PB:** ↑ PROD, ↑ BROD, ↑BQ **EGF:** ↑ DNA synthesis Positive controls behave as expected. Overall the results suggest that isoxaflutole induced of CYP3A (and CYP2B to a lesser extent) activity in ♂/♀ human hepatocyte cultures without a concomitant increase in DNA synthesis
Enzyme levels and DNA synthesis (In vitro) Primary rat (Sprague-Dawley) hepatocytes PMRA# 2737969, 2737964	**≥ 1 µM:** ↑ DNA synthesis (♀) **≥ 3 µM:** ↑ DNA synthesis (♂) **≥ 10 µM:** ↑ PROD and BROD activity (dose-dependent up to cytotoxic doses) **≥ 30 µM:** ↑ BQ activity (♀) **≥ 100 µM:** ↑ BQ activity (♂) **≥ 300 µM:** ↓ ATP levels indicating cytotoxicity **Positive controls:** **PB:** ↑ DNA synthesis at all dose levels, ↑ PROD, BROD, BQ activity at all dose levels **EGF:** ↑ DNA synthesis Overall the results suggest that, like phenobarbital, isoxaflutole induced both CYP2B and CYP3A enzyme activities in ♂/♀ SD rat primary hepatocyte cultures. Isoxaflutole also induced replicative DNA synthesis in a dose-dependent manner in hepatocyte cultures (up to 30 µM in ♂ and 10µM in ♀). The induction levels then fell in hepatocytes from both sexes possibly due to cytotoxicity.
Enzyme levels and DNA synthesis Primary mouse (CD-1) hepatocytes PMRA# 2737970, 2737965	**≥ 0.1 µM:** ↑ BROD (♂); ↑ PROD, ↑ DNA synthesis (♀) **≥ 0.3 µM:** ↓ ATP levels indicating cytotoxicity, ↑ DNA synthesis (♂); ↑ BROD (♀) **≥ 30 µM:** ↓ ATP levels indicating cytotoxicity (♀) **Positive controls** **PB:** ↑ PROD, ↑ BROD, ↑ BQ (♂/♀); ↑ DNA synthesis (♂) **EGF:** ↑ DNA synthesis Overall the results suggest that isoxaflutole induced CYP2b enzyme activity in and replicative DNA synthesis in ♂/♀ CD-1 mouse primary hepatocyte cultures.
7-Day Oral Toxicity (dietary) C57BL6 Mouse (WT) and PXR KO/CAR KO Mouse PMRA# 2737971	**WT:** **1225/1546 mg/kg bw/d:** ↑ liver wt, ↑ hepatocellular hypertrophy and mitosis, ↓ liver glycogen, ↑ liver BrdU labelling index, ↓ direct bilirubin, ↑ total CYPP450, ↑ PROD, BROD, EROD, BQ and LAH (slight) activity, ↑ CYP1A2, CYP2B10, CY3A11, EPHX1 and GSTM4 transcripts in the liver **PXR KO/CAR KO** **1288/1526 mg/kg bw/d:** No changes in liver wt or histopathological finding in the liver, ↓ EROD and BROD activity, ↑ CYP4A10 and CYP4A14 transcripts in the liver (♂/♀); ↑ liver BrdU labelling index, ↑ LAH(♂)

Study Type/Animal/PMRA#	Study Results
2-week oral toxicity (dietary) ♂ Sprague-Dawley Rat PMRA# 1175667	**500 mg/kg bw/d:** ↓ T_4, ↑ ^{125}I-thyroxine elimination rate, ↑ ^{125}I-thyroxine systemic clearance, ↑ thyroid wt, ↑ liver wt, ↑ liver enlargement, ↑ microsomal protein, ↑ CYP450, ↑ PROD and UGT activity in the liver **Positive control:** **Phenobarbital:** ↓ T_4, ↑^{125}I-thyroxine systemic clearance, ↑ thyroid wt, ↑ liver wt, ↑ liver enlargement, ↑ microsomal protein, ↑ CYP450, ↑ PROD and UGT activity in the liver, This study is supportive of the hypothesis that thyroid tumours in male rats are secondary to the effects on the liver and isoxaflutole perturbs thyroid hormone axis
2-week oral toxicity (dietary) CD-1 Mouse PMRA# 1175677	**≥ 23 mg/kg bw/d:** ↑ PROD and BROD activity **≥ 91 mg/kg bw/d:** ↑ liver wt, ↑ total CYP450, ↑ MROD activity **≥ 364 mg/kg bw/d:** ↑ EROD activity **910 mg/kg bw/d:** ↑ lauric acid 11-hydroxylase and lauric acid 12-hydroxylase activity When the data was normalized to CYP450, only PROD and BROD activity were statistically significantly increased at doses ≥91 and ≥ 364 mg/kg bw/d respectively.
2-week oral toxicity (dietary) Sprague-Dawley Rat PMRA# 1175678	**≥ 10 mg/kg bw/d:** ↑ total CP450, ↑ PROD, BROD and EROD activity. **≥ 100 mg/kg bw/d:** ↑ liver wt **400 mg/kg bw/d:** ↑ liver wt, ↑ lauric acid 11-hydroxylase and lauric acid 12-hydroxylase activity When the data was normalized to total CYP450, PROD and BROD activity were statistically significantly increased at doses ≥10mg/kg bw/d, EROD activity was statistically significantly reduced at the highest dose level and there was no significant change in LAH-11, or LAH 12 activity.
Metabolite-RPA 202248	
Acute oral toxicity (gavage) Sprague-Dawley Rat PMRA# 1175641	LD_{50} >5000 mg/kg bw **5000 mg/kg bw:** 2 ♀ and 2 ♂ died during the first two day of treatment. Clinical signs of toxicity on the day of dosing included palpebral ptosis, piloerection, and reduced motor activity.
Bacterial Reverse Mutation Assay Salmonella typhimurium TA98, TA100, TA1102, TA 1535, TA1537 PMRA# 1175648	Slight cytotoxicity at 5000 µg/plate +/-S9 activation **NEGATIVE for reverse gene mutations with or without metabolic activation.**

Study Type/Animal/PMRA#	Study Results
Metabolite-RPA 203328	
Acute oral toxicity (gavage) Sprague-Dawley Rat PMRA# 1175642	LD_{50} >5000 mg/kg bw **5000 mg/kg bw:** No mortalities or treatment-related clinical observations.
14-day oral toxicity (gavage) Sprague-Dawley PMRA# 2920239	**NOAEL ≥ 1000 mg/kg bw/d** **≥ 300 mg/kg bw/d:** ↑ salivation postdosing
28-day oral toxicity (dietary) Sprague-Dawley Rat PMRA# 175656	**NOAEL ≥ 1118/1269 mg/kg bw/d (♂/♀)** No treatment-related findings.
90-day oral toxicity (dietary) Sprague-Dawley Rat PMRA# 1189936	**NOAEL ≥ 769/952 mg/kg bw/d (♂/♀)** No treatment-related findings.
Developmental Toxicity (Gavage) Sprague-Dawley Rat PMRA# 1189948	**Maternal NOAEL = 75 mg/kg bw/d** **≥ 250 mg/kg bw/d**: ↑ clinical signs (salivation), ↓ fc, ↓ bw, ↓ bwg **≥ 750 mg/kg bw/d**: ↑ red nasal discharge **Developmental NOAEL ≥ 750 mg/kg bw/d** No treatment-related findings **No sensitivity of the young** **No evidence of treatment-related malformations**
Bacterial Reverse Mutation Assay Salmonella typhimurium TA98, TA100, TA1102, TA 1535, TA1537 PMRA# 1175649	Cytotoxicity at ≥ 2500 µg/plate +/-S9 activation **Negative with or without metabolic activation.**
In vitro gene mutation assay CHO-K1 cells (HGPRT locus) PMRA# 1189958	**Negative with or without metabolic activation**.
In vitro chromosomal aberration assay CHO cells	**Negative with or without metabolic activation**.

Study Type/Animal/PMRA#	Study Results
PMRA# 1189955	
In vivo Micronucleus assay CD-1 Mouse PMRA# 1189952	**Negative**

Table 3 Summary of relevant isoxaflutole metabolites in rats

Coded Name	Chemical name
RPA 202248	1 -(2-methylsulphonyl-4-trifluoro-methylphenyl)-2-cyano-3-cyclopropyl- propane-1,3-dione
RPA 203328	2-methylsulphonyl-4-trifluoromethylbenzoic acid.

Appendix IV Occupational exposure and risk assessment tables

Table 1 Short-term mixer/loader/applicator exposure and risk assessment

Crop	Formulation	Application Equipment	Max Rate (kg/ha)	ATPD (ha/day)	Dermal Exposure[a] (µg/kg bw/day)	Inhalation Exposure[b] (µg/kg bw/day)	Dermal MOE[c]	Inhalation MOE[c]	Combined MOE[d]
Open M/L (liquid), single layer with CR gloves; Open cab application, single layer with CR gloves									
Field Corn, Sweet Corn, Soybean	Liquid	Groundboom (custom)	0.105	360	5.946	1.091	300	1700	260
Open M/L (water dispersable granules), single layer with CR gloves; Open cab application, single layer with CR gloves									
Field Corn	WDG	Groundboom (custom)	0.105	360	7.764	11.09	230	160	100

M/L = mix/load, ATPD = area treated per day, MOE = margin of exposure, WDG = water dispersable granules; CR = chemical-resistant; Max = maximum; NOAEL = no observed adverse effect level; Exp = exposure

[a] Dermal exposure (µg/kg bw/day) = (dermal unit exposure × ATPD × maximum application rate × 15% dermal absorption)/80 kg body weight

[b] Inhalation exposure (µg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/80 kg body weight

[c] Based on an oral NOAEL of 1.8 mg/kg bw/day, target MOE = 100

[d] Combined MOE = NOAEL (mg/kg bw/day)/(Exp_{dermal} + $Exp_{inhalation}$)

Table 2 Postapplication dermal risk assessment

	Activity	TC (cm^2/hr)	Rate (kg a.i./ha)	Number of Applications per year	MOE[a] (Day 0)	REI[b]
Field Corn [c]	Irrigation (hand set)	1750	0.105	1	260	12 hours
	Scouting	1100			420	
	Hand Weeding	70			6500	

TC = transfer coefficient, REI = restricted-entry interval, MOE = margin of exposure; NOAEL = no observed adverse effect level; DFR = dislodgeable foliar residue.

Since no DFR studies were submitted, a peak standard DFR value of 25% was used.

[a] Based on an oral NOAEL of 1.8 mg/kg bw/day and a target MOE of 100

[b] Since the target MOE is met, the REI is set at 12 hours.

[c] Postapplication risk assessment was only required for field corn as it is the only crop with post-emergent applications.

Appendix V Environmental Data

Table 1 Physical and chemical properties of isoxaflutole relevant to the environment

Property	Test substance	Value	Comments
Water solubility	Isoxaflutole	6.2 mg/L at pH 5.5 6.8 mg/L at pH 5 Hydrolyses at pH 9	Low water solubility at environmentally relevant pHs
Vapour pressure	Isoxaflutole	1.0×10^{-6} Pa at 25°C 3.22×10^{-7} Pa at 20°C	Low potential to volatilize under field conditions
Henry's law constant	Isoxaflutole	1.87×10^{-5} Pa·m^3/mol	Low potential to volatilize from moist soil and water surfaces
log Kow	Isoxaflutole	2.32	Limited potential for bioconcentration
pKa	Isoxaflutole	No dissociable functionality	Active ingredient does not dissociate in water
UV-visible absorption	Isoxaflutole	No absorption at > 350 nm	Phototransformation is not expected to be an important route of transformation

Table 2 Fate and behaviour of isoxaflutole in the terrestrial environment

Study type	Test substance	Value	Major transformation products	Comments	Reference (PMRA#)
Abiotic transformation					
Hydrolysis	Isoxaflutole	$t_{½}$ at 25°C: pH 5 = 11.1 d pH 7 = 20.1 h pH 9 = 3.2 h	RPA 202248	Major route of transformation	1175680
Phototransformation on soil	Isoxaflutole	DT_{50} = 22.8 h (irradiated) DT_{50} = 19.7 h (non-irradiated)	RPA 202248 RPA 203328	Not a major route of transformation	1175691
Biotransformation					
Biotransformation in aerobic soil	Isoxaflutole	DT_{50} = 0.3–5.2 d DT_{90} = 4.4–15.3 d	RPA 202248 RPA 203328	Not persistent in soil under aerobic conditions	1175725; 3089857
	RPA 202248	DT_{50} = 14–126 d	NA RPA 202248 peaked (62 – 95% AR) at 1 and 7 DAT	Not persistent to moderately persistent under aerobic conditions	
	RPA 203328	DT_{50} = 360 d	NA RPA 203328 peaked (52 – 90% AR) between 91 and 180 DAT	Persistent under aerobic conditions	

Study type	Test substance	Value	Major transformation products	Comments	Reference (PMRA#)
	Isoxaflutole	DT_{50} = 0.28 – 4 d	RPA 202248 RPA 203328	Not persistent in soil under aerobic conditions	3089857
	RPA 202248	DT_{50} = 20 – 78.5 d	NA	Slightly to moderately persistent under aerobic conditions	
	Isoxaflutole at 10°C	DT_{50} = 5.9 d	RPA 202248 RPA 203328	Not persistent in soil under aerobic conditions	3089857
	RPA 202248	DT_{50} = 126.5 d	NA	Moderately under aerobic conditions	
	RPA 202248	DT_{50} = 14.2 d	None	Slightly persistent under aerobic conditions	3089857
Biotransformation in anaerobic soil	NA	NA	NA	See anaerobic biotransformation in water systems	
Mobility					
Adsorption/desorption in soil	Isoxaflutole	*K*d = 0.23 to 14.2 K_{oc} = 46.5 to 163.3	NA	Moderate to very high potential to be mobile in soil	1175684; 1409090
	RPA 202248	*K*d = 0.1 to 5.3 K_{oc} = 15.5 to 105.6	NA	Moderate to very high potential to be mobile in soil	1175682; 1409089
	RPA 203328	*K*d = 0.002 to 0.9 K_{oc} = 0.3 to 100.7	NA	High to very high potential to be mobile in soil	1175683; 1409087
Soil leaching	Isoxaflutole	Soils tested: Sandy loam Silty clay Clay loam Sand	NA	Isoxaflutole found only in the top 6 cm. RPA 202248 was detected up to 18 cm. RPA 203328 was detected up to 24 cm. RPA 202248 was found in the leachate in all soils. RPA 203328 was found in the leachate of sandy loam soil.	1175686
Volatilization	Henry's law constant and vapour pressure	NA	NA	Not subject to long-range transport	NA

Study type	Test substance		Value	Major transformation products	Comments	Reference (PMRA#)
Field studies						
Terrestrial field dissipation	Isoxaflutole	Springbank, ON	DT_{50} = 1.5 d	DT_{50} of TP: RPA 202248 = 10.97 d RPA 203328 = 11.75 d	Isoxaflutole and its major TPs are not persistent under field conditions	1175428
		Selkirk, ON	DT_{50} = 7.04 d	DT_{50} of TP: RPA 202248 = 26.05 d RPA 203328 = 72.95 d	Under field conditions, isoxaflutole is not persistent, RPA 202248 is slightly persistent and RPA 203328 is slightly persistent.	
		Carman, MB	DT_{50} = 3.07 d	DT_{50} of TP: RPA 202248 = 11.2 d RPA 203328 =8.9 d	Isoxaflutole and its major TPs are not persistent under field conditions	
		Ephrata, WA	DT_{50} = 2.2 d	DT_{50} of TP: RPA 202248 = 13.1 d	Isoxaflutole and RPA 202248 are not persistent under field conditions	1175433
		Other United States sites	DT_{50} = 1.4–3.0 d	DT_{50} of TP: RPA 202248 = 8.4–124.5 d	NA	
		EU sites	DT_{50} = 2.3–7.0 d	DT_{50} of TP: RPA 202248 = 17–24 d RPA 203328 = 22–64 d	NA	3089857
	RPA 202248 (AE0540092 WP 20)	EU sites	DT_{50} = 14–40 d	NA	NA	3089857

NA - NOT APPLICABLE

Table 3 Fate and behaviour of isoxaflutole in the aquatic environment

Study type	Test material	Value	Major Transformation products	Comments	PMRA#
Abiotic transformation					
Hydrolysis	Isoxaflutole	$t_{½}$ at 25°C: pH 5 = 11.1 d pH 7 = 20.1 h pH 9 = 3.2 h	RPA 202248	Major route of transformation	1175680

Study type	Test material	Value	Major Transformation products	Comments	PMRA#
Phototransformation in water	Isoxaflutole	DT_{50} = 40 h	None	Major route of transformation	1175713
	RPA 202248	Stable	None	Not a major route of transformation	3089857
Biotransformation					
Biotransformation in aerobic water systems	Isoxaflutole	DT_{50} = 0.3–0.7 d	RPA 202248 RPA 205834	Not persistent in aquatic systems under aerobic conditions	1175727
	RPA 202248	DT_{50} = 255 to 703 d	NA	Persistent	
	RPA 205834	DT_{50} = 52 to 97 d	NA	Moderately persistent	
Biotransformation in anaerobic water systems	Isoxaflutole	DT_{50} < 2 h	RPA 202248 RPA 203328	Not persistent in water/ sediment systems under anaerobic conditions	1175681;
	RPA 202248	DT_{50} = 316 d	NA	Persistent	1175681;

NA Not applicable

Table 4 Calculated EEC values in soil and water

Use	EEC Soil (mg a.i./kg soil)	EEC Water 15 cm (mg a.i./L)	EEC Water 80 cm (mg a.i./L)	Cumulative Application rate on leaf (g a.i./ha)
Soybean[a]	0.047	0.07	0.013	105

[a] Based on single maximum application of 105 g a.i./ha on corn/soybean.

Table 5 Summary of the toxicity endpoints for terrestrial organisms

Organism	Test compound	Study type	Endpoint	Toxicity Value	Toxicity classification[a]	Reference
Terrestrial Organisms						
Bobwhite quail (*Colinus virginanus*)	Isoxaflutole	Acute oral	14-d LD_{50}	**>2150 mg a.i./kg bw**	Practically nontoxic	1175719
	Isoxaflutole	Dietary	8-d LD_{50}	>530.9 mg a.i./kg bw/d	Practically nontoxic	1175722
	RPA 202248	Dietary	8-d LD_{50}	**>552.1 mg a.i./kg bw/d**	Slightly toxic	1175723
	RPA 203328	Dietary	5-d LD_{50}	**>596.7 mg /kg bw/d**	Slightly toxic	3089768

Organism	Test compound	Study type	Endpoint	Toxicity Value	Toxicity classification[a]	Reference
	RPA 202248	Reproductive	NOEL	**53.1 mg /kg bw/d**	NA	3089768
Mallard duck (*Anas platyrhynchos*)	Isoxaflutole	Acute oral	14-d LD_{50}	>2150 mg a.i./kg bw	Practically nontoxic	1175720
	Isoxaflutole	Dietary	8-d LD_{50}	**>282.8 mg a.i./kg bw/d**	Moderately nontoxic	1175729
Rat	Isoxaflutole	Acute oral	LD_{50}	**>2000** mg/kg bw	Practically nontoxic	2895652
		Sub-chronic	90-d NOAEL	**10 mg/kg** bw/day	NA	
		Chronic	2-generation reproduction: NOAEL LOAEL	**1.8 mg/kg** bw/day **18 mg/kg** bw/day	NA	
Honeybee (*Apis mellifera*)	Isoxaflutole	Acute contact	48-h LD_{50}	**>100 µg a.i./bee**	Practically nontoxic; no mortality or sublethal effects were observed	1175694
	Isoxaflutole	Acute contact	48-h LD_{50}	>100 µg a.i./bee		3089768
	Isoxaflutole	Acute oral	48-h LD_{50}	>168.7 µg a.i./bee	Practically nontoxic; no mortality or sublethal effects were observed	1175694
	isoxaflutole	Acute oral	48-h LD_{50}	**>108.9 µg a.i./bee**		3089768
	Isoxaflutole WG 75 W	Chronic	10-d NOEC	**4.9 µg a.i./bee/day**	NA	3089768
	Isoxaflutole WG 75 W + cyprosulfamide SC 500 G	Chronic brood	21-d NOEC	**0.25 g a.i./L**	NA	3089768
Earthworm (*Eisenia fetida*)	Isoxaflutole	Acute	14-d LC_{50}	**>1000 mg a.i./kg soil dw**	No-effect were noted at the highest test concentration	1175693
	Isoxaflutole	Chronic	56-d NOEC	**17.8 mg a.i./kg soil dw**	NA	3089768
	RPA 202248	Chronic	56-d NOEC	**16.0 mg/kg soil dw**	NA	3089768
	RPA 203328	Acute	14-d LC_{50}	**>1000 mg /kg soil dw**	NA	3089768
	RPA 203328	Chronic	56-d NOEC	**1000 mg /kg soil dw**	NA	3089768
Green lacewing (*Chrysoperia carnea*)	Isoxaflutole + cyprosulfamide SC	Extended lab study, leaf discs – maize (dried residues)	LR_{50} (larvae)	>100.8 g a.i./ha	No effects were observed on reproduction	1409050

Organism	Test compound	Study type	Endpoint	Toxicity Value	Toxicity classification[a]	Reference
Parasitic wasp (*Aphidius rhopalosiphi*)	Isoxaflutole + cyprosulfamide SC	Glass plate (dried residues)	LR_{50}	>100.8 g a.i./ha	NA	1409049
Parasitic wasp (*Aphidius rhopalosiphi*)	Isoxaflutole + cyprosulfamide SC	Extended lab study, barley plants (dried residues)	LR_{50}	**>100.8 g a.i./ha**	No effects on reproduction	1409051
Predatory mite (*Typhlodromus pyri*)	Isoxaflutole + cyprosulfamide SC	Glass plate (dried residues)	LR_{50}	**>100.8 g a.i./ha**	No effects on reproduction	1409048
Collembola (*Folsomia candida*)	Isoxaflutole	Chronic, mortality and reproduction	28-d LC_{50} 28-d NOEC	>1000 mg a.i./kg soil dw 1000 mg a.i./kg soil d.w.	NA	3089768
	RPA 202248	Chronic, mortality and reproduction	28-d LC_{50} 28-d NOEC	**>100 mg /kg soil dw** 100 mg a.i./kg soil d.w.	NA	3089768
	RPA 203328	Chronic, mortality and reproduction	28-d LC_{50} 28-d NOEC	**>100 mg /kg soil dw** 100 mg a.i./kg soil d.w.	NA	3089768
Soil mite (*Hypoaspis aculeifer*)	Isoxaflutole	Mortality and reproduction; artificial soil	14-d LC_{50} 14-d NOEC	**>1000 mg a.i./kg soil dw** 562 mg a.i./kg soil d.w.	NA	3089768
	RPA 202248	Mortality and reproduction; artificial soil	14-d LC_{50} 14-d NOEC	**>100 mg /kg soil dw** 100 mg/kg soil d.w.	No reduction in juvenile numbers	3089768
	RPA 203328	Mortality and reproduction; artificial soil	15-d LC_{50} 28-d NOEC	**>100 mg /kg soil dw** 100 mg/kg soil d.w.	No reduction in juvenile numbers	3089768
Plants	Isoxaflutole	Seedling emergence; turnip, shoot length (most sensitive endpoint of ten species tested)	ER_{50}	**1.23 g a.i./ha**	Toxic to vascular plants	1175731

Organism	Test compound	Study type	Endpoint	Toxicity Value	Toxicity classification[a]	Reference
		Vegetative vigour; lettuce, shoot weight (most sensitive endpoint of ten species tested)	ER_{50}	**0.280 g a.i./ha**	Toxic to vascular plants	

[a] USEPA classification, where applicable
NA - Not applicable

Table 6 Summary of the toxicity endpoints for isoxaflutole and its transformation products to aquatic organisms

Organism	Test compound	Study type	Endpoint	Toxicity Value[1] (mg/L)	Toxicity Classification[a]	Reference (PMRA#)
Freshwater aquatic organisms						
Daphnia (*Daphnia magna*)	Isoxaflutole	Acute	48-h EC_{50}	**>1.5 No effects were seen at any test concentration**	Moderately toxic	1175697
		Chronic	21-d NOEC	**0.35**	NA	1175701
		Chronic	21-d NOEC	5.7	NA	3089768
	RPA 202248	Acute	48-h EC_{50}	**>59.6**	Slightly toxic	1175699
	RPA 203328	Acute	48-h EC_{50}	**>150.0**	Practically nontoxic	1175698
	RPA 205834	Acute	48-h EC_{50}	**>60.1**	Slightly toxic	1175700
Rainbow trout (*Oncorhynchus mykiss*)	Isoxaflutole	Acute	96-h LC_{50}	**>1.7 No effects were seen at any test concentration**	Moderately toxic	1175710
	RPA 202248	Acute	96-h LC_{50}	**>33.8**	Slightly toxic	1175711
	RPA 203328	Acute	96-h LC_{50}	**160.0**	Practically nontoxic	1175712
	RPA 205834	Acute	96-h LC_{50}	**>77.1**	Slightly toxic	1175714
	Isoxaflutole	Chronic (early life cycle)	28-d NOEC	**0.1**	NA	1175718
Bluegill sunfish (*Lepomis macrochirus*)	Isoxaflutole	Acute	96-h LC_{50}	>4.5	Moderately toxic	1175715

Organism	Test compound	Study type	Endpoint	Toxicity Value[1] (mg/L)	Toxicity Classification[a]	Reference (PMRA#)
Fathead minnow (*Pimephales promelas*)	Isoxaflutole	Chronic (early-life stage)	33-d NOEC	0.1025	NA	3089768
African clawed frog (*Xenopus laevis*)	Isoxaflutole	Acute (tadpoles)	48-h EC_{50}	**>3.7**	Moderately toxic	3089768
Selenastrum capricornutum	Isoxaflutole	Biomass	5-d EC_{50}	**0.12**	Highly toxic	1175752
	RPA 202248	Cell density	72-h EC_{50}	**8.7**	Moderately toxic	3089768
	RPA 203328	Biomass	5-d EC_{50}	**>9.4**	Moderately toxic	1175753
Anabaena flos-aquae	Isoxaflutole	Biomass	5-d EC_{50}	**0.17**	Highly toxic	1175751
Navicula pelliculosa	Isoxaflutole	Biomass	5-d EC_{50}	**0.38**	Highly toxic	1175754
Scenedesmus subspicatus	RPA 202248	Biomass	72-h EC_{50}	**>20.0**	Slightly toxic	1175755
	RPA 205834	Biomass	72-h EC_{50}	**>15.0**	Slightly toxic	1175756
	Balance 75 (end-use product)	Biomass	72-h EC_{50}	10.5	Slightly toxic	1175415
Duckweed (*Lemna gibba*)	Isoxaflutole	Biomass	14-d EC_{50}	**0.0032**	Very highly toxic	1175732
	RPA 202248	Biomass	14-d EC_{50}	**0.055**	Very highly toxic	3089768
	RPA 203328	Acute	14-d EC_{50}	**>10**	Slightly toxic	3089768
	RPA 205834	Biomass	14-d EC_{50}	**1.1**	Moderately toxic	3089768
Estuarine/Marine aquatic organisms						
Mysid shrimp (*Mysidopsis bahia*)	Isoxaflutole	Acute	96-h EC_{50}	**0.018**	Very highly toxic	1175705
	RPA 202248	Acute	96-h EC_{50}	**3.7**	Moderately toxic	1175704
	RPA 203328	Acute	96-h LC_{50}	**150**	Practically nontoxic	3089768
	Isoxaflutole	Chronic	28-d NOEC	**0.001**	NA	1175708
Eastern oyster (*Crassostrea virginica*)	Isoxaflutole	Shell growth	96-h EC_{50}	**3.4**	Moderately toxic	1175707
Sheepshead minnow (*Cyprinodon variegatus*)	Isoxaflutole	Acute	96-h LC_{50}	**>6.4**	Moderately toxic	1175716
	RPA 202248	Acute	96-h LC_{50}	**>78**	Slightly toxic	3089768

Organism	Test compound	Study type	Endpoint	Toxicity Value[1] (mg/L)	Toxicity Classification[a]	Reference (PMRA#)
Skeletonema costatum	Isoxaflutole	Biomass	5-d EC_{50}	**0.11**	Highly toxic	1175730
Chironomid (*Chironomus riparius*)	Isoxaflutole	Acute	48-h EC_{50}	**>1.5**	Moderately toxic	3089768

[1] Low solubility of technical isoxaflutole in water, limited the concentration range used in all aquatic toxicity studies; therefore, most end points are given as greater than the highest concentration measured.
[a] USEPA classification, where applicable
NA - Not applicable

Table 7 Screening level risk assessment of isoxaflutole to non-target terrestrial organisms other than birds and mammals

Organism	Study	Endpoint Value	Converted Value[1]	EEC value[2]	RQ	LOC Exceeded
TERRESTRIAL INVERTEBRATES						
Earthworm	Acute Mortality LC_{50}	>1000	>500	0.047 mg a.i./kg soil	<0.1	No
	Chronic NOEC	17.8	17.8	0.047 mg a.i./kg soil	<0.1	No
Soil mite (*Hypoaspis aculeifer*)	Acute EC_{50}	>1000	>500	0.047 mg a.i./kg soil	<0.1	No
	Chronic NOEC	562	562	0.047 mg a.i./kg soil	<0.1	No
Honey bee (*Apis mellifera*)	Acute oral LD_{50}	>100	>108.9	3.0 µg a.i./bee	<0.1	No
	Acute contact LD_{50}	>100	>100	0.252 µg a.i./bee	<0.1	No
	Chronic adult NOED	4.9	4.9	3.0 µg a.i./bee	0.6	No
	Chronic larval NOED	250	250	1.28 µg a.i./bee	<0.1	No
Parasitic wasp	Acute LR_{50}	>100.8	>100.8	105 g a.i./ha	1.0	No
Predatory mite	Acute LR_{50}	>100.8	>100.8	105 g a.i./ha	1.0	No
Plants	Vegetative Vigour	HD_5: 0.242 g a.i./ha (using endpoints from ten species)	0.242	In-field: 105 g a.i./ha	434	Yes
				Off-field (ground appl., 6% drift): 6.3 g a.i./ha	26	Yes

[1] The uncertainty factor of ½ and 1/10 times of the EC_{50}/LC_{50} are used for acute endpoints. An uncertainty factor of one is applied to chronic endpoints. An uncertainty factor of one is applied to the HD_5 endpoint.
[2] EEC calculations are based on the maximum label application rate of 105 g a.i./ha.

Table 8 Screening level risk assessment for non-target terrestrial organisms to RPA 202248, RPA 203328 and RPA 205834

Organism	Test substance	Study	Ecotox Endpoint Value	Converted Ecotox Endpoint Value[1]	EEC Value	RQ	LOC Exceeded
Earthworm (*Eisenia fetida*)	RPA 202248	Chronic NOEC	16.0 mg a.i./kg soil dw	16	0.047	<0.1	No
	RPA 203328	Acute LC_{50}	>1000 mg a.i./kg soil dw	>500	0.035	<0.1	No
Soil mite (*Hypoaspis aculeifer*)	RPA 202248 (AE 0540092)	Acute EC_5	>100 mg a.i./kg soil dw	>50	0.047	<0.1	No
	RPA 203328 (AE B197555)	Acute EC_5	>100 mg a.i./kg soil dw	>50	0.035	<0.1	No

[1] The uncertainty factor of ½ and 1/10 times of the EC_{50}/LC_{50} are used for acute endpoints. An uncertainty factor of one is applied to chronic endpoints.

Table 9 Screening level risk assessment of isoxaflutole, RPA 202248 and RPA 203328 to birds

	Test compound	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)					
Acute	Isoxaflutole	215	Insectivore	8.55	0.04
Reproduction	RPA 202248	53.1	Insectivore	8.55	0.16
Medium Sized Bird (0.1 kg)					
Acute	Isoxaflutole	215	Insectivore	6.67	0.03
Reproduction	RPA 202248	53.1	Insectivore	6.67	0.13
Large Sized Bird (1 kg)					
Acute	Isoxaflutole	215	Herbivore (short grass)	4.31	0.02
Reproduction	RPA 202248	53.1	Herbivore (short grass)	4.31	0.08

Table 10 Screening level risk assessment of isoxaflutole to small mammals

	Toxicity (mg a.i./kg bw/d	Feeding Guild (food item)	EDE (mg a.i./kg bw)	RQ
Small Mammal (0.015 kg)				
Acute	200	Insectivore	4.92	0.02
Reproduction	1.80	Insectivore	4.92	2.73
Medium Sized Mammal (0.035 kg)				
Acute	200	Herbivore (short grass)	9.53	0.05
Reproduction	1.80	Herbivore (short grass)	9.53	5.30
Large Sized Mammal (1 kg)				
Acute	200	Herbivore (short grass)	5.09	0.03
Reproduction	1.80	Herbivore (short grass)	5.09	2.83

Table 11 Expanded risk assessment of isoxaflutole to small mammals

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Mammal (0.015 kg										
Reproduction	1.80	Insectivore	4.9	2.7	0.29	0.16	3.39	1.89	0.20	0.11
	1.80	Granivore (grain and seeds)	0.76	0.42	0.05	0.03	0.36	0.20	0.02	0.01
	1.80	Frugivore (fruit)	1.5	0.85	0.09	0.05	0.73	0.40	0.04	0.02
Medium Sized Mammal (0.035 kg)										
Reproduction	1.80	Insectivore	4.3	2.4	0.26	0.14	2.98	1.7	0.18	0.10
	1.80	Granivore (grain and seeds)	0.67	0.37	0.04	0.02	0.32	0.18	0.02	0.01
	1.80	Frugivore (fruit)	1.3	0.74	0.08	0.04	0.64	0.35	0.04	0.02
	1.80	Herbivore (short grass)	9.5	5.3	0.57	0.32	3.39	1.9	0.20	0.11
	1.80	Herbivore (long grass)	5.8	3.2	0.35	0.19	1.90	1.1	0.11	0.06
	1.80	Herbivore (Broadleaf plants)	8.8	4.9	0.53	0.29	2.92	1.6	0.17	0.10
Large Sized Mammal (1 kg)										
Reproduction	1.80	Insectivore	2.3	1.3	0.14	0.08	1.59	0.88	0.10	0.05
	1.80	Granivore (grain and seeds)	0.36	0.20	0.02	0.01	0.17	0.09	0.01	0.01
	1.80	Frugivore (fruit)	0.71	0.40	0.04	0.02	0.34	0.19	0.02	0.01
	1.80	Herbivore (short grass)	5.1	2.8	0.31	0.17	1.81	1.0	0.11	0.06
	1.80	Herbivore (long grass)	3.1	1.7	0.19	0.10	1.02	0.56	0.06	0.03
	1.80	Herbivore (Broadleaf plants)	4.7	2.6	0.28	0.16	1.56	0.87	0.09	0.05

Table 12 Screening level risk assessment of isoxaflutole to aquatic organisms

Organism	Study	Endpoint Value (mg a.i./L)	Converted Endpoint Value (mg a.i./L)[1]	EEC (mg a.i./L)[2]	RQ	LOC Exceeded
FRESHWATER SPECIES						
Freshwater Pelagic Invertebrate: Water flea (*Daphnia magna*)	Acute (48-hour EC_{50})	>1.5	>0.75	0.013	0.2	No
	Chronic (21-day NOEC)	0.35	0.35	0.013	0.4	No
Freshwater Benthic Invertebrate: Midge (*Chironomus riparius*)	Acute (48-h EC_{50})	>1.5	>0.75	0.013	<0.1	No
Rainbow Trout (*Oncorhynchus mykiss*)	Acute (96-hour LC50)	>1.7	>0.17	0.013	<0.1	No
	ELS (28-d NOEC)	0.1	0.1	0.013	0.1	No
Fathead minnow (Pimephales promelas)	Chronic ELS (33-d)	102.5	102.5	0.013	<0.1	No
Freshwater Green Alga (*Selenastrum capricornutum*)	Acute biomass (5 day EC_{50})	0.12	0.06	0.013	0.2	No
Freshwater Blue-green Alga (*Anabaena flos-aquae*)	Acute biomass (5-day EC_{50})	0.17	0.09	0.013	0.1	No
Freshwater diatom (Navicula pelliculosa)	Acute biomass (5-day EC_{50})	0.38	0.19	0.013	0.1	No
Freshwater Macrophyte (*Lemna gibba G3*)	Acute biomass (9-d EC_{50})	0.0032	0.0016	0.013	**8.1**	Yes
Amphibians (fish data used as surrogate)	Acute (48-hour EC_{50})	>3.7	>0.37	0.07	0.2	No
	Rainbow trout ELS (NOEC)	0.1	0.1	0.07	0.7	No
MARINE SPECIES						
Marine Invertebrate: Mysid shrimp (*Americamysis bahia*)	Acute (96-hour EC_{50})	0.018	0.009	0.013	**1.4**	Yes
	Chronic (28-day NOEC)	0.001	0.001	0.013	**13**	Yes
Marine Invertebrate:	Acute (96-hour	3.4	1.7	0.013	<0.1	No

Organism	Study	Endpoint Value (mg a.i./L)	Converted Endpoint Value (mg a.i./L)[1]	EEC (mg a.i./L)[2]	RQ	LOC Exceeded
Eastern oyster (*Crassostrea virginica*)	EC_{50})					
Marine Fish: Sheepshead minnow (*Cyprinodon variegatus*)	Acute (96-hour EC_{50})	>6.4	>3.2	0.013	<0.1	No
Marine alga: Diatom (*Skeletonema costatum*)	Acute reproduction (96-hour EC_{50})	0.11	0.06	0.013	0.2	No

[1] The uncertainty factor of ½ and 1/10 times of the EC_{50}/LC_{50} are used for acute endpoints. An uncertainty factor of one is applied to chronic endpoints.

[2] EEC calculations are based on the maximum label application rate of 105 g a.i./ha. The EEC for aquatic organisms are based on a water depth of 80 cm while the EEC for amphibians are based on a depth of 15 cm.

Table 13 Screening level risk assessment for non-target organisms exposed to RPA 202248, RPA 203328 and RPA 205834

Organism	Test substance	Study	Endpoint Value (mg a.i./L)	Converted Endpoint Value (mg a.i./L)[1]	EEC (mg a.i./L)[2]	RQ	LOC Exceeded
Aquatic organisms							
Rainbow trout (*Oncorhynchus mykiss*)	RPA 202248	Acute LC_{50}	>33.8 mg a.i./L	>3.38	0.013	<0.1	No
	RPA 203328	Acute LC_{50}	160.0 mg a.i./L	16	0.0097	<0.1	No
	RPA 205834	Acute LC_{50}	>77.1 mg a.i./L	>7.71	0.013	<0.1	No
Daphnia (*Daphnia magna*)	RPA 202248	Acute EC_{50}	>59.6 mg a.i./L	>29.8	0.013	<0.1	No
	RPA 203328	Acute EC_{50}	>150.0 mg a.i./L	>75	0.0097	<0.1	No
	RPA 205834	Acute EC_{50}	>60.1 mg a.i./L	30	0.013	<0.1	No
Selenastrum capricornutum	RPA 202248	Cell density EC_{50}	8.7 mg a.i./L	4.4	0.013	<0.1	No
	RPA 203328	Biomass EC_{50}	>9.4 mg a.i./L	4.7	0.0097	<0.1	No
Scenedesmus subspicatus	RPA 202248	Biomass EC_{50}	>20.0 mg a.i./L	>10	0.013	<0.1	No
	RPA 205834	Biomass EC_{50}	>15.0 mg a.i./L	>7.5	0.013	<0.1	No
Duckweed (*Lemna*	RPA 202248	Biomass EC_{50}	0.055 mg a.i./L	0.0275	0.013	0.5	No

Organism	Test substance	Study	Endpoint Value (mg a.i./L)	Converted Endpoint Value (mg a.i./L)[1]	EEC (mg a.i./L)[2]	RQ	LOC Exceeded
gibba)	RPA 203328	Acute EC_{50}	>10 mg a.i./L	>5	0.0097	<0.1	No
	RPA 205834	Biomass EC_{50}	1.1 mg a.i./L	0.55	0.013	<0.1	No
Sheepshead minnow (*Cyprinodon variegatus*)	RPA 202248	Acute LC_{50}	>78 mg a.i./L	>7.8	0.013	<0.1	No
Mysid shrimp (*Mysidopsis bahia*)	RPA 202248	Acute EC_{50}	3.7 mg a.i./L	1.85	0.013	<0.1	No
	RPA 203328	Acute EC_{50}	150 mg a.i./L	75	0.0097	<0.1	No

[1] The uncertainty factor of ½ and 1/10 times of the EC_{50}/LC_{50} are used for acute endpoints. An uncertainty factor of one is applied to chronic endpoints.
[2] For the screening level risk assessment for the transformation products (TPs), it is assumed that 100% of isoxaflutole is instantly transformed to the TP. The ratio of the molecular weight of isoxaflutole to the molecular weight of the TP is used to convert the isoxaflutole EEC to that of the TP. For RPA 202248: 0.013 × (359.32/359.32) = 0.013 mg a.i./L; RPA 205834: 0.013 × (361.34/359.32) = 0.013 mg a.i./L; RPA 203328: 0.013 × (268.27/359.32) = 0.0097 mg a.i./L.

Table 14 Refined aquatic risk assessment of isoxaflutole for spray drift

Organism	Study	Endpoint Value (mg a.i./L)	Converted Endpoint Value (mg a.i./L)[1]	EEC (mg a.i./L)[2]	RQ	LOC Exceeded
Freshwater Macrophyte (*Lemna gibba G3*)	Acute biomass (9-d EC_{50})	0.0032	0.0016	0.00078	0.5	No
Marine Invertebrate: Mysid shrimp (*Americamysis bahia*)	Acute (96-hour EC_{50})	0.018	0.009	0.00078	<0.1	No
	Chronic (28-day NOEC)	0.001	0.001	0.00078	0.8	No

[1] The uncertainty factor of ½ and 1/10 times of the EC_{50}/LC_{50} are used for acute endpoints. An uncertainty factor of one is applied to chronic endpoints
[2] For spray drift, a ground application drift of 6% is applied to the screening level EEC.

Table 15 Toxic substances management policy - Considerations to TSMP track 1 criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints	Transformation Products Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]	Soil	Half-life ≥ 182 days	0.3–5.2 days	RPA 202248 = 14–126 days RPA 203328 = 360 days
	Water	Half-life ≥ 182 days	0.3–0.7 days	RPA 202248 = 255–703 days RPA 203328 = not available
	Sediment	Half-life ≥ 365 days	< 2 hours	RPA 202248 = 316 days RPA 203328 = not available
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (1.0×10^{-6} Pa) and Henry's law Constant (1.87×10^{-5} Pa·m^3/mol).	Not available
Bioaccumulation[4]	Log $K_{ow} \geq 5$		2.32	Not available
	BCF ≥ 5000		Not available	Not available
	BAF ≥ 5000		Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered toxic or toxic equivalent, according to the Canadian Environmental Protection Act (CEPA), for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (that is, all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

Appendix VI Summary of modelling and monitoring for water

Modelled concentrations in drinking water

The estimated environmental concentrations (EECs) in surface water were calculated using the PRZM/EXAMS models on standard Level 1 scenarios, a small reservoir. EECs in groundwater were calculated using the PRZM-GW model. For modelling, the parent (isoxaflutole) and one transformation product (RPA 202248) were included in a combined residue. All scenarios were run using 50-year weather data.

The predicted EECs of isoxaflutole in potential surface drinking water sources are reported as three different surface water EECs in Table 1. Table 2 provides the groundwater 90th percentile of the daily average and 90th percentile of the 1 year moving average along with two additional values, the simulation average value and the postbreakthrough average which are provided for consideration in the chronic and cancer dietary assessment.

Table 1 Level 1 estimated environmental concentrations of isoxaflutole combined residue (parent and RPA 202248) in potential sources of surface water

Crop	Surface Water (µg a.i./L)		
	Daily[1]	Yearly[2]	Simulation average[3]
Field corn, soybeans	6.1	1.3	0.57

1 90th percentile of yearly peak concentrations
2 90th percentile of yearly average concentrations
3 average of yearly average concentrations

Table 2 Level 1 estimated environmental concentrations of isoxaflutole combined residue (parent and RPA 202248) in potential sources of ground water

Scenario	Daily[1]	Yearly[2]	Average BT time (days)	Post BT average	Simulation average
Corn-PEI	4.4	4.4	2523	4.0	3.5

1 90th percentile of daily average concentrations
2 90th percentile of 365-day moving average concentration

Water monitoring data

Monitoring data and modelling estimates are complementary and are considered in conjunction with each other when estimating the potential exposure of aquatic organisms or humans. The PMRA regularly communicates with the Federal, Provincial and Territorial representatives from all of the provinces and territories in Canada along with Environment and Climate Change Canada, the Department of Fisheries and Oceans and the drinking water subcommittee through Health Canada to acquire monitoring data that would be relevant to current re-evaluation programs. Additionally, data on residues present in water samples taken in the United States (USGS Water Quality Data Portal and USDA annual Summary Reports) are also considered in the Canadian water assessment, given the extensive monitoring programs that exist in the United States.

Monitoring data was collected in 2014 and updated in 2020. Isoxaflutole and its transformation products were not detected in finished drinking water or groundwater samples. Although groundwater data were available (508 groundwater samples for isoxaflutole; 383 groundwater samples for isoxaflutole degradate identity not specified), very little surface water data were available (isoxaflutole: 1 surface water sample, 46 drinking water samples; RPA 203328 and diketonitrile-isoxaflutole: 1 surface water sample). Use information was not available on the timing and location of sampling versus the timing and areas of use; thus, there is uncertainty associated with the non-detects. The non-detects may be a result of sampling in areas or during periods of time where isoxaflutole was not used.

Given the limited monitoring data available and its uncertainties, the information available is not considered sufficient to describe the potential for isoxaflutole and its transformation products to reach Canadian water bodies under normal use.

The concentrations estimated via modelling represent reasonable high-end exposure estimates for drinking water and should be considered in the human health dietary risk assessment.

Appendix VII Label amendments for products containing isoxaflutole

Information on approved labels of currently registered products should not be removed unless it contradicts the label statements provided below.

I. For isoxaflutole technical products:

The following must appear under a section titled “ENVIRONMENTAL PRECAUTIONS”:

TOXIC to aquatic organisms and terrestrial plants.

DO NOT discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters.

II. For commercial end-use products:

Label amendments relating to the health risk assessment

General label improvements

In order to promote best practices, and to minimize human exposure from spray drift or from spray residues resulting from drift due to the use of isoxaflutole, the following label statement is proposed:

> “Apply only to agricultural crops when the potential for drift to areas of human habitation and human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings.”

Personal protective equipment

For mixing, loading, and application, the following statement is proposed for all commercial-class product labels unless similar or more protective statements are already present (or unless indicated otherwise):

> “Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair. Gloves are not required during applications within a closed cab.”

Restricted-entry interval

The following statement is proposed for all commercial-class product labels:

> “**DO NOT** enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours.”

Label amendments relating to the environmental risk assessment

a) The following statements are to be added to the "Environmental Precautions" section:

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

b) The following statements are required under the "Directions for Use" Section on all product labels:

• To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay.

• Avoid application of this product when heavy rain is forecast.

• Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative filter strip between the treated area and the edge of the water body.

• DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

• As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests.

• 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 (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

• **DO NOT** apply by aerial application equipment.

• **Spray Buffer Zones:**

- A spray buffer zone is not required for:
  - uses with hand-held application equipment permitted on this label,
  - low-clearance hooded or shielded sprayers that prevent spray contact with crop, fruit or foliage

- The spray buffer zones specified in the table below are for isoxaflutole. These spray buffer zones 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, riparian areas and shrublands), freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop	Spray Buffer Zones (metres) Required for the Protection of:				
		Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:		Terrestrial Habitat:
		Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Field corn, seed corn, Isoxaflutole-tolerant soybeans	1	1	1	1	15

• For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

• The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

c) The following statement is required under the STORAGE heading:

• To prevent contamination, store this product away from food and feed

d) The following statements are required under the DISPOSAL heading; inclusion of these statements is dependant on the end-use product.

• For recyclable containers

The following statement would apply to plastic or metal containers that contain agricultural and non-crop land uses (for example, forestry) pesticide products, and that are designed to contain 23 L or less of product.

Disposal of Container*:*

DO NOT reuse this container for any purpose. This is a recyclable container, and is to be disposed of at a container collection site. Contact your local distributor/dealer or municipality for the location of the nearest collection site. Before taking the container to the collection site:

1. Triple- or pressure-rinse the empty container. Add the rinsings to the spray mixture in the tank.
2. Make the empty, rinsed container unsuitable for further use.

If there is no container collection site in your area, dispose of the container in accordance with provincial requirements.

• For returnable containers

Disposal of Container:

DO NOT reuse this container for any purpose. For disposal, this empty container may be returned to the point of purchase (distributor/dealer).

• For containers that can be refilled for the user by the distributor/dealer

Disposal of Container:

For disposal, this container may be returned to the point of purchase (distributor/dealer). It must be refilled by the distributor/dealer with the same product. Do not reuse this container for any other purpose.

• Disposal of unused, unwanted product

A revised standard label statement providing directions for the disposal of unused, unwanted product will be added to labels of agricultural and non-crop land control products:

For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in case of a spill, and for clean-up of spills.

Label amendments relating to the value assessment

For all isoxaflutole end-use products:

- "Non-target adverse effects may occur on fields planted or sugar beets, due to carryover of isoxaflutole degradate residues in the soil."

- Products must add "suppression" also where "control" is mentioned in the label.

References

A. Information Considered in the Chemistry Assessment

List of Studies/Information Submitted by Registrant

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B. Studies/Information Considered in the Toxicological Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
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1175605	RPA 201772: Delayed Contact Hypersensitivity Study In Guinea-Pigs. P. Rees. Date: October 22, 1992. (92/Rha481/0673; RHA/481;92/0673). (Isoxaflutole Technical,Subn#97-0653), DACO: 4.2.6
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1175621	RPA 201772: Acute Inhalation Toxicity In Rats: 4 Hour Exposure. G. Jackson. Date: February 28, 1994.(Rnp435/932339). (Isoxaflutole Technical,Subn#97-0653), DACO: 4.2.3
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Additional Information Considered

i) Published Information

Human and Animal Health

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ii) Unpublished Information

Human and Animal Health

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C. Information Considered in the Dietary Risk Assessment

Additional Information Considered

i) Published Information

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PMRA Document Number	Reference
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D. Information Considered in the Occupational and Residential Assessment

Studies/Information Provided by Task Forces

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E. Information Considered in the Environmental Assessment

Studies/Information Submitted By the Registrant

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1175680	14C-RPA 201772 HYDROLYSIS
1175681	RPA 201772 ANAEROBIC AQUATIC METABOLISM
1175682	[14C]-RPA 202248: ADSORPTION/DESORPTION TO AND FROM FOUR SOILS AND AN AQUATIC SEDIMENT
1175683	[14C]-RPA 203328: ADSORPTION/DESORPTION TO AND FROM FOUR SOILS AND A SEDIMENT
1175684	RPA 201772: ADSORPTION/DESORPTION TO AND FROM FOUR SOILS AND AN AQUATIC SEDIMENT
1175686	RPA 201772: AGED LEACHING STUDY IN FOUR SOILS AND A SEDIMENT
1175691	RPA 201772: SOIL PHOTOLYSIS. E.FERREIRA. STUDY COMPLETED ON: 4TH FEBRUARY 1994.(P93/122).(ISOXAFLUTOLE TECHNICAL,SUBN#97-0653)
1175713	14C-RPA 201772 (ISOXAFLUTOLE) PHOTODEGRADATION IN WATER
1175725	RPA 201772: AEROBIC SOIL METABOLISM
1175727	RPA 201772: DEGRADATION AND RETENTION IN TWO WATER/SEDIMENT SYSTEMS
1175693	THE ACUTE TOXICITY OF RPA 201772 TO EARTHWORMS (*EISENIA FOETIDA).* J.HANDLEY & P.WETTON. DATE OF ISSUE: 21 JULY 1993 (FINAL).(282/389).(ISOXAFLUTOLE TECHNICAL,SUBN#97-0653)
1175694	LABORATORY TESTING FOR TOXICITY (ACUTE CONTACT AND ORAL LD50) OF RPA 201772 TO HONEY BEES (*APIS MELLIFERA* L.)(HYMENOPTERA, APIDAE). R.PETTO. STUDY COMPLETION DATE: SEPTEMBER 26,1994.(463500).(ISOXAFLUTOLE TECHNICAL,SUBN#97-0653)
1175697	RPA 201772: ACUTE TOXICITY TO DAPHNIDS (*DAPHNIA MAGNA*) UNDER FLOW-THROUGH CONDITIONS
1175698	RPA 203328- ACUTE TOXICITY TO DAPHNIDS (*DAPHNIA MAGNA*) UNDER FLOW-THROUGH CONDITIONS
1175699	RPA 202248- ACUTE TOXICITY (48 HOURS) TO DAPHNIDS (*DAPHNIA MAGNA)* UNDER SEMI-STATIC CONDITIONS
1175700	RPA 205834- ACUTE TOXICITY (48 HOURS) TO DAPHNIDS (*DAPHNIA MAGNA)* UNDER SEMI-STATIC CONDITIONS
1175701	ISOXAFLUTOLE: *DAPHNIA MAGNA* LIFE CYCLE (21 DAY FLOW-THROUGH) CHRONIC TOXICITY STUDY

1175703	LABORATORY STUDIES WITH OTHER SPECIES
1175704	RPA 202248: ACUTE TOXICITY TO MYSIDS (*MYSIDOPSIS BAHIA*) UNDER STATIC RENEWAL CONDITIONS
1175705	RPA 201772 TECHNICAL- ACUTE TOXICITY TO MYSID SHRIMP (*MYSIDOPSIS BAHIA*) UNDER FLOW-THROUGH CONDITIONS
1175707	RPA 201772 TECHNICAL-ACUTE TOXICITY TO EASTERN OYSTER (*CRASSOSTREA VIRGINICA*) UNDER FLOW-THROUGH CONDITIONS
1175708	ISOXAFLUTOLE-CHRONIC TOXICITY TO MYSIDS (*MYSIDOPSIS BAHIA*) UNDER FLOW-THROUGH CONDITIONS
1175710	RPA 201772-ACUTE TOXICITY TO RAINBOW TROUT (*ONCORHYNCHUS MYKISS*) UNDER FLOW-THROUGH CONDITIONS. FINAL REPORT. M.BETTENCOURT. STUDY COMPLETION DATE: 8 DECEMBER 1993.(93-7-4860;10566.0493.6284.108).(ISOXAFLUTOLE TECHNICAL,SUBN#97-0653)
1175711	RPA 202248: ACUTE TOXICITY (96 HOURS) TO RAINBOW TROUT (*ONCORHYNCHUS MYKISS*) UNDER SEMI-STATIC CONDITIONS. A.MCELLIGOTT. STUDY COMPLETED ON: NOVEMBER 03,1995.(SA95141).(ISOXAFLUTOLE TECHNICAL,SUBN#97-0653)
1175712	RPA 203328-ACUTE TOXICITY TO RAINBOW TROUT (*ONCORHYNCHUS MYKISS*) UNDER FLOW-THROUGH CONDITIONS. FINAL REPORT. M.MACHADO. DATE: 22 JUNE 1995.(95-5-5861;10566.0194.6328.108).(ISOXAFLUTOLE TECHNICAL,SUBN#97-0653)
1175714	RPA 205834: ACUTE TOXICITY (96 HOURS) TO RAINBOW TROUT (*ONCORHYNCHUS MYKISS*) UNDER SEMI-STATIC CONDITIONS. P.SUTEAU. STUDY COMPLETED ON: NOVEMBER 10,1995.(SA95139).(ISOXAFLUTOLE TECHNICAL,SUBN#97-0653)
1175715	RPA 201772-ACUTE TOXICITY TO BLUEGILL SUNFISH (*LEPOMIS MACROCHIRUS*) UNDER FLOW-THROUGH CONDITIONS
1175716	RPA 201772 TECHNICAL-ACUTE TOXICITY TO SHEEPSHEAD MINNOW (*CYPRINODON VARIEGATUS*) UNDER FLOW-THROUGH CONDITIONS
1175718	ISOXAFLUTOLE: FISH, JUVENILE GROWTH TEST-28 DAYS. I.SEWELL & A.BARTLETT. DATE OF ISSUE: 23 NOVEMBER 1995 (FINAL).(282/465).(ISOXAFLUTOLE TECHNICAL,SUBN#97-0653)
1175719	RPA 201772 TECHNICAL: 14-DAY ACUTE ORAL LD50 STUDY IN BOBWHITE QUAIL. C.PEDERSEN & S.THOMPSON. STUDY COMPLETION: MARCH 15,1994.(108-025-03).(ISOXAFLUTOLE TECHNICAL,SUBN#97-0653)
1175720	RPA 201772 TECHNICAL: 14-DAY ACUTE ORAL LD50 STUDY IN MALLARD DUCKS
1175722	RPA 201772 TECHNICAL: 8-DAY ACUTE DIETARY LC50 STUDY IN BOBWHITE QUAIL.
1175723	RPA 202248: SUBACUTE DIETARY TOXICITY (LC50) TO THE BOBWHITE QUAIL

1175729	RPA 201772 TECHNICAL: 8-DAY ACUTE DIETAY LC50 STUDY IN MALLARD DUCKLINGS
1175730	RPA 201772 TECHNICAL- ACUTE TOXICITY TO THE MARINE DIATOM, *SKELETONEMA COSTATUM*
1175731	RPA 201772 DETERMINATION OF EFFECTS ON SEED GERMINATION, SEEDLING EMERGENCE AND VEGETATIVE VIGOR OF TEN PLANT SPECIES
1175732	RPA 201772 TECHNICAL-TOXICITY TO DUCKWEED, *LEMNA GIBBA*
1175751	RPA 201772 TECHNICAL-ACUTE TOXICITY TO THE FRESHWATER BLUE-GREEN ALGA, *ANABAENA FLOS-AQUAE*
1175752	RPA 201772 TECHNICAL- TOXICITY TO THE FRESHWATER GREEN ALGA, *SELENASTRUM CAPRICORNUTUM*
1175753	RPA 203328- 5-DAY TOXICITY TO THE FRESHWATER GREEN ALGA, SELENASTRUM CAPRICORNUTUM
1175754	RPA 201772 TECHNICAL- ACUTE TOXICITY TO THE FRESHWATER DIATOM, *NAVICULA PELLICULOSA*
1175755	RPA 202248: ALGAL INHIBITION TEST
1175756	RPA 205834: ALGAL INHIBITION TEST
1175415	EXP 31130A: FRESHWATER ALGAL GROWTH INHIBITION STUDY (72 HOURS) (*SCENDESMUS SUBSPICATUS*)
1175428	A TERRESTRIAL FIELD BARE SOIL DISSIPATION STUDY WITH ISOXAFLUTOLE, STUDY PROTOCOL INCLUDING AMENDMENTS, 1996 TRIAL SITE LAYOUT & WEATHER OBSERVATIONS,ANALYTICAL REPORT, ANALYTICAL CHROMATOGRAMS, REPORT, VOL 1 OF 8,J. KELLY, MARCH 11, 1997 (CA96J02R;97RP11.REP) SUBN. 97-0654 (BALANCE 75WDG HERBICIDE)
1175433	A TERRESTRIAL SOIL DISSIPATION STUDY WITH ISOXAFLUTOLE (RPA 201772)
1409087	(14C)-RPA 203328: Adsorption/desorption in five soils
1409089	(14C)-RPA 202248: Adsorption/desorption to and from four soils and an aquatic sediment - Addendum report
1409090	(14C)-RPA 201772: Adsorption/desorption to and from four soils and an aquatic sediment - Addendum report
1409048	Toxicity to the predatory mite *Typhlodromus pyri* SCHEUTEN (Acari, Phytoseiidae) in the laboratory; Isoxaflutole & Cyprosulfamide SC 240 + 240 g/l
1409049	Toxicity to the parasitoid wasp *Aphidius rhopalosiphi* (DeStephani-Perez) (Hymenoptera: Braconidae) in the laboratory - isoxaflutole & cyprosulfamide SC 240 + 240 g/l
1409050	Toxicity to the green lacewing *Chrysoperla carnea* STEPH. (Neuroptera, Chrysopidae) using an extended laboratory test; Isoxaflutole & Cyprosulfamide SC 240 + 240 g/l
1409051	Toxicity to the parasitoid wasp *Aphidius rhopalosiphi* (DESTEPHANIPEREZ) (Hymenoptera: Braconidae) using an extended laboratory test; Isoxaflutole & Cyprosulfamide SC 240 + 240 g/l

Additional Information Considered

i) Published Information

PMRA Document Number	Reference
3089757	European Commission: Draft Renewal Assessment Report prepared according to the Commission Regulation (EU) N°844/2012 - Document MCA - Section 9: Fate and behaviour in the environment - Isoxaflutole, Volume 3 - Annex B.8
3089768	European Commission: Draft Renewal Assessment Report prepared according to the Commission Regulation (EU) N°844/2012 - Isoxaflutole, Volume 3 - Annex B.9
1918520	Cohen, S.Z., S.M. Creeger, R.F. Carsel and C.G. Enfield, 1984. Potential for pesticide contamination of groundwater resulting from agricultural uses. Pages 297-325. In R.F. Krugger and J.N. Seiber, eds., Treatment and Disposal of Pesticide Wastes. ACS Symposium Series No. 259. American Chemical Society, Washington, DC, pp. 297-325.
1918522	Fletcher, John S. 1994. Literature Review and Evaluation of the EPA Food-Chain (Kenaga) Nomogram, an Instrument for Estimating Pesticide Residues on Plants - Environmental Toxicology and Chemistry, Volume 13, Number 9, Pages 1383 to 1391, DACO: 9.9
1918526	Hoerger, F. and E.E. Kenaga, 1972. Pesticide Residues on Plants: Correlation of Representative Data as a Basis for Estimation of Their Magnitude in the Environment - Environmental Quality and Safety: Chemistry, Toxicology, and Technology, Pages 9 to 28, DACO: 9.9
1918527	Kenaga, E. E. 1973. Factors to be considered in the Evaluation of the Toxicity of Pesticides to Birds in Their Environment - Environment Quality and Safety, Volume 2, Pages 166 to 181, DACO: 9.9
1918529	Nagy, Kenneth A. 1987, Field Metabolic Rate and Food Requirement Scaling in Mammals and Birds, Ecological Monographs, Volume 57, Number 2, Pages 111 to 128, DACO: 9.9