Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

# Regulatory Note

# REG2000-16

## Isoxaflutole

The active ingredient isoxaflutole and the formulated product Converge 75 WDG, for control of specific annual grass and broadleaf weeds in field corn, have been granted Section 17 temporary registrations.

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

*(publié aussi en français)*

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## Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a limited term registration for Converge 75 WDG, a herbicide developed by Rhône-Poulenc Inc., now owned by Aventis for use on field corn. Converge 75 WDG herbicide, which contains the active ingredient isoxaflutole, is effective against several annual grass and broadleaf weed species common to corn producing areas of eastern Canada.

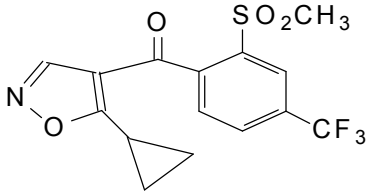
Methods for analyzing isoxaflutole residues in environmental media are available to research and monitoring agencies upon request to the PMRA.

Aventis will be carrying out rotational crop studies as a condition of this temporary registration. Following the review of this new data, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

# Table of Contents

# 1.0 The active substance, its properties, uses, proposed classification and labelling

## 1.1 Identity of the active substance and preparation containing it

| | |
|---|---|
| Active substance: | isoxaflutole |
| Function: | herbicide |
| Chemical name: (International Union of Pure and Applied Chemistry): | 5-cyclopropyl-4-(2-methylsulfonyl-4-trifluoromethylbenzoyl) isoxazole |
| (Chemical Abstracts Service [CAS]): | 5-cyclopropyl-4-isoxazolyl [2-(methylsulfonyl)-4-(trifluoromethyl)phenyl] methanone |
| CAS number: | 141112-29-0 |
| Nominal purity of active: | 98% |
| Identity of relevant impurities of toxicological, environmental and other significance: | Compounds such as nitrosamines, chlorinated dibenzodioxins, chlorinated dibenzofurans and hexachlorobenzene would not form in this product, given the absence of precursors in the manufacturing process. |
| Molecular formula: | $C_{15}H_{12}F_3NO_4S$ |
| Molecular mass: | 359.53 |
| Structural formula: |  |

## 1.2 Physical and chemical properties of active substance

**Table 1.1 Technical product: isoxaflutole**
Properties of technical material (technical grade active ingredient [TGAI]), except where marked PAI (pure active ingredient)

| Property | Result | Comment |
|---|---|---|
| Colour and physical state | PAI: white crystals<br>TGAI: yellow granular powder | |
| Odour | PAI: odourless<br>TGAI: slight acetic acid-like odour | |
| Melting point or range | PAI: 140EC<br>TGAI: 135–136EC | |
| Boiling point or range | Not applicable | |
| Density | PAI: 1.590 g/L<br>TGAI: 1.419 g/L | |
| Vapour pressure | Temperature (EC) / Vapour pressure (Pa)<br>20 / $3.22 \times 10^{-7}$<br>25 / $1.0 \times 10^{-6}$ | Relatively nonvolatile |
| Henry's Law Constant | TGAI: $1.87 \times 10^{-5}$ Pa m$^3$/mol | Low potential to volatilize under field conditions and from moist soil and water surfaces |
| Ultraviolet (UV) and visible spectrum at 26EC | No absorption at 8 > 350 nm | Exposure to light does not affect phototransformation |
| Solubility (mg/L) in water at 20EC | pH / Solubility<br>water (pH 5.5) / 6.2<br>5 / 6.8<br>9 / Decomposes | Low solubility in water at environmentally relevant pHs, low potential for mobility in soil |
| Solubility (g/L) in organic solvents at 20EC | Solvent / Solubility<br>hexane / 0.10<br>acetonitrile / 233.0<br>dichloromethane / 346.0<br>ethyl acetate / 142.0<br>acetone / 293.0<br>toluene / 31.2<br>methanol / 13.8<br>octanol / 0.76 | |
| *n*-Octanol–water partition coefficient ($K_{ow}$) | log $K_{ow}$ = 2.32 | Limited potential for bioaccumulation |
| Dissociation constant (p$K_a$) | No dissociable functionality | Active ingredient does not dissociate in water |

| Property | Result | Comment |
|---|---|---|
| Oxidizing properties | No evidence of decomposition with presence of iron, aluminum or tin powder over 30–150EC, degrades at 40–90EC in the presence of $FeCl_3$ powder | |

**Table 1.2 End-use product: Converge 75 WDG Herbicide**

| Property | Result |
|---|---|
| Colour | Tan |
| Odour | None |
| Physical state | Granular powder |
| Formulation type | Water dispersible granule |
| Guarantee | 75% |
| Container material and description | Anticipated to be nonpermeable polyethylene and fiber container overpack or polyethylene lined containers |
| Tap density (g/mL) | 1.4397 ± 0.0490 |
| pH of 1% dispersion at 20EC | 4.66 |
| Oxidizing or reducing action | Mild oxidation with potassium permanganate, no reaction with granular zinc, compatible with water, monoammonium phosphate and mineral spirits |
| Storage stability | Stable after storage at 54EC for 14 days in its initial package, a laboratory stored sample found to be stable for one year under ambient conditions |
| Flammability | No flash point below 100EC observed |
| Explodability | Lower dust explosion limit with a particle size of less than 63 Fm is 30 $g/m^3$ in air |
| Surfactants | Lignosulfonic acid, sodium salt |

## 1.3 Details of uses and further information

Isoxaflutole is a member of a new class of herbicides referred to as isoxazoles. Isoxaflutole inhibits the enzyme *p*-hydroxy phenyl pyruvate dioxygenase (HPPD), which converts *p*-hydroxy phenyl pyruvate to homogentisate, a key step in plastoquinone biosynthesis. The end-use product, Converge 75 WDG, is a water dispersible granular formulation that contains the active ingredient isoxaflutole at a concentration of 75%.

Converge 75 WDG may be used for pre-emergent application on conventionally tilled field corn grown in eastern Canada for control of several annual grass and broadleaf weeds. Converge 75 WDG provides control of witchgrass, large crabgrass, smooth crabgrass, common lamb's-quarters, redroot pigweed, common ragweed, eastern black nightshade, wormseed mustard, wild mustard, velvetleaf, plantain (seedlings) and dandelion (seedlings) when applied at a rate of 105 g product/ha (79 g active ingredient [a.i.]/ha) and the additional control of barnyard grass and green foxtail when applied at a rate of 140 g product/ha (105 g a.i./ha). Application must be made after crop seeding but prior to emergence with ground equipment only.

Converge 75 WDG may also be applied at 105 g product/ha (79 g a.i./ha) in a tank mixture with atrazine at 800 g a.i./ha for control of all the above weeds (including barnyard grass and green foxtail) in addition to lady's-thumb.

# 2.0 Methods of analysis

## 2.1 Methods for analysis of the active substance as manufactured

Two reversed phase high performance liquid chromatography methods using UV detection (HPLC–UV) at 250 nm were used for the determination of the active substance and significant impurities (content $ 0.1%) in the technical product. The methods have been shown to have satisfactory specificity, linearity, precision and accuracy.

## 2.2 Method for formulation analysis

A reversed phase HPLC–UV detection method at 280 nm was used for the determination of active substance in the formulation. The method has been shown to have satisfactory specificity, linearity, precision and accuracy.

## 2.3 Methods for residue analysis

### 2.3.1 Multiresidue methods for residue analysis

Isoxaflutole and its metabolites could not be quantified by multi-residue methods.

### 2.3.2 Methods for residue analysis of plants and plant products

The residue of concern (ROC) was defined from the plant metabolism study as isoxaflutole and its metabolites RPA 202248 and RPA 203328.

The proposed method for data gathering and enforcement purposes was a common moiety method that involved hydrolysis of the isoxazole ring to form the cyclopropyl propan-1,3-dione moiety (RPA 202248), which was further hydrolysed to the trifluoromethyl benzoic acid moiety (RPA 203328). RPA 203328 residues were

derivatized to a methyl ester and quantified by gas chromatography using mass selective detection (GC–MSD). The limit of quantitation (LOQ) of the method was 0.01 parts per million (ppm) for isoxaflutole and its metabolites in field corn matrices. The method was validated, in the range of expected residues, for accuracy and precision. The recoveries obtained from a large number of spiked samples were acceptable. The method was also successfully validated by an independent laboratory.

### 2.3.3 Methods for residue analysis of food of animal origin

The ROC was defined from the animal metabolism studies as isoxaflutole and its metabolites RPA 202248 and RPA 203328.

The proposed method for data gathering and enforcement purposes was a common moiety method that involved base hydrolysis of isoxaflutole to form RPA 202248. Residues of RPA 202248 were quantified by HPLC–UV. The LOQs for isoxaflutole and its metabolites were 0.01 ppm (milk or eggs), 0.4 ppm (beef or poultry liver), 0.2 ppm (beef or poultry muscle and fat) and 0.2 ppm (beef kidney). The method was validated, in the range of expected residues, for accuracy and precision. The recoveries obtained from a large number of spiked samples were acceptable. The method was also successfully validated by an independent laboratory.

## 3.0 Impact on human health

### 3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities in the active substance or to their transformation products

### 3.1.1 Absorption, distribution, metabolism and excretion

The absorption, distribution, metabolism and excretion of $^{14}$C-phenyl labelled isoxaflutole ($^{14}$C-RPA 201772, purity > 98%) was examined in Sprague–Dawley (SD) rats. For the single oral low- and high-dose groups, five animals/sex received a single dose of either 1 or 100 mg/kg body weight (bw) of $^{14}$C-RPA 201772, respectively, by oral gavage. For the repeat oral low-dose, another five animals/sex received a nonradiolabelled low dose (1 mg/kg bw) for 14 consecutive days followed by a single dose of 1.0 mg/kg bw of $^{14}$C-RPA 201772 by oral gavage. For blood pharmacokinetic experiments another five animals/sex received a single dose of 1.0 or 100 mg/kg bw $^{14}$C-RPA 201772 by oral gavage. All animals were sacrificed at 168 h post-dosing. RPA 201772 was rapidly absorbed at both 1.0 and 100 mg/kg bw. The maximal whole blood concentration was achieved within one hour at both dose levels. On the basis of available urinary excretion data (radioactivity detected in urine, cage washes and tissues) the mean estimated proportion of the administered dose absorbed was approximately 39, 73 and 75% for the high-, low- and repeat-dose groups, respectively. Tissue distribution of radioactivity between the sexes appeared to be similar. In the high-dose group, the highest levels in both sexes were found in the blood and plasma and to a lesser extent in the liver and

kidneys of males and in the liver, kidneys, lungs and heart of females. In the single and repeat low-dose groups, higher tissue concentrations were found in the liver and kidneys. Elimination was rapid and dose dependent. The major route of elimination in the high-dose group was via the feces (approximately 55–63% of the administered dose) and in the single and repeat low-dose groups was via the urine (68–74% of the administered dose). The majority of the activity was eliminated within 24 and 48 h post-dosing for the low- and high-dose groups, respectively. The terminal elimination phase $T_{½}$ was about 60 h in both sexes at both dose levels. Higher fecal elimination at the high dose may be due to saturation of absorption, resulting in elimination of unchanged parent compound. Mean recovery of radioactivity in the tissues at 168 h post-dosing was low, indicating that there was most likely a good systemic clearance of the test substance with little potential for accumulation. RPA 201772 was rapidly and extensively metabolized. The major metabolite was the diketonitrile RPA 202248 (70–85% of the administered dose). Minor metabolites included RPA 203328 (0.6–3.6% of the administered dose), RPA 207048, RPA 205834 and RPA 205568. The parent compound, RPA 201772, was only detected in fecal extracts in the single high-dose group during the first 24 h. Data suggest that only Phase I reactions occurred; there was no indication of any metabolites resulting from Phase II (conjugation) reactions. The proposed metabolic pathway is summarized in Figure 1. The absorption, distribution, metabolism and excretion were not influenced by repeat oral administration.

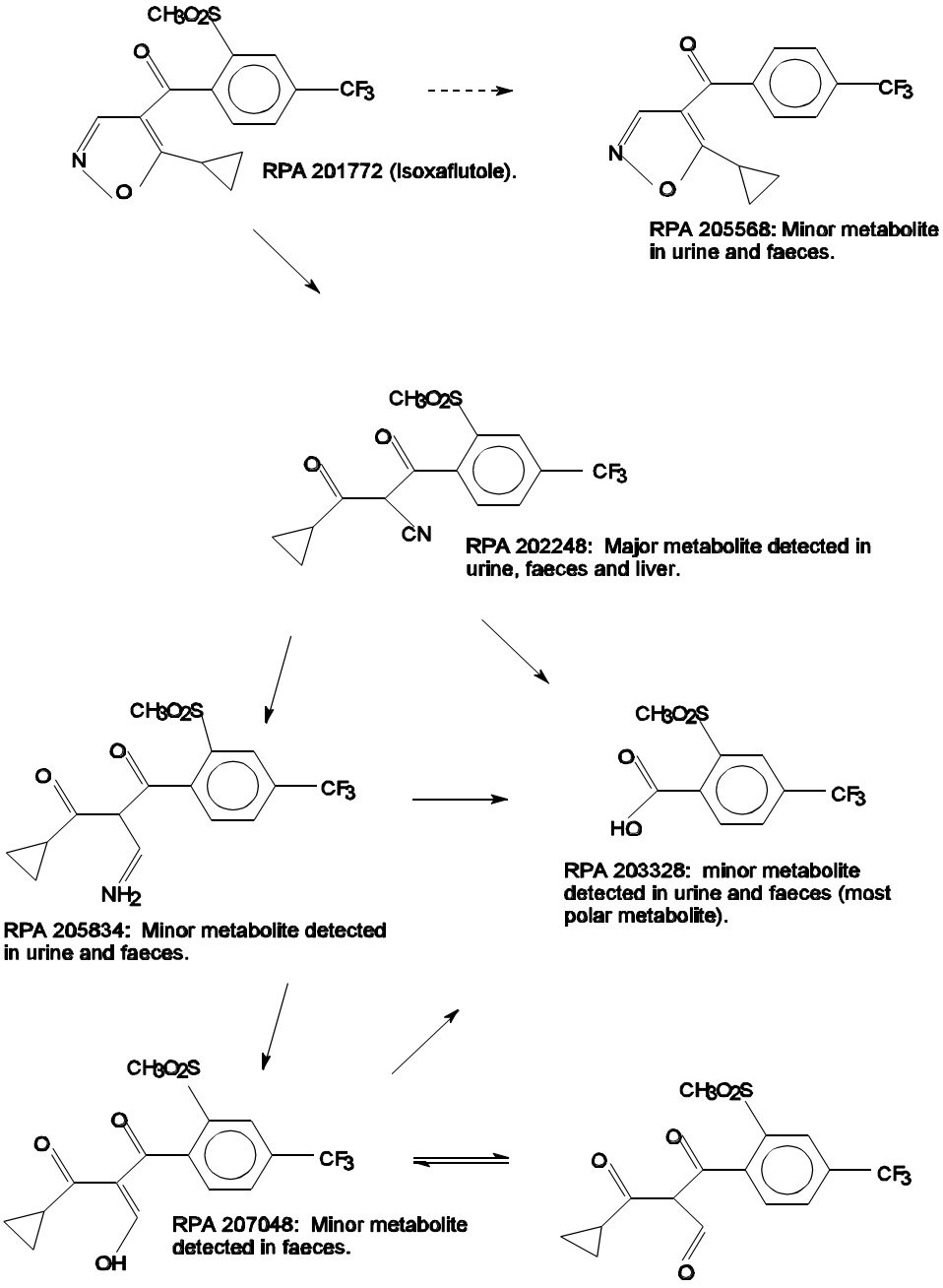
### 3.1.2 Acute toxicity: technical and formulation

Technical isoxaflutole (RPA 201772) has low acute toxicity via the oral (lethal dose 50% [$LD_{50}$] > 5000 mg/kg bw) and inhalation (lethal concentration 50% [$LC_{50}$] > 5.23 mg/L) routes of exposure in rats and via the dermal ($LD_{50}$ > 2000 mg/kg bw) route of exposure in rabbits. In rabbit eyes, the maximum irritation score (MIS) was 5.8/110 at one hour, indicating that it was minimally irritating. The maximum average score (MAS) at 24, 48 and 72 h for dermal irritation in rabbits was 0/8; therefore, RPA 201772 was considered to be nonirritating to rabbit skin. It was not a skin sensitizer in guinea pigs, according to the Buehler and the Magnusson–Kligman guinea pig maximization test methods.

Converge 75 WDG herbicide formulation has low acute toxicity via the oral ($LD_{50}$ > 5000 mg/kg bw) and inhalation ($LC_{50}$ > 5.26 mg/L) routes of exposure in rats and via the dermal ($LD_{50}$ > 2000 mg/kg bw) route of exposure in rabbits. The MIS for primary ocular irritation in rabbits was 13.5/110 at one hour, indicating that it was minimally irritating. In rabbits the MIS for primary dermal irritation was 0.83/8 at one hour; therefore, Converge 75 WDG was considered to be slightly irritating to rabbit skin. It was not a skin sensitizer in guinea pigs, according to the Buehler method.

On the basis of a review of the acute toxicity studies submitted for the end-use formulation and of the current draft of the product label, there are no labelling recommendations at this time.

**Figure 1. Proposed metabolic pathway in rats**



### 3.1.3 Genotoxicity

Isoxaflutole did not induce gene mutations in bacterial cells in vitro in the presence or the absence of metabolic activation system prepared from Aroclor 1254 induced rat livers (S9) metabolic activation. Under the conditions of in vitro mammalian cell gene mutations assays with L5178Y TK and either mouse lymphoma cells or Chinese hamster V79 lung cells, isoxaflutole did not induce increases in mutant colony numbers or in mutation frequency in the presence or absence of S9 metabolic activation. Isoxaflutole was not clastogenic in the presence or absence of S9 metabolic activation at any dose level in either in vitro chromosome aberration assay using human lymphocytes. In an in vivo micronucleus assay with mouse bone marrow cells, there was no evidence that isoxaflutole induced chromosomal damage or other damage leading to micronucleus formation in polychromatic erythrocytes of treated mice. On the basis of the results of the data presented, isoxaflutole was not considered to be genotoxic under the conditions of the studies performed.

### 3.1.4 Short-term toxicity and chronic toxicity and oncogenicity

The short-term toxicity and chronic toxicity and oncogenicity of isoxaflutole were investigated in mice, rats and dogs. A series of 28- and 90-day dietary studies were conducted initially. These studies were used to establish appropriate dose levels to be used in the chronic toxicity and oncogenicity studies. A 21-day dermal study was also carried out in rats.

#### 3.1.4.1 Short-term toxicity and chronic toxicity and oncogenicity in the mouse

In a 28-day preliminary dietary study, groups of 10 male or female CD-1 mice received isoxaflutole (99.9% purity) via dietary administration at concentrations of 0, 175, 700, 2800 or 7000 ppm daily for 28 days. The dose levels were equal to 0, 29.4, 120.7, 474.6 and 1140.1 mg/kg bw/day in males and 0, 34.7, 142.9, 534.4 and 1347.4 mg/kg bw/day in females.

There were no treatment-related mortalities, clinical or ophthalmoscopic observations or treatment-related effects on body weight, body-weight gain or food consumption. The liver appeared to be the target organ. Significant treatment-related clinical chemistry findings included increased alanine aminotransferase (ALAT) (males at 2800 and 7000 ppm and females at 700, 2800 and 7000 ppm) and aspartate aminotransferase (ASAT) (males at 2800 and 7000 ppm and females at 7000 ppm) activity. Increased liver weights were observed at all dose levels in both sexes. Significant treatment-related gross pathological observations were noted in the liver and included enlarged liver (males at 700, 2800 and 7000 ppm and females at 2800 and 7000 ppm) and white striations (both sexes at 7000 ppm). Treatment-related histopathological findings in the liver included centrilobular hepatocellular hypertrophy (both sexes at 700 ppm and above) and hepatocellular necrosis (males at 2800 and 7000 ppm and females at 7000 ppm). Other histopathological findings included increased extramedullary hematopoiesis in spleen

(both sexes at 7000 ppm) and X-zone cell vacuolation in the adrenal glands (females at 7000 ppm). In the absence of any other significant findings at 175 ppm, the increased liver weights were considered a minor adaptive change; therefore, the no observed adverse effect level (NOAEL) was 175 ppm, equal to 29 mg/kg bw/day in males and 35 mg/kg bw/day in females.

In a 90-day preliminary dietary study, groups of 12 CD-1 mice/sex/dose level received 0, 50, 1000 or 2000 ppm isoxaflutole (purity 983 g/kg) via dietary administration daily for 13 weeks and five days. The dose levels were equal to 0, 7.6, 170.0 and 324.1 mg/kg bw/day in males and 0, 8.7, 181.2 and 376.2 mg/kg bw/day in females.

There were no treatment-related mortalities, clinical, ophthalmoscopic or gross pathological observations, or treatment-related effects on body weight, body-weight gain, food consumption or food efficiency. The liver appeared to be the target organ. Significant treatment-related clinical observations were increased ASAT and ALAT activity at 2000 ppm (both sexes). Increased absolute liver weights were observed in males at 50, 1000 and 2000 ppm and in females at 2000 ppm. Increased relative liver weights were observed in males at 1000 and 2000 ppm and in females at 2000 ppm. Periacinar hepatocytic hypertrophy was observed in males at 1000 and 2000 ppm and in females at 2000 ppm. At 50 ppm, the lowest dose tested, the only significant observation was an increase in absolute liver weight in males. In the absence of a similar increase in females and in the absence of any biochemical, gross pathological or histopathological observations at 50 ppm in either sex, this was considered to be a minor adaptive change; therefore, the NOAEL for isoxaflutole was 50 ppm equal to 7.6 mg/kg bw/day in males and 8.7 mg/kg bw/day in females.

In a 78-week carcinogenicity study, 64 or 76 mice/sex/dose, CD-1 mice received a daily dose of isoxaflutole (purity $ 98.7% a.i.) via dietary admixture at dose levels of 0, 25, 500 or 7000 ppm (equal to 0, 3.2, 64.4 or 977.3 mg/kg bw/day, respectively, for males; and 0, 4.0, 77.9 or 1161.1 mg/kg bw/day, respectively, for females). Interim sacrifices were made at 26 (12 mice/sex at the 0 and 7000 pm doses) and 52 weeks (12 mice/sex at all dose levels).

There was no treatment-related effect on mortality and no treatment-related ophthalmoscopic or hematological observations. Treatment-related clinical observations included distended abdomen (males) and cyanosis in the ventral abdomen (both sexes) at 7000 ppm. Body weight and body-weight gain was significantly lower in males at 500 ppm and in both sexes at 7000 ppm. Food consumption was unaffected by treatment. Food efficiency was significantly lower in both sexes at 7000 ppm during the first 14 weeks of the study (not determined after week 14). There was a treatment-related increase in absolute and relative liver weights in both sexes at 7000 ppm after 26, 52 and 78 weeks of treatment, which was associated with a higher incidence of liver masses (both sexes), enlarged or swollen livers (males) and liver “areas of change” (males). Liver masses and “areas of change” were observed in males at 7000 ppm at the 52-week interim sacrifice. Abdominal distension was also observed in males at 7000 ppm at both the

52-week interim sacrifice and at the 78-week terminal sacrifice; this was most likely associated with the findings in the liver. Treatment-related non-neoplastic findings were observed in the liver and were first apparent at the 26-week interim sacrifice. At the 26-week interim sacrifice, all animals (males and females) at 7000 ppm exhibited periacinar hepatocytic hypertrophy. Other treatment-related non-neoplastic findings in the liver at 7000 ppm at the 26-week interim sacrifice included necrosis of individual hepatocytes (males and females) and pigmented Kupffer cells (males). At the 52-week interim sacrifice, treatment-related findings in the liver at 7000 ppm included periacinar hepatocytic hypertrophy (males and females), necrosis of individual hepatocytes (males), pigment laden hepatocytes and Kupffer cells (males), periacinar hepatocytic fatty vacuolation (females) and extramedullary hematopoiesis in the spleen (males). In scheduled and unscheduled deaths in the 78-week terminal phase group, treatment-related findings in the liver included increased incidence of periacinar hepatocytic hypertrophy, necrosis of individual hepatocytes and erythrocytes in hepatocytes in both sexes at 7000 ppm. Other treatment-related findings in the liver at the 78-week terminal sacrifice included increased incidence of pigment laden hepatocytes and Kupffer cells, basophilic foci and increased ploidy as well as a nonsignificant increase in clear cell foci in males at 7000 ppm and an increased incidence of periacinar hepatocytic fatty vacuolation in females at 7000 ppm. Significant findings at 500 ppm included periacinar hepatocytic hypertrophy in males after the 52-week interim sacrifice and necrosis of individual hepatocytes in males at the 72-week terminal sacrifice. Treatment-related neoplastic findings were observed in the liver in both sexes at 7000 ppm and in males at 500 ppm. At the 52-week interim sacrifice, there was a significant increased incidence of hepatocellular adenomas in males at 7000 ppm. In the scheduled and unscheduled deaths in the 78-week study there was a significant increased incidence of hepatocellular adenomas in males and females at 7000 ppm, hepatocellular carcinomas in males at 7000 ppm and a non-statistically significant increased incidence of hepatocellular carcinomas in females at 7000 ppm. The incidences of hepatocellular adenomas and carcinomas in both sexes at 7000 ppm exceeded the upper limit of the historical control range with this species in this laboratory. The incidence of hepatocellular adenomas and carcinomas combined was significantly increased in males and in females at 7000 ppm. In the scheduled and unscheduled deaths in the 78-week study there was also an increased incidence of hepatocellular carcinomas in males at 500 ppm; this was slightly beyond the upper limit of the historical control range with this species in this laboratory. There were no hepatic tumours observed at the 26-week interim sacrifice. There was no dose-related trend in the appearance of hepatocellular adenomas in either sex; they appeared in males at approximately one year (52–55 weeks) and in females at approximately 77–78 weeks. The appearance of hepatocellular carcinomas, however, showed a dose-related trend from 78 weeks in the control group, 71 weeks at 25 ppm, 52 weeks at 500 ppm and 47 weeks at 7000 ppm. Hepatocellular carcinomas were not observed in any control or treated females up to and including 500 ppm; in the 7000 ppm group hepatocellular carcinomas first appeared at 60 weeks. The increased liver weight, gross pathological findings and non-neoplastic and neoplastic histopathological findings in both sexes at 7000 ppm, including hepatocellular adenomas and carcinomas, indicate that the liver was adversely affected by treatment. Under the conditions of this study, isoxaflutole appeared to induce

hepatocellular adenomas and carcinomas in male and female mice. The lowest observed effect level (LOEL) was 500 ppm (equivalent to 64.4 mg/kg bw/day in males and 77.9 mg/kg bw/day in females) on the basis of decreased body-weight gain, increased liver weights, the increased incidence of periacinar hepatocytic hypertrophy and necrosis of individual hepatocytes in the liver. Males at 500 ppm also exhibited an increased incidence of hepatocellular carcinomas that exceeded the upper limit of the historical control range with this species in this laboratory. There were no treatment-related findings at 25 ppm; therefore, the no observed effect level (NOEL) was 25 ppm (equal to 3.2 mg/kg bw/day for males and 4.0 mg/kg bw/day for females).

#### 3.1.4.2 Short-term toxicity and chronic toxicity and oncogenicity in the rat

In a preliminary 90-day dietary study, groups of 10 CD rats/sex/dose received 0, 25, 100, 400 or 1000 mg/kg bw/day isoxaflutole (purity 99.4%), via dietary administration daily for six weeks. Owing to clinical and ophthalmoscopic observation (corneal lesions) the animals were observed for a further seven weeks without treatment to investigate the reversibility of the eye lesions. The concurrent control group received an untreated basal diet for 17 weeks. The treated animals were sacrificed after week 13 and the control animals were sacrificed after week 17. This study was not acceptable for determination of short-term toxicity; treatment was terminated seven weeks early and the control animals were sacrificed four weeks after the treatment groups.

There were no treatment-related mortalities. There was a treatment-related effect on body-weight gain and food efficiency in both sexes at 400 and 1000 mg/kg bw/day and on food consumption in females at 1000 mg/kg bw/day. These findings appeared to be reversed or partially reversed during the recovery phase. Organ weight comparisons between the treated groups and the respective control groups could not be adequately made, since the treated animals were sacrificed after 13 weeks and the control animals after 17 weeks. Significant clinical and ophthalmoscopic findings were observed in the eye and included an increased incidence of opaque eyes and focal corneal opacity at all dose levels (except females at 25 mg/kg bw/day) with an associated keratitis (males at 100 mg/kg bw/day and above) and vascularization (males and females at 100 mg/kg bw/day), respectively. The rate of incidence was not dose related and males appeared to be more susceptible. Clinical and ophthalmoscopic observations during the recovery phase suggest that the corneal lesions were reversible by week 11. Histopathological examination of the cornea of a limited number of animals (five animals of each sex) after the recovery phase revealed generalized thickening of the epithelium, subepithelial fibroblastic reaction and vascularization of the stroma at 100 mg/kg bw/day and above in both sexes. The clinical and ophthalmoscopic and histopathological observations at all dose levels (except females at 25 mg/kg bw/day) indicate that the eye (cornea) was adversely affected by treatment, with males being more susceptible. Histopathological data after the recovery phase suggest that long-term administration of isoxaflutole may render the gross corneal lesions permanent. On the basis of the corneal eye lesions at all dose levels, especially in the males, neither a NOEL nor a NOAEL was established.

In a 90-day dietary study, groups of 10 CD rats/sex/dose received either 0, 1.0, 3.0, 10 or 100 mg/kg bw/day isoxaflutole (purity 99.4%) via dietary administration daily for 13 weeks and three days. There were no treatment-related mortalities and no treatment-related effects on body weight, body-weight gain, food consumption or food efficiency. There were no significant treatment-related effects on hematological, clinical chemistry or urinalysis parameters examined. Treatment-related findings in males at 100 mg/kg bw/day included increased absolute and relative liver weights, with an associated increased incidence of periacinar hepatocytic hypertrophy; these were considered to be an adaptive response and not adverse. Significant treatment-related clinical, ophthalmoscopic, gross pathological and histopathological findings were observed in the eye in males at 10 mg/kg bw/day and in both sexes at 100 mg/kg bw/day. Clinical and ophthalmoscopic observations included increased incidences of bilateral and unilateral opaque eyes and focal corneal opacity, respectively. Focal corneal opacity was first apparent during week 3 and persisted throughout the study. Significant gross pathological observation included an increased incidence of corneal opacity (unilateral and bilateral) in both sexes at 100 mg/kg bw/day. The overall incidence of corneal lesions was similar in both sexes, although the severity of the lesions was more significant in the males. The most notable histopathological findings included vacuolation (males and females) and superficial exfoliation of the epithelial cells (males and females), epithelial thickening (males), necrosis and inflammation (males and females), subepithelial fibroblastic reaction (males and females) and vascularization of the stroma (males and females). The changes were considered by the study author to be reversible after a short recovery period following cessation of treatment in the previous study (Chase, K.R., February 9, 1994, Study ID 93/RHA468/0906), with the exception of residual evidence of tissue repair detectable only by histopathological examination. There were no treatment-related effects at 1.0 or 3.0 mg/kg bw/day; therefore, the NOEL for isoxaflutole was 3.0 mg/kg bw/day.

In a combined chronic toxicity and carcinogenicity study, isoxaflutole (purity batch number FPI 1308, 98.3% a.i. and batch number 40 ADM, 93–99.2% a.i.) was continuously administered to 75 SD rats/sex/dose at dietary levels of 0, 0.5, 2.0, 20 or 500 mg/kg bw/day for 104 weeks. An additional 20 animals/sex/dose were treated for 52 weeks, after which 10 animals/sex/dose were sacrificed and the remainder were held for a maximum of eight weeks without treatment to assess the reversibility of treatment-related changes.

There was no treatment-related effect on mortality. There were no significant treatment-related findings in the hematological parameters examined. Significant treatment-related clinical findings were observed in both sexes at 500 mg/kg bw/day and included opaque eyes, thin body build, abnormal gait and limited use of limbs. Body-weight gain was significantly reduced in both sexes at 500 mg/kg bw/day throughout the study. This was associated with decreased food consumption and food efficiency in females and decreased food efficiency in males. During the recovery phase the treatment-related effect on body-weight gain appeared to be partially reversible. Ophthalmoscopic examinations revealed treatment-related corneal lesions, ranging from small focal superficial opacities

to large corneal opacities with associated vascularization and iritis, in males at 20 mg/kg bw/day and in both sexes at 500 mg/kg bw/day with the rate of incidence greater in females and severity of the lesions greater in males.

There were treatment-related clinical chemistry and urinalysis findings in both sexes at 20 and 500 mg/kg bw/day; however, after a seven-week recovery period there were no findings that were considered to be biologically or toxicologically significant in either sex. Males at 20 mg/kg bw/day and both sexes at 500 mg/kg bw/day exhibited treatment-related elevated liver weights and males at 20 and 500 mg/kg bw/day exhibited treatment-related elevated thyroid weights, these were first observed at the 52-week interim sacrifice. Treatment-related gross pathological findings at 20 and 500 mg/kg bw/day included swollen livers (males at 20 and 500 mg/kg bw/day), “areas of change” (males at 500 mg/kg bw/day) and masses (males and females at 500 mg/kg bw/day) in the liver, opaque eyes (males at 20 and 500 mg/kg bw/day) and dark enlarged thyroids with masses (males at 20 and 500 mg/kg bw/day). Treatment-related non-neoplastic findings in the liver included periacinar hepatocytic hypertrophy (both males and females at 20 and 500 mg/kg bw/day), focal cystic degeneration (males at 20 and 500 mg/kg bw/day), midzonal foamy hepatocytes (males at 20 mg/kg bw/day and both males and females at 500 mg/kg bw/day), portal tract senile changes in bile duct (both males and females at both 20 and 500 mg/kg bw/day), basophilic and clear cell foci (females at 500 mg/kg bw/day) and pigment laden hepatocytes (females at 500 mg/kg bw/day). Treatment-related lesions of the eye were observed in males and included increased incidences of keratitis (2.0, 20 and 500 mg/kg bw/day), vascularization of the stroma (500 mg/kg bw/day), epithelial thickening (20 and 500 mg/kg bw/day) and superficial exfoliated epithelial cells (500 mg/kg bw/day). Other treatment-related non-neoplastic findings included increased incidences of thyroid cystic follicular hyperplasia, axonal and myelin sciatic nerve degeneration, focal degeneration and inflammation of the thigh muscle in males at 20 and 500 mg/kg bw/day and in females at 500 mg/kg bw/day. Males at 0.5 mg/kg bw/day in the unscheduled sacrifice group exhibited a significantly increased incidence of keratitis; however, the overall incidence (104-week terminal sacrifice and unscheduled sacrifices) was not significantly increased over the control group.

Treatment-related neoplastic findings were observed in the liver in both sexes at 500 mg/kg bw/day and in the thyroid of males at 500 mg/kg bw/day. The overall incidence (104-week terminal sacrifice and unscheduled sacrifices) of hepatocellular adenomas, carcinomas, and adenomas and carcinomas combined was statistically significantly increased in both sexes at 500 mg/kg bw/day compared with the control group. The overall incidence of hepatocellular adenomas and carcinomas in both sexes at 500 mg/kg bw/day was above the upper limit of the historical control range for animals of this strain provided from this laboratory. The increased incidences of liver tumours in both sexes at 500 mg/kg bw/day were associated with significantly increased liver weights, masses, swellings and “areas of change” in the liver and non-neoplastic lesions at the 52-week interim sacrifice and at the 104-week terminal sacrifice. Hepatocellular adenomas were first observed at 365 days in males at 500 mg/kg bw/day and at 427 days in females at 500 mg/kg bw/day compared with 728 days in both male and female control

groups. Hepatocellular carcinomas were first observed at 646 days in males at 500 mg/kg bw/day compared with 594 days in the control group males and at 426 days in females at 500 mg/kg bw/day compared with 728 days in the control group females. The overall incidence (104-week terminal sacrifice and unscheduled sacrifices) of thyroid follicular cell adenomas was statistically significantly increased in males at 500 mg/kg bw/day compared with the control group. The overall incidence of thyroid follicular cell adenomas was above the upper limit of the historical control range for animals of this strain from this laboratory. There were no significant differences in the overall incidence of follicular cell carcinomas. The overall incidence of follicular adenomas and carcinomas combined was 18/75 (24%) for males at 500 mg/kg bw/day compared with 3/74 (4.1%) for males in the control group. The increased incidence of thyroid follicular cell adenomas in males at 500 mg/kg bw/day was accompanied by a significantly increased incidence of cystic follicular hyperplasia of the thyroid but no increase in the incidence of follicular cell hyperplasia or parafollicular cell hyperplasia of the thyroid. In addition most of the males at 500 mg/kg bw/day with liver tumours also had follicular cell adenomas of the thyroid at the termination of the study. The overall incidence of thyroid follicular cell adenomas in males at 500 mg/kg bw/day was above the upper limit of the historical control range for animals of this strain provided from this laboratory. Thyroid follicular cell adenomas were first observed at 612 days in males at 500 mg/kg bw/day compared with 647 days in the control group males.

Under the conditions of this study, isoxaflutole was carcinogenic to both sexes at 500 mg/kg bw/day. The chronic LOEL for females was 20 mg/kg bw/day on the basis of non-neoplastic histopathological findings in the liver (periacinar hepatocytic hypertrophy and portal tract, senile, changes in bile duct). The chronic LOEL for males was 2.0 mg/kg bw/day on the basis of the significantly increased incidence of keratitis in the eye. There were no significant treatment-related findings in females at 2.0 mg/kg bw/day; therefore, the chronic NOEL for females was 2.0 mg/kg bw/day. Males at 0.5 mg/kg bw/day in the unscheduled sacrifice group exhibited a significantly increased incidence of keratitis; however, the overall incidence (104-week terminal sacrifice and unscheduled sacrifices) was not significantly increased over the control group; therefore, the chronic NOEL for males was 0.5 mg/kg bw/day.

#### 3.1.4.3 Short-term toxicity in the dog

In a preliminary study, two pure-bred beagle dogs (one male and one female) were administered isoxaflutole (purity 97%) daily by oral capsule (days 1–39) and by dietary admixture (days 48–59) with an eight-day washout period (days 40–47, no treatment) between the different dosing regimens. The dose levels were 1000 mg/kg bw/day via oral capsule and 25 000 ppm (approximately 1000 mg/kg bw/day) via dietary admixture. The animals were sacrificed on day 60. The objective of this study was to assess suitability of 1000 mg/kg bw/day for repeated dosing in the dog and to investigate if there were any marked differences between the capsule and dietary routes of oral administration to select the appropriate route for a subsequent one-year toxicity study. There were no unscheduled deaths and no treatment-related effects on body weight, body-weight gain or food

consumption and no treatment-related clinical, ophthalmoscopic or gross pathological observations. There were no significant effects on hematology, blood chemistry or urinalysis parameters examined, although alkaline phosphatase (AP) activity increased during treatment periods. Relative liver weights exceeded the normal upper limit of 4% of terminal body weight (as indicated by the study report) in both the male and the female dog (4.45 and 4.55% for the male and female dog, respectively). Histopathological examination revealed congestion in the liver with minimal centrilobular rarefaction of hepatocytes in the female dog with no significant findings in the male dog. On the basis of increased liver weight and histopathological findings in the liver of the female dog, the liver appeared to be adversely affected in both sexes. Food consumption was similar whether the test substance was administered as oral capsule or as dietary admixture in both animals; therefore, there appears to be no palatability problem with the dietary admixture. There was no NOAEL or NOEL established in this study.

In a one-year dietary study, isoxaflutole (purity 98.7%) was administered daily to five pure-bred beagle dogs/sex/dose at dose levels of 0, 240, 1200, 12 000 or 30 000 ppm (equivalent to 0, 8.56, 44.81, 453 or 1265 mg/kg bw/day, respectively, for males and 0, 8.41, 45.33, 498 or 1254 mg/kg bw/day, respectively, for females) via dietary administration for 52 weeks.

There were no treatment-related mortalities (all males at 30 000 ppm were sacrificed after 26 weeks because of severe anemia). Notable clinical observations included thin appearance and pale gums in males at 30 000 ppm. There were no treatment-related ophthalmoscopic observations or any significant treatment-related changes in urine parameters. Significant treatment-related decreased body-weight gains were observed at 12 000 ppm (females) and 30 000 ppm (both sexes). Food consumption was comparable between the control and treatment groups, indicating that lower body-weight gains were not due to loss of appetite or to a food palatability problem. Regenerative hematolytic anemia was observed in males at 30 000 ppm and in females at $12 000 ppm. Effects included decreased red cell parameters (red blood cells [RBC], hemoglobin [Hb] and hematocrit [Hct]) and increased incidence of polychromatic erythrocytes and extramedullary hematopoiesis. Hematological symptoms and histopathological observations correlated well with classical symptoms of chronic hematolytic anemia. The liver was also a target organ, with increased weights, clinical chemistry (elevated AP, ALAT, 5'-nucleotidase (5'-NT) and (-glutamyltransferase ((-GT) activity) and histopathological (hepatocellular swelling, centrilobular clumping and margination of cytoplasmic staining, centrilobular necrosis and fibrosis, vacuolated hepatocytes and centrilobular glycogen depletion) findings at $12 000 ppm in both sexes. There was no neoplastic tissue observed in the animals in the treatment or control groups. On the basis of reduced body-weight gains, reduced RBC parameters, elevated clinical chemistry parameters, elevated liver weights and associated gross pathological and histopathological observations, the LOEL for isoxaflutole was 12 000 ppm (453 mg/kg bw/day for males, 498 mg/kg bw/day for females). There were no significant treatment-related findings at 240 or 1200 ppm; therefore, the NOEL for isoxaflutole was 1200 ppm (44.81 mg/kg bw/day for males, 45.33 mg/kg bw/day for females).

### 3.1.4.4 Short-term dermal toxicity in the rat

The 21dose repeat dose dermal toxicity of isoxaflutole (purity 983 g/kg) was determined in CD rats (remote SD). Eight animals/sex/dose received a daily dermal application of 0, 10, 100 or 1000 mg/kg bw/day of the test substance in 0.5% weight per volume (w/v) methyl cellulose under occlusive wrapping for eight hours per day, seven days per week for three weeks. The control group received 0.5% w/v methyl cellulose. The dosing volume was kept constant at 2.0 mL/kg bw. There were no treatment-related mortalities, clinical, ophthalmoscopic, gross pathological or histopathological observations, and no treatment-related effects on body weight, body-weight gain, food consumption or the food conversion ratio. There were no treatment-related effects on the hematological or blood chemistry parameters examined. The only treatment-related finding was a marginal increase in the liver weights at 1000 mg/kg bw/day in both sexes. In the absence of any significant blood chemistry, gross pathological or histopathological observations, the increase in the liver weights could be considered a minor adaptive change and not biologically or toxicologically significant. On the basis of the results of the study, the NOAEL for isoxaflutole was 1000 mg/kg bw/day.

## 3.1.5 Reproductive and developmental toxicity

In a one-generation reproductive study, 10 rats/sex/group continuously received dietary admixtures at the target dose levels of 0, 0.5, 2.0, 20 or 500 mg/kg bw/day isoxaflutole (purity 98.7%) for six weeks premating and throughout mating, gestation and lactation. The $F_1$ offspring received the same dietary admixture at the same target concentrations from weaning (day 21) through at least three weeks post-weaning until sacrifice.

There were no treatment-related mortalities or clinical observations. In the $F_0$ generation, there was a treatment-related effect on body weight, body-weight gain and food consumption in both sexes at 500 mg/kg bw/day. There was a treatment-related increased incidence of chronic keratitis in the $F_0$ generation females at 500 mg/kg bw/day. In the $F_1$ offspring, both sexes at 500 mg/kg bw/day exhibited a treatment-related decreased body weight throughout lactation and weanling phases as well as an increased incidence of chronic keratitis. $F_1$ female offspring also exhibited an increased incidence of subepithelial corneal deposits, which were considered to represent early changes leading to keratitis. There were no significant differences in the reproductive performance parameters examined between the treatment and control groups. At 500 mg/kg bw/day the viability index was statistically significantly lower. This was, however, most likely not treatment-related, since it was attributed mostly to the death of all pups in one litter. Other notable findings at 500 mg/kg bw/day included slightly lower numbers of pups per litter and numbers of live pups per litters and an increase in the number of $F_1$ offspring dying, killed, missing or cannibalized during lactation days 0–4 at 500 mg/kg bw/day. There were no treatment-related gross pathological observations in the $F_0$ adults or $F_1$ offspring. There were no significant treatment-related effects at 0.5, 2.0 or 20 mg/kg bw/day. The NOEL for systemic toxicity was 20 mg/kg bw/day on the basis of decreased body weight, body-weight gain and food consumption in both sexes and

increased incidence of chronic keratitis in females at 500 mg/kg bw/day. There were no significant differences in reproductive performance parameters examined between the treated groups and the control group. The NOEL for reproductive toxicity was 20 mg/kg bw/day on the basis of decreased fetal body weight throughout lactation and weanling phases.

In a two-generation reproduction (one litter per generation) study, isoxaflutole (purity 98.7%) was administered to CD rats at target dose levels of 0, 0.5, 2, 20 or 500 mg/kg/day (actual levels in males: 0, 0.45, 1.76, 17.4 or 414 mg/kg/day; females: 0, 0.46, 1.79, 17.7 or 437 mg/kg/day, respectively). Thirty $F_0$ animals/sex received the diets containing the test substance 10 weeks prior to mating and throughout gestation and lactation. Thirty $F_1$ animals/sex/dose were selected to produce the $F_2$ generation. The $F_1$ animals were treated similarly to the $F_0$ animals.

There were no mortalities and no treatment-related clinical observations in the $F_0$ or $F_1$ adults. There were no treatment-related clinical observations in the $F_1$ or $F_2$ pups during lactation. Body weight and body-weight gain were significantly reduced in $F_0$ and $F_1$ adult males during pre- and post-mating at 500 mg/kg bw/day; this was associated with lower food consumption. Body weight and body-weight gain were significantly reduced in $F_0$ adult females throughout the premating period; this was associated with lower food consumption. $F_1$ adult males and females began the second generation premating period at significantly lower body weight compared with the control group. In $F_1$ adult females, body weight was significantly lower throughout the premating period; however, body-weight gain was comparable to or slightly higher than the control group. During gestation and lactation, body weight was significantly reduced in both $F_0$ and $F_1$ adult females. Body-weight gain during gestation was adversely affected in $F_0$ adult females and was associated with a reduction in food consumption. There was no treatment-related effect in body-weight gain in $F_1$ adult females during gestation. Body weight was significantly lower in both $F_0$ and $F_1$ adult females at 500 mg/kg bw/day during lactation. Body-weight gain, however, was not affected by treatment, despite lower food consumption in $F_0$ and $F_1$ adult females during lactation. There were no treatment-related ophthalmic observations in $F_0$ adults. $F_1$ adult (both sexes) at 500 mg/kg bw/day exhibited a treatment-related increased incidence of chronic keratitis and an increased incidence of unilateral and bilateral subacute corneal inflammation. There were no significant effects observed in mating or fertility indices, gestation, live birth or weaning indices. The number of females with stillborn pups increased in the $F_0$ generation at 500 mg/kg bw/day. The number of stillborn pups increased slightly in the $F_1$ pups at 20 and 500 mg/kg bw/day. A reduced viability index was observed in the $F_1$ and $F_2$ pups at 500 mg/kg bw/day and in the $F_1$ pups at 20 mg/kg bw/day. This was associated with a dose-related increase in pup mortality during lactation days 0–4. Significant findings in both $F_1$ and $F_2$ pups at 500 mg/kg bw/day included reduced body weight (both sexes) throughout lactation, the absence of milk in the stomach (both sexes) and underdeveloped renal papilla (both sexes), which may indicate a slight developmental effect in these animals. $F_2$ pups and weanlings at 500 mg/kg bw/day also exhibited an increased incidence of chronic keratitis. Increased liver weights were observed in $F_0$ and $F_1$ adult

males and females at 20 and 500 mg/kg bw/day. Increased liver weights were associated with mottled livers in $F_0$ and $F_1$ males and females at 500 mg/kg bw/day, centrilobular hepatocellular hypertrophy in $F_0$ and $F_1$ males and females at 20 and 500 mg/kg bw/day, and hepatocellular vacuolation in $F_0$ and $F_1$ males at 500 mg/kg bw/day and in $F_1$ males at 20 mg/kg bw/day. The LOEL for systemic toxicity was 20 mg/kg bw/day on the basis of increased liver weights, hepatocellular hypertrophy and hepatocellular vacuolation at this dose level. There were no treatment-related findings in either generation at 0.5 or 2.0 mg/kg bw/day; therefore, the NOEL for systemic toxicity was 2.0 mg/kg bw/day. There were no effects observed in mating or fertility indices, gestation, live birth or weaning indices. On the basis of the increased number of females with stillborn pups in the $F_0$ generation at 500 mg/kg bw/day, the increased number of stillborn pups in the $F_1$ pups at 20 and 500 mg/kg bw/day, the reduced viability index in the $F_1$ pups at 20 and 500 mg/kg bw/day and in the $F_2$ pups at 500 mg/kg bw/day and the reduced body weight and the underdeveloped renal papilla in $F_1/F_2$ pups at 500 mg/kg bw/day, the NOEL for reproductive toxicity was 2.0 mg/kg bw/day.

The developmental toxicity of isoxaflutole (purity 99.2%) was evaluated in SD CD rats. The test substance (prepared in 0.5% methylcellulose – distilled water) was administered via oral gavage (at a dosing volume of 5.0 mL/kg bw) to 25 mated females/group at dose levels of 0 (vehicle only), 10, 100 or 500 mg/kg bw/day from gestational days 6–15. The dams were sacrificed on gestation day 20.

There were no mortalities, no treatment-related clinical or gross pathological observations and no treatment-related effects on water consumption. There was a treatment-related reduction in body weight and body-weight gain in dams at 500 mg/kg bw/day during treatment (gestation days 6–15). This was accompanied by reduced food consumption during the first week of treatment (gestation days 6–8 and 9–11). There were no treatment-related effects observed on any of the reproductive parameters examined. Mean fetal weight was significantly lower at 100 and 500 mg/kg bw/day. This was associated with an increased incidence of small fetuses (<2.98 g) and a subsequent decreased incidence of large fetuses (>4.1 g) at 100 and 500 mg/kg bw/day. There were no significant treatment-related external findings at 10 mg/kg bw/day or visceral findings at any dose level. There was an increased incidence of incomplete ossification of the 3rd sternebra at all dose levels, and of the 4th and 5th sternebrae at 100 and 500 mg/kg bw/day, respectively. At 500 mg/kg bw/day, there was a decreased incidence of 13/13 ribs, an increased incidence of 13/14 and 14/14 ribs and an increased incidence of enlargement of the 14th rib or ribs. There was an increased incidence of unossified 1st thoracic vertebral centrums and an increased incidence of 27th presacral vertebrae at 500 mg/kg bw/day. Increased incidence of incomplete ossification of caudal vertebrae (fewer than five ossified), incomplete or unossified metacarpals and metatarsals and incomplete or unossified pubic bones (one or more) were observed at 100 and 500 mg/kg bw/day. There was a decreased incidence of 4/4 metacarpals and metatarsals and a dose-related increased incidence of 3/4 metacarpals and metatarsals at all dose levels. Free-hand serial sectioning findings included an increased incidence of subcutaneous hemorrhage of cervical area at 500 mg/kg bw/day, an increased incidence

of subcutaneous hemorrhage in the fore- and hind-limbs at 100 and 500 mg/kg bw/day and an increased incidence of subcutaneous edema at 500 mg/kg bw/day, with a slight increase at 10 and 100 mg/kg bw/day. Skeletal and free-hand serial sectioning findings at 100 and 500 mg/kg bw/day were considered to be treatment-related. The increased incidence of incomplete ossification of the 3rd sternebra, decreased incidence of 4/4 metacarpals and metatarsals and increased incidence of 3/4 metacarpals and metatarsals were apparent at all dose levels. The increased incidences at 10 mg/kg bw/day were considered to be treatment-related. They were within the historical control range, however, for animals of this age and strain, and thus could most likely be considered not adverse; therefore, the NOAEL for developmental toxicity was 10 mg/kg bw/day. The skeletal findings could represent a transient delay in development. There was no evidence of irreversible structural effects; therefore, isoxaflutole does not appear to be teratogenic in rats under the conditions of this study. The NOEL and LOEL for maternal toxicity were 100 and 500 mg/kg bw/day, respectively, on the basis of decreased body-weight gain and reduced food consumption in dams at 500 mg/kg bw/day.

The developmental toxicity of isoxaflutole (purity 996 g/kg) was evaluated in New Zealand white (NZW) rabbits. The test substance (prepared in 1.0% w/v methylcellulose in distilled water) was administered via oral gavage (at a dosing volume of 5.0 mL/kg bw) to 25 mated females/group at dose levels of 0 (vehicle only), 5, 20 and 100 mg/kg bw/day from gestational days 6 to 19, inclusive. The dams were sacrificed on day 29 of gestation.

There were no treatment-related mortalities or gross pathological observations. At 100 mg/kg bw/day, there was a treatment-related decrease in the overall body-weight gain during treatment (gestation days 6–20) owing to a body-weight loss during the first week of treatment (gestation days 6–14) and a decrease in body-weight gain during the second week of treatment (gestation days 14–20). The decreased body-weight gain was associated with a concomitant reduction in food consumption. Reduced food consumption was associated with a reduction in fecal output in dams at 100 mg/kg bw/day. The pregnancy rate, number of corpora lutea, number of implantations and the extent of preimplantation loss were comparable between the control and treated groups. At 100 mg/kg bw/day, there was an increase in the number of late resorptions (above upper limit of historical control data) with an associated increase in postimplantation losses and a slightly reduced number of viable pups per litter. There were no significant treatment-related changes in fetal weight per litter or in placental weight. There were no significant treatment-related external or visceral findings at any dose level. Significant treatment-related skeletal findings included decreased incidence of 12/12 ribs and increased incidence of 13/13 ribs (at 20 and 100 mg/kg bw/day, respectively), increased incidences of 27th presacral vertebrae (at 5, 20 and 100 mg/kg bw/day), increased incidences of rudimentary 1st rib or ribs (at 100 mg/kg bw/day), a reduction or lack of ossification of heads of limb long-bones (at 20 and 100 mg/kg bw/day), incompletely ossified pubic bones (at 100 mg/kg bw/day) and reduced or lack of ossification of the metacarpals and phalanges (at 20 and 100 mg/kg bw/day). The generalized reduction in the degree of skeletal ossification at 20 and 100 mg/kg bw/day was possibly associated with delayed fetal growth. The incidences

of these skeletal findings at 20 and 100 mg/kg bw/day were above the upper limit of the historical control range provided in the study report for animals of this age and strain; therefore, they were considered to be treatment-related. At 5 mg/kg d, the increased incidence of fetuses with 27 presacral vertebrae was at or slightly higher than the upper limit of the historical control range; although this finding was not associated with effects on the number of ribs, it was considered to be treatment-related but not adverse. There was also an increased incidence of fetuses (litters) with incisors not erupted at 100 mg/kg bw/day, suggesting a delay in development. Incidental skeletal findings at 100 mg/kg bw/day included increased incidences of medium anterior fontanelle, incomplete ossification of hyoid body and an additional bone between the 5th and 6th sternebrae. The skeletal findings at 20 and 100 mg/kg bw/day were considered to possibly represent a transient developmental delay and there was no evidence of irreversible structural effects; therefore, isoxaflutole does not appear to be teratogenic in rabbits under the conditions of this study. The NOEL and LOEL for maternal toxicity were 20 and 100 mg/kg bw/day, respectively, on the basis of clinical observations (decreased fecal output), decreased body-weight gain and reduced food consumption in dams at 100 mg/kg bw/day. At 5 mg/kg bw/day, the increased incidence of 27th presacral vertebrae was considered to be treatment-related but not adverse; therefore, the NOAEL for developmental toxicity was 5 mg/kg bw/day, the lowest dose tested.

### 3.1.6 Neurotoxicity (acute and short-term)

The acute neurotoxicity potential of isoxaflutole (purity 99.2%) was evaluated in male and female CD rats. Ten rats/sex/group received a single dose of 0 (vehicle only), 125, 500 or 2000 mg/kg bw isoxaflutole in 0.5% methylcellulose by oral gavage at a dosing volume of 10 mL/kg bw. There were no mortalities, no treatment-related clinical observations and no treatment-related effects on body weight, body-weight gain or food consumption. There was a statistically significant decrease in landing foot splay measurements on day 15 in males at 500 and 2000 mg/kg bw. This effect was not observed at any other interval and the values were comparable to pretest values at these dose levels; therefore, in the absence of any other effects on the hindlimb function they were most likely not indicative of impairment of neuromuscular function. There were no other significant effects on any other functional observational battery (FOB) or motor activity parameters measured. There were no treatment-related gross pathological observations and no treatment-related histopathological findings in the brain, spinal cord or peripheral nervous system in the control or high-dose groups. On the basis of the results of the study, the NOEL for systemic and neurotoxicity for both sexes was 2000 mg/kg bw.

The short-term neurotoxicity potential of isoxaflutole (purity 99.2%) was evaluated in male and female SD CD rats. The test substance was administered orally, via dietary admixture, to 10 animals/sex/group at dose levels of 0, 25, 250 or 750 mg/kg bw/day for at least 90 days. Control animals received an untreated standard laboratory diet under identical conditions. There were no treatment-related mortalities, clinical observations or effects on food consumption. There was a treatment-related effect on body weight and

body-weight gain in males at 750 mg/kg bw/day. Males at 25 mg/kg bw/day and above exhibited a statistically significant decrease in hind-limb strength and a slight decrease in forelimb strength during week 13. These findings were most likely not indicative of neurotoxicity and not toxicologically significant, since they were considered slight, were not observed in both trials and were not observed at any other interval at these dose levels. In addition, other measures of neuromuscular function in these groups, such as gait and locomotion scores, landing foot splay and righting reflex were comparable to control values. There were no other significant effects on any other FOB or motor activity parameters measured. There were no gross pathological observations and no histopathological findings in the brain, spinal cord or peripheral nervous system. On the basis of the results of the study, the NOEL for systemic toxicity was 250 mg/kg bw/day in males and 750 mg/kg bw/day in females. The NOEL for neurotoxicity was 750 mg/kg bw/day in both males and females.

### 3.1.7 Special mechanistic studies in rat and mouse

To assess the underlying mechanism for the increased incidence of thyroid tumours in male rats induced by isoxaflutole and to determine the relationship between the thyroid tumours and the induction of hepatic drug metabolizing enzyme, 14 male SD rats received 500 mg/kg bw/day isoxaflutole (purity 99.7%), via dietary admixture daily for 14 days. A negative and a positive control (80 mg/kg bw/day sodium pentobarbital) were also included in the study. On the completion of the 14-day treatment period, six animals from each group received an intravenous dose of sodium $^{125}$I-thyroxine (0.4 mL, 10 FCi) after which blood samples were collected during a 48-h post-dosing period for thyroxine kinetic studies. Six animals from each dose group were sampled for tri-iodothyronine ($T_3$) and thyroxine ($T_4$) levels, selected organ weights and assessment of liver drug metabolizing enzymes.

There were no mortalities, no treatment-related clinical observations and no treatment-related effects on body weight, body-weight gain, food consumption or food efficiency. $T_4$ levels were significantly decreased with little or no change in $T_3$ levels. There was a treatment-related increase in Phase I (cytochrome P-450 dependent mixed function oxidase system, as indicated by increased pentoxyresorufin *O*-dependentylase (PROD) activity) and Phase II (as indicated by increased uridine 5'-diphosphate-glucuronyltransferase (UDPGT) activity) drug metabolizing enzyme activities, which were considered to be related to the increased systemic clearance of $^{125}$I-thyroxine and concomitant decrease in plasma $T_4$ concentration and biological half-life ($T_{½}$). The significantly increased concentration and total weight of hepatic microsomal protein and microsomal cytochrome P-450 concentrations were related to the increased Phase I and Phase II drug metabolizing enzyme activities. Absolute and relative liver and absolute thyroid (not statistically significant) weights were increased. Gross pathological examination revealed enlarged livers. Following intravenous administration of $^{125}$I-thyroxine, the thyroid iodine uptake was slightly higher (although thyroid iodine uptake per gram of tissue was lower) and thyroid weights were significantly higher in the treated groups compared with the control group. The results of the study appear to

support the hypothesis that the increased incidence of thyroid tumours in male rats at 500 mg/kg bw/day in the carcinogenicity study may be due to an imbalance of thyroid hormones created by an induction of UDPGT followed by decreased plasma $T_4$ levels, increased clearance of $T_4$ and decreased $T_{½}$ for $T_4$. Isoxaflutole appears to act like a phenobarbital-type inducer of hepatic Phase I and Phase II drug metabolizing enzymes. The development of thyroid tumours in male rats treated with isoxaflutole at 500 mg/kg bw/day may be secondary to the treatment-related effects on the liver that, in turn, produced alterations in thyroid–pituitary hormonal feedback mechanisms and a concomitant hormonal imbalance.

To establish the dose–response and to investigate the role of mixed function oxidase system with respect to liver enlargement, groups of 25 male CD-1 mice were administered isoxaflutole (purity 99.6%) in their diet at dose levels of 0, 175, 700, 2800 or 7000 ppm for 14 days. There were no mortalities, no treatment-related clinical observations and no effects on body weight or food consumption. Absolute and relative liver weights were significantly increased at 700 ppm and above. Total cytochrome P-450 levels were increased in a dose-dependent manner; this was statistically significant at 700 ppm and above. Analysis of P-450 isoenzymes indicated that the elevated P-450 levels were mainly due to a significant increase in absolute and relative PROD activity (P-450 2 family, B1 isoenzymes) at 175 ppm and above and at 700 ppm and above, respectively, and to a significant increase in absolute and relative benzoxyresorufin *O*-debenzylase (BROD) activity (P-450 2B family, B1 and B2 isoforms) at 175 ppm and above. Absolute ethoxyresorufin *O*-deethylase (EROD) activity (P-450 1 family, A1 isoenzymes) was significantly increased at 2800 and 7000 ppm. Absolute methoxyresorufin *O*-demethylase (MROD) activity (P-450 1 family, A2 isoenzymes) was significantly increased at 700 ppm and above but there was no dose–response relationship. Absolute lauric acid 11- and 12-hydroxylase activity (peroxisome proliferation) was significantly increased at 7000 ppm. The results suggest that isoxaflutole caused a dose-related increase in liver weight in male mice owing to marked elevation in cytochrome P-450 enzymes of the P-450 2B family, similar to phenobarbital. It does not appear to induce other P-450 isoenzymes significantly or cause peroxisome proliferation. There was no NOEL. The LOEL was 175 ppm on the basis of elevated absolute and relative BROD activity and absolute PROD activity.

To establish the dose–response and to investigate the role of mixed function oxidase system with respect to liver enlargement, groups of five male SD rats were administered isoxaflutole (purity 99.6%) in their diet at dose levels of 0, 10, 100 or 400 mg/kg bw/day for 14 days. There were no mortalities, no treatment-related clinical observations and no effects on body weight or food consumption. Absolute and relative liver weights were significantly increased at 100 and 400 mg/kg bw/day. Total cytochrome P-450 levels were increased in a dose-dependent manner; this was statistically significant at all dose levels. Analysis of P-450 isoenzymes revealed a statistically significant increase in absolute and relative (relative to total liver P-450) PROD (P-450 2 family, B1 isoenzymes) and BROD (P-450 2B family, B1 and B2 isoforms) activity at all dose levels. Absolute EROD activity (P-450 1 family, A1 isoenzymes) was significantly, but

not dose-relatedly, increased in all dose groups and was decreased in relation to total liver P-450 at 100 and 400 mg/kg bw/day (statistically significant at 400 mg/kg bw/day). MROD activity (P-450 1 family, A2 isoenzymes) was not markedly altered in comparison with other P-450 isoenzymes. Absolute lauric acid 11- and 12-hydroxylase activity (peroxisome proliferation) was significantly increased at 400 mg/kg bw/day. The results suggest that isoxaflutole caused a dose-related increase in liver weight in male rats that may be due to marked elevation in cytochrome P-450 enzymes of the P-450 2B family (PROD and BROD), similar to phenobarbital. It does not appear to induce other P-450 isoenzymes significantly or cause peroxisome proliferation. There was no NOEL. The LOEL was 10 mg/kg bw/day on the basis of elevated absolute and relative PROD and BROD activity.

### 3.1.8 Integrated toxicological summary

A detailed review of the toxicological database available for the new herbicide, isoxaflutole (RPA 201772), has been completed. Data submitted were complete and comprehensive, and included the full battery of studies currently required for registration purposes. Studies were well conducted and conformed with currently acceptable international testing protocols. The scientific and regulatory quality of the toxicology database is high and is considered sufficient to clearly define the toxicity of this chemical.

Isoxaflutole (RPA 201772) was rapidly absorbed with maximal whole blood concentration achieved within one hour. The mean estimated proportion of the administered dose absorbed was approximately 39, 73 and 75% for the high-, low- and repeat-dose groups, respectively. In the high-dose group, the highest tissue levels were found in the blood and plasma and to a lesser extent in the liver and kidneys of males and in the liver, kidneys, lungs and heart of females. In the single and repeat low-dose groups, higher tissue concentrations were found in the liver and kidneys. The major route of elimination was via the feces (approximately 55–63% of the administered dose) in the high-dose group and via the urine (68–74% of the administered dose) in the single and repeat low-dose groups. The majority of the activity was eliminated within 24 and 48 h post-dosing for the low- and high-dose groups, respectively. Mean recovery of radioactivity in the tissues at 168 h post-dosing was low, indicating that there was most likely a good systemic clearance of the test substance with little potential for accumulation. Isoxaflutole was rapidly and extensively metabolized. The major metabolite was the diketonitrile RPA 202248 (70–85% of the administered dose). Minor metabolites included RPA 203328 (0.6–3.6% of the administered dose), RPA 207048, RPA 205834 and RPA 205568. The parent compound, isoxaflutole, was only detected in fecal extracts in the single high-dose group during the first 24 h. There were no sex differences in absorption, distribution, metabolism or excretion.

Isoxaflutole has low acute toxicity via the oral and inhalation routes of exposure in rats and via the dermal route of exposure in rabbits. In rabbits, it was minimally irritating to the eyes and nonirritating to the skin. It was not a dermal sensitizer in guinea pigs.

Converge 75 WDG herbicide has low acute toxicity via the oral and inhalation routes of exposure in rats and via the dermal route of exposure in rabbits. In rabbits, it was minimally irritating to the eyes and slightly irritating to the skin. It was not a dermal sensitizer in guinea pigs.

Isoxaflutole did not induce gene mutations in bacterial or mammalian cells in vitro in the presence or absence of S9 metabolic activation. In two in vitro chromosome aberration assays isoxaflutole did not induce chromosomal aberrations in either the presence or the absence of S9 metabolic activation. In an in vivo micronucleus assay with mouse bone marrow cells, there was no evidence that isoxaflutole induced chromosomal damage or other damage leading to micronucleus formation in polychromatic erythrocytes of treated mice. On the basis of the results of the data presented, isoxaflutole was not considered to be genotoxic under the conditions of the studies performed.

In short-term and chronic toxicity and oncogenicity studies, toxicologically significant effects included hematological changes (dog), liver toxicity (mouse, rat and dog), thyroid toxicity (rat), ocular toxicity (rat) and neurotoxicity (rat).

Hematological changes were observed in a 52-week dietary study in dogs and included decreases in red cell parameters (RBC, Hb and Hct), increased incidence of polychromatic erythrocytes and extramedullary hematopoiesis indicative of regenerative hematolytic anemia. These changes were observed in males at 30 000 ppm and in females at $12 000 ppm.

The liver was a target organ in all species, as indicated by increased liver weights, changes in clinical chemistry and gross pathological and histopathological findings. In mice increased liver weights with associated changes in clinical chemistry (increased ALAT and ASAT activity), gross pathological and histopathological changes including increased incidence of periacinar hypertrophy, necrosis of individual hepatocytes and periacinar hepatocytic fatty vacuolation were observed in males at $1000 ppm and in females at 2000 ppm in the 90-day dietary study and in males at $500 ppm and in females at 7000 ppm in the 78-week oncogenicity study. In rats, increased liver weights were observed in males at 500 mg/kg bw/day in the 90-day dietary study and in males at $20 mg/kg bw/day and in females at 500 mg/kg bw/day in the 104-week chronic toxicity and oncogenicity study. The increased liver weights were associated with gross pathological and histopathological changes, including periacinar hepatocytic hypertrophy. Increased liver weights and centrilobular hypertrophy were also observed in both sexes at $20 mg/kg bw/day in a two-generation reproductive toxicity study in rats. In dogs, increased liver weights with associated changes in clinical chemistry (elevated AP, ALAT, 5'-NT and (-GT activity) and histopathological findings (hepatocellular swelling, centrilobular clumping and margination of cytoplasmic staining, centrilobular necrosis and fibrosis, vacuolated hepatocytes and centrilobular glycogen depletion) were observed at $12 000 ppm in both sexes.

In the 104-week chronic toxicity and oncogenicity study in rat, thyroid weights were significantly increased in males at $20 mg/kg bw/day; this was associated with gross pathological and histopathological changes, including thyroid follicular cystic hyperplasia.

In a 78-week oncogenicity study in mice, neoplastic findings were observed in the liver and included an increased incidence of hepatocellular adenomas and carcinomas in both sexes at 7000 ppm and hepatocellular carcinomas in males at 500 ppm. In a 104-week chronic toxicity and oncogenicity study in rats, neoplastic findings were observed in the liver and thyroid and included an increased incidence of hepatocellular adenomas, carcinomas, and adenomas and carcinomas combined in both sexes at 500 mg/kg bw/day and an increased incidence of thyroid follicular cell adenomas in males at 500 mg/kg bw/day. No neoplastic tissues were observed in dogs in the 52-week dietary study.

The lack of mutagenic potential of isoxaflutole in a range of in vitro mammalian and bacterial cell assays and in an in vivo mouse assay suggest that the presence of tumours in mouse or rat may be linked to nongenotoxic mechanisms.

The increased incidence of thyroid follicular cell adenomas in males in rats were considered to be secondary to microsomal enzyme induction in the liver, which produced alterations in thyroid–pituitary hormonal feedback mechanisms with a concomitant hormonal imbalance. In a 14-day oral gavage study in CD rats, isoxaflutole was found to decrease $T_4$ with little or no change in $T_3$, increase liver and thyroid weights, increase concentration and total weight of hepatic microsomal protein and increase microsomal cytochrome $P_{450}$ concentration, increase Phase I PROD and Phase II UDPGT activity, increase systemic clearance of $^{125}$I-thyroxine with concomitant decreased $T_4$ concentration and $T_{½}$ and increase thyroid iodine uptake. Thyroid stimulating hormone levels were not measured. In the 104-week dietary study, there was evidence of progression from hyperplasia to neoplasia in rats (increased incidence of cystic follicular hyperplasia and thyroid follicular cell adenomas in males at 500 mg/kg bw/day). These results are supportive of the hypothesis that isoxaflutole may have induced thyroid tumours in male rats secondary to treatment-related effects on the liver that produced alterations in thyroid–pituitary hormonal feedback mechanisms with a concomitant hormonal imbalance.

In both species, the increased incidence of liver tumours was attributed to a nongenotoxic mechanism triggered by marked microsomal enzyme induction. In 14-day dietary studies in the rat and the mouse, it was shown that liver weight induction was associated with microsomal proliferation accompanied by increased P-450 enzyme induction (increased PROD and BROD activity). There was no peroxisome proliferation (no induction of lauric acid hydroxylases). The results suggest that isoxaflutole may act like a phenobarbital-type inducer of hepatic Phase I and Phase II drug metabolizing enzymes. The highest dose tested resulted in maximal enzyme induction and tumour production; lower doses failed to produce maximal induction of mixed function oxidase enzymes and

showed no evidence of induction of tumours, which suggests that a threshold may exist for the induction of liver tumours in rodents. The liver enzyme studies were conducted over a short period of time (14 days) and there is inadequate data to link precursor events with tumour formation; therefore, the studies submitted to show a mechanistic basis for the liver tumours were considered to be suggestive but not convincing.

According to the National Toxicology Program criteria, clear evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (*i*) increase of malignant neoplasms, (*ii*) increase of a combination of malignant and benign neoplasms or (*iii*) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumours to progress to malignancy. On the basis of this definition, there is clear evidence that isoxaflutole exhibits carcinogenic activity. The weight of evidence suggests that isoxaflutole be characterized as "likely" to be carcinogenic to humans by all routes of exposure. This classification was on the basis of the increased incidence of liver tumours in two rodent species in adequate long-term studies. Liver tumours occurred in both sexes in both the rat and the mouse and had an early onset in male mice and male and female rats. There was also an increased incidence of thyroid tumours in male rats.

The margin of exposure (MOE), calculated as NOEL for the end point of concern divided by acceptable daily intake (ADI), was calculated for the incidence of hepatocellular adenomas and carcinomas in male and female mice and rats and for thyroid follicular adenomas in male rats (end point of concern used was the NOEL for the tumour of concern). The MOE for hepatocellular adenomas in mice is 12 800 for males and 15 600 for females compared with the ADI. The MOE for hepatocellular carcinomas in mice is 640 for males and 15 600 for females compared with the ADI. The MOE for hepatocellular adenomas and carcinomas in male and female rats is 4000 compared with the ADI. The MOE for thyroid follicular adenomas in male rats is 4000 compared with the ADI.

According to the Federal Register (September 23, 1998, Vol. 63, No. 184, pp. 50773–50784), the EPA decided that for the purpose of risk characterization, a nonlinear MOE approach be applied to the most sensitive precursor lesion in the male rat thyroid, and that a linear low-dose extrapolation be applied for the tumours of the rat liver. The NOEL of 2 mg/kg bw/day in males from a 104-week combined chronic toxicity and carcinogenicity study in rats was used for the nonlinear MOE cancer risk assessment. For the nonlinear MOE cancer risk assessment, cancer MOEs are estimated by dividing the carcinogenic NOEL by the chronic exposure. The end point of concern and lowest observed adverse effect level (LOAEL) was 20 mg/kg/day on the basis of thyroid hyperplasia. Tumours first appeared in this study at the 500 mg/kg bw/day dose. It was later decided that there was no reason not to include the results from the 78-week feeding and carcinogenicity study in mice when determining the cancer estimate risk number ($Q_1$*) to be used for risk assessment for the linear low-dose extrapolation. A $Q_1$* was developed for each of the female and male mouse livers and female and male rat livers, and the $Q_1$* with the highest unit of potency was used for risk assessment. The four

resulting estimates of unit potency were $3.55 \times 10^{-3}$ for female CD-1 mouse liver, $3.84 \times 10^{-3}$ for female rat liver, $1.14 \times 10^{-2}$ for male CD-1 mouse liver, and $5.27 \times 10^{-3}$ for male rat liver. The unit risk, $Q_1^*$ (mg/kg bw/day)$^{-1}$ of isoxaflutole, on the basis of male mouse liver tumours (adenomas and carcinomas) is $1.14 \times 10^{-2}$ in human equivalents, converted from animals to humans by use of the 3/4's scaling factor (1994, Tox-Risk, 3.5-K. Crump). Using the linear approach and a $Q_1^*$ of $1.14 \times 10^{-2}$ resulted in an upper bound cancer risk of $9.3 \times 10^{-8}$. This linear risk estimate, for use of isoxaflutole on corn, is below the EPA's level of concern for life-time cancer risk.

Ocular toxicity was observed in the short-term, chronic toxicity and oncogenicity, and reproductive studies in the rat. These lesions were not observed in the mouse or dog. In a 90-day dietary study in the rat, significant treatment-related clinical, ophthalmoscopic and gross pathological and histopathological findings were observed in the eyes of males at $10 mg/kg bw/day and in females at 100 mg/kg bw/day. Clinical and ophthalmoscopic observations included increased incidences of opaque eyes and focal corneal opacity, respectively. Focal corneal opacity was first apparent during week 3 and persisted throughout the study. Significant gross pathological observation included an increased incidence of corneal opacity in both sexes at 100 mg/kg bw/day. The overall incidence of corneal lesions was similar in both sexes, although the severity of the lesions was more significant in the males. Significant histopathological findings in the eye included vacuolation and superficial exfoliation of the epithelial cells, epithelial thickening, necrosis and inflammation, subepithelial fibroblastic reaction and vascularization of the stroma. In a 104-week chronic toxicity and oncogenicity study in rats, ocular toxicity was observed primarily in males at $20 mg/kg bw/day and included keratitis, vascularization of the stroma, epithelial thickening and superficial exfoliated cells. Males at 2.0 mg/kg bw/day exhibited an increased incidence of chronic keratitis. In a two-generation dietary reproduction study in rat, treatment-related eye lesions (chronic keratitis and subacute corneal inflammation) were observed in male and female $F_1$ adults and $F_2$ pups and weanlings at 500 mg/kg bw/day.

Mechanistic studies submitted by the registrant suggest that the ocular lesions may be biochemically linked to the inhibition of the enzyme, 4-hydroxyphenyl pyruvate dioxygenase (4-HPPDase), which is involved in the normal catabolism of tyrosine. Inhibition of this enzyme leads to increased tyrosine and 4-hydroxyphenyl pyruvate (4-HPP) levels in blood (tyrosinemia), which is thought to be correlated with the increased incidence of corneal lesions. Keratitis subsequent to the corneal lesions was thought to be due to the deposition of tyrosine crystals in the corneal epithelium, causing disruption of cell membranes and lysosomes. Although increased plasma tyrosine levels appear to be linked to the development of eye lesions in rats, other factors may be involved, since these lesions were not observed in mice even in the presence of elevated plasma tyrosine levels. The eye lesions appeared to be species specific, since they were observed only in rats and not in mice or dogs. Studies suggest that if 4-HPPDase is inhibited, alternative pathways may be utilized to remove excess tyrosine and 4-HPP and that the species specificity may be linked to the capacity to utilize this bypass route. A study with rats and mice suggests that mice may have a greater capacity to utilize this

bypass route compared with rats, and thus the normal catabolic route of tyrosine, by converting tyrosine and 4-HPP to 4-hydroxyphenyl lactate (4-HPLA) and 4-hydroxyphenyl acetate (4-HPPA), which are excreted in the urine.

Corneal opacity is observed in humans suffering from tyrosinemia Type II or Richer Hanhart syndrome. This disease is caused by a lack of tyrosine amino transferase (TAT), the enzyme involved in the conversion of tyrosine to 4-HPPA in the liver. The therapeutic agent 2-(2-nitro-4-trifluoromethylbenzoyl)cyclohexane-1,3-dione (NTBC) used in humans specifically blocks 4-HPPDase and is used in the treatment of Type I tyrosinemia (a hereditary and often fatal disease because of a lack of fumaryl acetoacetase). NTBC is an effective treatment for this disease and does not produce corneal lesions. NTBC is also a more potent inhibitor of 4-HPPDase than isoxaflutole (specifically the metabolite RPA 202248). According to the registrant, the literature also suggests that eye lesions are not observed in humans when there is a hereditary lack of HPPDase and that humans may have the capacity to bypass the normal tyrosine catabolic route when 4-HPPDase is deficient or blocked, similar to mice.

Mechanistic studies suggest that the corneal lesions may be linked to the inhibition of an enzyme (4-HPPDase) in the catabolic pathway of tyrosine. Furthermore, there is evidence that the rat may be more sensitive to this effect than either mice or dogs. This may be caused by a poorly developed bypass route for the catabolism of tyrosine in the rat. The results of the comparative metabolism study in rats and mice treated with isoxaflutole suggest that there may be a difference in the excretion pattern of tyrosine between rats and mice. Since a control group was not included in the study, however, it is not clear what the relevance of the interspecies difference is and whether the interspecies differences in metabolism are responsible for the differences in susceptibility for the development of eye lesions, and if so, whether they are relevant to humans. Therefore, it cannot be justified to consider the eye lesions in rats irrelevant to human risk assessment, especially since it has been reported in the literature that tyrosinemia in humans can give rise to ocular lesions.

In the 104-week chronic toxicity and oncogenicity study in the rat, axonal and myelin nerve degeneration, focal degeneration and inflammation of the thigh muscle were observed in males at $20 mg/kg bw/day and females at 500 mg/kg bw/day. These findings were associated with abnormal gait and limited use of limbs observed in both sexes at 500 mg/kg bw/day and were not apparent until later in the study. In the acute and short-term neurotoxicity studies, there were no treatment-related neurotoxic effects at the highest doses tested (2000 mg/kg bw in the acute neurotoxicity study and 750 mg/kg bw/day in the short-term neurotoxicity study).

In rats, reproductive effects included an increased number of stillbirths and a decreased viability index primarily at 20 and 500 mg/kg bw/day. No changes were observed in mating, fertility, gestation, live birth, or weaning indices. Developmental effects included decreased body weight, absence of milk in the stomach and underdeveloped renal papilla in pups at 500 mg/kg bw/day.

In rats and rabbits, developmental effects were observed at dose levels that were not maternally toxic (developmental NOEL was lower than the maternal NOEL). In rats, the increased sensitivity was manifested as growth retardation characterized by decreased fetal body weight and increased incidence of delayed ossification of sternebrae, metacarpals and metatarsals. In rabbits, increased sensitivity was manifested as fetuses with increased presacral vertebrae at the lowest dose tested as well as fetuses with increased incidence of skeletal anomalies at the next two higher doses. In both species, a NOAEL was established for developmental toxicity, 5 mg/kg bw/day for the rabbit and 10 mg/kg bw/day for the rat. Isoxaflutole was not considered to be teratogenic in either species.

## 3.2 Determination of acceptable daily intake

The most appropriate NOEL was 0.5 mg/kg bw/day in the 104-week dietary study in the rat on the basis of an increased incidence of ocular toxicity (increased incidence of keratitis) in males at the next highest dose, 2.0 mg/kg bw/day. A safety factor (SF) of 100 to account for intra- and inter-species variations was applied to this NOEL to determine the ADI.

In rats and rabbits, developmental effects were observed at dose levels that were not maternally toxic (developmental NOEL was lower than the maternal NOEL). In rats, the increased sensitivity was manifested as growth retardation characterized by decreased fetal body weight and increased incidence of delayed ossification of sternebrae, metacarpals and metatarsals. In rabbits, increased sensitivity was manifested as fetuses with increased presacral vertebrae at the lowest dose tested as well as fetuses with increased incidence of skeletal anomalies at the next two higher doses. In both cases a NOAEL was established for developmental toxicity, 5 mg/kg bw/day for rabbits and 10 mg/kg bw/day for rats. Isoxaflutole was not considered to be teratogenic in either species. It was determined, however, that an additional SF to account for this increased sensitivity in rat and rabbit fetuses was not warranted, since an additional SF was incorporated into the selection of the critical end-point NOEL for determination of the ADI (0.5 mg/kg bw/day vs. 2.0 mg/kg bw/day in the 104-week dietary study in the rat on the basis of hepato, thyroid, ocular and neurotoxicity in males and hepatotoxicity in females at 20 mg/kg bw/day as determined by the EPA). The MOE (calculated as the developmental NOAEL divided by the ADI) for developmental toxicity is at least 1000 compared with the ADI.

Therefore, the proposed ADI is 0.005 mg/kg bw/day on the basis of the NOEL of 0.5 mg/kg bw/day and a SF of 100.

## 3.3 Acute reference dose

Because of the increased sensitivity of rat and rabbit fetuses (developmental effects were observed at dose levels that were not maternally toxic) to isoxaflutole exposure, an acute reference dose (ARD) was determined for the subpopulation females (13+ years). The

recommended ARD is 0.017 mg/kg bw/day on the basis of the lowest developmental NOAEL of 5.0 mg/kg bw/day (the lowest dose tested) in the rabbit developmental study. In this study, there was an increased incidence of 27th presacral vertebrae at 5.0 mg/kg bw/day. The fetal incidence of this anomaly was dose dependent and exceeded the upper limit of the historical control range provided in the study report for animals of this strain from this laboratory. Since the increased incidence of 27th presacral vertebrae at 5.0 mg/kg bw/day was not associated with effects on the number of ribs, it was considered to be treatment-related but not adverse. Also, at the next higher dose, 20 mg/kg bw/day, there was an increased incidence of rudimentary 1st rib/ribs and 13/13 ribs, decreased incidence of 12/12 ribs and increased incidence of fetuses with reduced ossification. A SF of 100 to account for intra- and inter-species variations and an additional SF of 3 to account for the increased sensitivity in both rat and rabbit fetuses were applied to this NOEL (SF = 300).

An ARD for the general population was not established, since isoxaflutole was considered unlikely to present an acute hazard. There were no significant treatment-related findings in the acute or short-term toxicity studies or in the acute or subchronic neurotoxicity studies to indicate a concern in acute dietary risk assessment for the general population.

### 3.4 Toxicology end point selection for occupational and bystander risk assessment

Converge 75 WDG herbicide has low acute toxicity via the oral and inhalation routes of exposure in rats and via the dermal route of exposure in rabbits. In rabbits, it was minimally irritating to the eyes and slightly irritating to the skin. It was not a dermal sensitizer in guinea pigs.

Given the short-term nature of the exposure period (i.e., single applications for farmers and maximum two weeks for custom applicators), and the predominantly dermal exposure route, a dermal toxicity study would be the most relevant to use in the risk assessment. In a 21day dermal toxicity study in the rat, a slight increase in liver weight was observed in both sexes at the highest dose, 1000 mg/kg bw/day. In the absence of any corroborating clinical chemistry and gross pathological or histopathological findings at this dose level; this was considered to be a minor adaptive change and not biologically or toxicologically significant; therefore, the NOAEL was 1000 mg/kg bw/day.

There was an increased incidence of developmental effects in rat and rabbit fetuses at dose levels that were not maternally toxic (developmental NOEL was lower than the maternal NOEL). In rats, the increased sensitivity was manifested as growth retardation characterized by decreased fetal body weight and increased incidence of delayed ossification. In rabbits, increased sensitivity was manifested as fetuses with increased presacral vertebrae at the lowest dose tested as well as fetuses with increased incidence of skeletal anomalies at the next two higher doses. In both species, a NOAEL was established for developmental toxicity (5 mg/kg bw/day for the rabbit and 10 mg/kg bw/day for the rat). In both rats and rabbits, no teratogenic effects were

observed up to the highest dose tested (500 and 100 mg/kg bw/day for rats and rabbits, respectively); therefore, isoxaflutole was not considered to be teratogenic in either species. On the basis of the maternal and developmental NOELs in the two-generation reproductive toxicity study, no increased susceptibility of rat pups was demonstrated.

There were no signs of neurotoxicity. Ocular toxicity was observed in the short-term, chronic toxicity and oncogenicity, and reproductive studies in the rat. These lesions were not observed in the mouse or dog. The most appropriate NOEL for ocular toxicity is 3.0 mg/kg bw/day on the basis of an increased incidence of corneal opacity with associated histopathological findings in males at 10 mg/kg bw/day (the next highest dose) in the 90day dietary study in the rat. In this study, corneal opacity was first apparent at 3 weeks in males at $10 mg/kg bw/day and in females at 100 mg/kg bw/day.

An increased incidence of hepatocellular adenomas and carcinomas was observed in both male and female mice and rats. Male rats also exhibited an increased incidence of thyroid follicular cell adenomas. The lowest NOEL for tumourigenicity was 3.2 mg/kg bw/day, on the basis of the increased incidence of hepatocellular carcinomas in males in the 78-week oncogenicity study in mice. The lack of mutagenic potential of isoxaflutole in a range of in vitro mammalian and bacterial cell assays and in an in vivo mouse assay suggests that the presence of tumours in mouse or rat may be linked to nongenotoxic mechanisms. The thyroid tumours were considered secondary to microsomal enzyme induction in the liver that produced alterations in thyroid–pituitary hormonal feedback mechanisms with a concomitant hormonal imbalance. The increased incidence of liver tumours was attributed to a nongenotoxic mechanism triggered by marked microsomal enzyme induction. Mechanistic studies suggest that a threshold may exist for the induction of liver tumours in rodents; however, the evidence was not conclusive.

The weight of evidence suggests that isoxaflutole be characterized as “likely” to be carcinogenic to humans by all routes of exposure on the basis of the increased incidence of liver tumours in two rodent species (both sexes) and thyroid tumours in male rats in adequate long-term studies.

According to the Federal Register (September 23, 1998, Vol. 63, No. 184, pp. 50773–50784), the EPA decided that for the purpose of risk characterization, a nonlinear MOE approach be applied to the most sensitive precursor lesion in the male rat thyroid, and that a linear low-dose extrapolation be applied for the tumours of the rat liver. The NOEL of 2 mg/kg bw/day in males from a 104-week combined chronic toxicity and carcinogenicity study in rats was used for the nonlinear MOE cancer risk assessment. For the nonlinear MOE cancer risk assessment cancer MOEs are estimated by dividing the carcinogenic NOEL by the chronic exposure. The end point of concern and LOAEL was 20 mg/kg/day on the basis of thyroid hyperplasia. Tumours first appear in this study at the 500 mg/kg bw/day dose. It was later decided that there was no reason not to include the results from the 78-week feeding and carcinogenicity study in mice when determining the $Q_1$* to be used for risk assessment for the linear low-dose extrapolation. A $Q_1$* was developed for each of female and male mouse livers and female and male rat livers, and

the $Q_1$* with the highest unit of potency was used for risk assessment. The four resulting estimates of unit potency were $3.55 \times 10^{-3}$ for female CD-1 mouse liver, $3.84 \times 10^{-3}$ for female rat liver, $1.14 \times 10^{-2}$ for male CD-1 mouse liver, and $5.27 \times 10^{-3}$ for male rat liver. The unit risk, $Q_1$* $(mg/kg\ bw/day)^{-1}$ of isoxaflutole, on the basis of male mouse liver tumours (adenomas and carcinomas) is $1.14 \times 10^{-2}$ in human equivalents, converted from animals to humans by use of the 3/4's scaling factor (1994, Tox-Risk, 3.5-K. Crump). This value is the 95% confidence limit upper bound.

For female workers, a SF of 100 to account for intra- and inter-species differences and an additional SF of 3 to account for the increased sensitivity of rat and rabbit fetuses is recommended for the developmental end point. A SF of 100 should be sufficient for all other end points in female workers and for all end points in male workers.

## 3.5 Drinking water limit

The drinking water limit will be addressed in section 4.2.

## 3.6 Impact on human and animal health arising from exposure to the active substance or to impurities contained in it

### 3.6.1 Operator exposure assessment

A farmer applying Converge 75 WDG by ground equipment could typically treat 80 ha/day one time in a growing season, applied pre-emergently. A custom applicator could typically treat up to 140 ha/day and be exposed for up to a 2-week period.

In an in vivo dermal absorption study, male rats were dosed with $^{14}C$-labelled isoxaflutole at doses of 0.865, 7.32 and 79.00 Fg/$cm^2$. Groups of four animals were sacrificed 0.5, 1, 2, 4, 10 and 24 h after application. Urine and feces were collected during each sampling period. Excreta, skin at the application site, blood, carcass and cage wash were analysed for $^{14}C$ content to determine dermal absorption. The 10-h dermal absorption value was 3.46% and the amount remaining in the skin and available for absorption was 6% for the low dose, equalling 9.5% dermal absorption. This value was the most appropriate for use in the occupational exposure assessment.

Pesticide operator exposure was estimated using the Pesticide Handler Exposure Database (PHED) Version 1.1. The PHED is a compilation of generic mixer, loader, applicator and flagger passive dosimetry data with associated software that facilitates the generation of scenario specific exposure estimates. The following PHED estimates meet North American Free Trade Agreement criteria for data quality, specificity and quantity.

To estimate total dermal and inhalation exposure for groundboom application, appropriate subsets of A and B grade data were created from the mixer, loader and applicator PHED database files. There were no relevant data available in the mixer, loader and applicator database file. The mixer and loader file was subset for open mixing

and dry flowable formulations and to exclude replicates for packaging in water soluble packets. The applicator file was subset for application by groundboom tractors or trucks with open cabs. The number of replicates for inhalation and dermal data were acceptable. Estimates were derived for individuals wearing one layer of clothing during mixing, loading and application, as well as gloves during mixing and loading. An additional protection factor was added when coveralls were placed over top of the single layer of clothing for mixing, loading and application. Table 3.1outlines the exposure estimates for farmers and custom applicators.

**Table 3.1 Exposure estimates from PHED 1.1 for isoxaflutole**

| Type of mixer, loader or applicator | Sex of mixer, loader or applicator | Exposure estimate[1] (dermal deposition + inhalation) (mg/kg bw/day) | Systemic dose (mg/kg bw/day) corrected for dermal absorption |
|---|---|---|---|
| Farmers | Male | 0.014 | 0.0016 |
| | Female | 0.0178 | 0.0021 |
| Custom | Male | 0.0244 | 0.0029 |
| | Female | 0.0311 | 0.0037 |

[1] On the basis of either a 70 or a 55 kg operator, typical Canadian use patterns of 80 ha/day for farmers and 140 ha/day for custom applicators, a maximum label rate of 105 g a.i./ha, and a protection factor of 75% with the mixer, loader or applicator wearing coveralls over long-sleeved shirt and long pants during all phases of use as well as gloves during mixing and loading.

The exposure estimates for the worst case scenario of custom applicators was used to determine the margins of exposure. The margins of exposure are outlined in Table 3.2.

**Table 3.2 Margins of exposure for isoxaflutole**

| Toxicological study | NOAEL (mg/kg bw/day) | Appropriate exposure estimate (mg/kg bw/day) | Margin of exposure |
|---|---|---|---|
| 21-day dermal | 1000 | 0.0244 | 40 984 |
| Developmental studies | 5 | 0.0037 | 1351 |
| Ocular effects | 3 | 0.0029 | 1034 |

These margins of exposure are considered adequate.

The quantitative calculation of carcinogenic risk resulted in an overall life-time risk of $4.7 \times 10^{-7}$. This is considered adequate. Actual risk is likely less than this, as many of the assumptions of the exposure estimate are conservative. These assumptions include the use of open cabs, which is not common for custom applicators, and a conservative estimate of dermal absorption. Further, market share considerations were not factored in.

The above margins of exposure and cancer risk assessment are considered adequate provided the following precautionary statements replace those on the draft label.

- Wear coveralls over long-sleeved shirt and pants and rubber boots during all activities.

- Wear chemical resistant gloves and protective eyewear during mixing, loading, clean-up and repair.

### 3.6.2 Bystanders

Given that the application is restricted to agricultural areas, and that the product would be applied using ground equipment only, exposure and risk to bystanders is expected to be negligible.

### 3.6.3 Workers

Given that isoxaflutole is applied pre-emergent, there would not be any significant postapplication activities associated with the use of Converge 75 WDG.

## 4.0 Residues

### 4.1 Definition of the residues relevant to maximum residue limits

### 4.1.1 Definition of the residues in field corn relevant to maximum residue limits

**Plant metabolism**
The field corn metabolism study elucidated the nature of the residues in field corn. Metabolism of isoxaflutole in field corn proceeded via hydrolysis of isoxazole ring to form RPA 202248, which further hydrolysed to RPA 203328.

The parent isoxaflutole was not identified in any of the corn matrices. The major metabolite was RPA 203328 in forage, fodder and grain; RPA 202248 was the only other metabolite identified.

Field corn forage samples were collected 41 days after treatment (DAT). Field corn grain and fodder samples were collected at maturity, 122 DAT and 138 DAT, respectively.

**Confined crop rotation studies**
Isoxaflutole was applied to soil. A leafy vegetable, a root crop and a small grain were planted subsequently at crop rotation intervals of 34, 123 and 365 days, representing a plant-back after crop failure, a winter crop following corn, or an annual crop rotation, respectively. Isoxaflutole was found only in trace amounts for certain 34-day raw agricultural commodities (RACs). The two metabolites (RPA 20248 and RPA 203328) were present and decreased as a function of time. These data indicated that no crop rotational restrictions were required for secondary crops when isoxaflutole was applied to corn at the proposed maximum labelled rate.

**Storage stability**
Samples of raw and processed corn fractions were spiked with residues of isoxaflutole and its metabolites (ROC) and stored at –10EC. Isoxaflutole and its metabolites were shown to be stable in raw corn and its processed fractions for up to 15 months and three months, respectively. All samples (from metabolism and residue studies) were stored, prior to analysis, within the storage periods studied.

### 4.1.2 Definition of the residue in food of animal origin relevant to maximum residue limits

**Animal metabolism**
Animal metabolism studies were carried out in lactating goats, laying hens and rats, indicating a similar metabolic profile. Metabolites identified in either the goat or the laying hen metabolism studies were also found in the rat.

The goat metabolism study elucidated the nature of the residues in ruminants. Metabolism of isoxaflutole in ruminants proceeded via hydrolysis of the isoxazole ring to form RPA 202248 and RPA 205834 (further hydrolysed to produce RPA 207048). The goats were dosed (balling gun) at a dietary burden of 10 ppm for seven days. The administered radioactivity was mainly eliminated via the urine and feces with the remaining radioactivity found in tissues, milk and cage wash and debris. Isoxaflutole was not identified in any of the tissues and milk. RPA 202248 was identified as a major component in all tissues, including milk. RPA 207048 was identified as a minor component in tissues and milk.

Dairy cows were fed isoxaflutole in their diets for 42 days at levels of 4.6 ppm (3×), 13.8 ppm (10×) and 46 ppm (35×), on the basis of the estimated maximum dietary burden of 1.4 ppm. At the highest feeding level, residues of isoxaflutole were less than 0.05 ppm (LOQ) in liver, kidney, muscle, fat and milk. As well, the metabolite RPA 202248 was less than 0.05 ppm (LOQ) in muscle and fat and 0.02 ppm in milk (41 DAT). Average residues of RPA 202248 were observed, however, in liver (0.62 ppm) and kidney (0.14 ppm) at the lowest feeding level. Therefore, maximum residue limits (MRLs) will be established in tissues and milk to cover the potential residues of isoxaflutole and its metabolite RPA 202248.

The laying hen metabolism study was adequate in defining the nature of the residues in poultry. Metabolism of isoxaflutole in poultry involved hydrolysis of the isoxazole ring to form RPA 202248 and RPA 205834. Metabolite RPA 205834 was further hydrolysed to produce RPA 207048 (further degrades to RPA 203328) and RPA 203328. Hens were dosed (gelatin capsule) at a dietary burden of 10 ppm for 14 consecutive days. The administered radioactivity was mainly eliminated via the excreta with the remaining radioactivity found in cage wash and debris, eggs and tissues. Isoxaflutole was not identified in any of the tissues and eggs. RPA 202248 was identified as a major component in all tissues. RPA 203328 was identified as a minor component only in muscle.

Laying hens were fed isoxaflutole in their diet for 42 days at levels of 0.18 (0.9×), 0.54 (2.7×) and 1.8 ppm (9×), on the basis of the estimated maximum dietary burden of 0.2 ppm. At the highest feeding level, residues of isoxaflutole were less than 0.05 ppm (LOQ) in liver, muscle, skin (+ fat) and eggs. As well, the metabolite RPA 202248 was less than 0.05 ppm (LOQ) in eggs, muscle and skin (+ fat). Residues of RPA 202248 were observed, however, in liver (0.14 ppm) at the lowest feeding level. Therefore, MRLs will be established in tissues and eggs to cover the potential residues of isoxaflutole and its metabolite RPA 202248.

**Storage stability**
Samples of animal tissues and milk were spiked with residues of isoxaflutole and its metabolites (RPA 202248 and RPA 203328) and stored at –10EC for up to 130 days. Isoxaflutole degraded (approximately 50%) in stored milk samples (after 85–127 days), with no degradation of its metabolites. Isoxaflutole was immediately converted to RPA 202248 in the egg matrix and RPA 202248 was found to be stable in eggs for up to 129 days. Isoxaflutole and its metabolites were stable in muscle (85 days), liver (130 days) and kidneys and fat (115 days). Therefore, there was no degradation of isoxaflutole and its metabolites in tissues during the conditions of the study.

## 4.2 Residues relevant to consumer safety

Good agricultural practice was defined on the proposed Canadian label as a single pre-emergence application (0.079–0.105 kg a.i./ha). The result obtained from Canadian field trials demonstrated that the residues of isoxaflutole and its metabolites would be below 0.01 ppm (LOQ). The results from U.S. field trials indicated that the residues of isoxaflutole and its metabolite could reach up to 0.11 ppm. The PMRA concluded that the petitioner had submitted adequate residue data to support a domestic registration of isoxaflutole on field corn.

Processing studies in field corn indicated that no concentration of the residues was observed in any of the processed fractions, including oil.

For the chronic dietary risk assessment, the potential daily intake (PDI) was determined using the proposed MRLs and the Dietary Exposure Evaluation Model™ (DEEM™) Software. The assessment was conducted using the 1994–1996 Continuing Survey of Food Intake for Individuals. The PDI, including 10% water allocation, was 26% of the ADI for the U.S. population, 28% for all infants (less than one year), 48% for children (1–6 years), 35% for children (7–12 years), 29% for children (13–19 years) and 20% for seniors aged 55+ years. Consequently, the proposed domestic use of isoxaflutole on field corn does not pose an unacceptable dietary (food including water) chronic risk to any segment of the population, including infants, children and adults.

Using $Q_1$* of $1.14 \times 10^{-2}$ mg/kg bw/day in human equivalents and a linear relationship (dose–response) approach, the dietary risk was estimated to be in the range of $1 \times 10^{-7}$ to $9.8 \times 10^{-8}$ mg/kg bw for all population subgroups, including infants and children. Therefore, this linear risk estimate for use of isoxaflutole on corn is below the level of concern for life-time cancer risk.

In the acute dietary risk assessment, the PDI, including 10% water allocation, for the subgroup of females aged 13+ years was 25% of the ARD. Consequently, the proposed domestic use of isoxaflutole as a pre-emergent treatment for field corn does not pose an unacceptable acute dietary (both food and water) risk to all females aged 13+ years.

## 4.3 Residues relevant to worker safety

Residues relevant to worker safety have been addressed in section 3.6.3.

## 4.4 Proposed maximum residue limits and compliance with existing maximum residue limits

### 4.4.1 Compliance with existing maximum residue limits in Canada

Since the active ingredient is a new chemical, there are no existing MRLs.

### 4.4.2 Proposed maximum residue limits

The results of the Canadian field trials demonstrated that residues of isoxaflutole and its metabolites in field corn grain were below the LOQ (0.01 ppm). Residues up to 0.11 ppm were observed in the U.S. field trials. As field corn and its processed fractions are fed to livestock, the transfer of residues into edible commodities was examined. After consideration of the data submitted, Canada will establish MRLs of 0.5 ppm in liver, 0.3 ppm in poultry liver, 0.2 ppm in or on field corn and meat, 0.1 ppm in meat by-products, 0.02 ppm in milk and 0.01 ppm in eggs to cover potential residues of isoxaflutole and its metabolites.

### 4.5 Proposed import tolerances

The proposed MRLs for domestic use of isoxaflutole in or on field corn (meat, milk and eggs) are identical to the U.S. tolerances.

### 4.6 Basis for differences, if any, in established or proposed maximum residue limits

CODEX has not established MRLs for isoxaflutole.

## 5.0 Fate and behaviour in the environment

### 5.1 Physicochemical properties

Isoxaflutole has a low solubility in water (6.2 mg/L). It has a low potential to volatilize under field conditions (vapour pressure, $1.0 \times 10^{-6}$ Pa), and from water and moist soil surfaces (Henry's Law Constant, $1.87 \times 10^{-5}$ Pa $m^3$/mol). The log $K_{ow}$ of 2.32 indicates that isoxaflutole has a limited potential for bioconcentration.

### 5.2 Fate and behaviour in soil

The three modes of transformation of isoxaflutole in soils, i.e., hydrolysis, phototransformation and biotransformation, were investigated in detail under laboratory and field conditions. Studies were performed using radiolabelled [$^{14}$C-phenyl] isoxaflutole. It was demonstrated that chemical hydrolysis and microbial degradation were the principal mechanisms of transformation. The dissipation and accumulation of isoxaflutole under field conditions in the corn-growing areas in Canada and the northern United States was also studied.

#### 5.2.1 Phototransformation in soil

Isoxaflutole transformed in sandy loam soil (Lacama, North Carolina) exposed to xenon irradiation source (Heraeus Suntest with less than 290 nm filtered out) for a 31-day period (16.1 h light – 7.9 h dark cycle), with the dissipation time for 50% ($DT_{50}$) of 22.8 h. The corresponding value in dark control was 19.7 h, indicating that exposure to light does not affect the transformation of isoxaflutole on soil surfaces, as it is rapid under both dark and light conditions. The major transformation products (see Figure 1) detected were RPA 202248 (>70% of applied radioactivity) and RPA 203328 (>30% of applied).

#### 5.2.2 Aerobic soil biotransformation

Isoxaflutole transformed in sandy loam and clay soils under aerobic conditions with $DT_{50}$ and dissipation time for 90% ($DT_{90}$) values ranging from 1.4 to 2.4 days and from 5.4 to 8.1 days, respectively. These values indicated that isoxaflutole was not persistent in soils under aerobic conditions. The amount of extractable radioactivity decreased with time for both soils from 108 to 52% and from 91 to 30% in sandy loam and clay soils,

respectively. The quantity of unextractable radioactivity increased from 0.9 to 19% and from 4.5 to 28% of the dose applied in sandy loam and clay soil, respectively. The amount of radioactivity in potassium hydroxide traps ($CO_2$) reached a maximum of 16.8 and 39.5% of the doses applied in sandy loam and clay soil, respectively. Very little radioactivity (less than 0.4% of applied) was found in ethylene glycol traps, indicating that no significant volatile organic transformation products were produced. The major transformation products were identified as RPA 202248 and RPA 203328 (see Figure 2) reaching maximum values of 83.0 and 68.4%, and 55.1 and 33.7% of applied radioactivity in sandy loam and clay soils, respectively. The $DT_{50}$ values for the parent compound and one major transformation product were calculated by the reviewer (Table 5.1). These values indicated that major transformation products of isoxaflutole are moderately to very persistent in soil under aerobic conditions.

**Table 5.1 $DT_{50}$ and $DT_{90}$ values for isoxaflutole and its major transformation products**

| Soil type | $DT_{50}/DT_{90}$ values (days) | | |
|---|---|---|---|
| | Isoxaflutole | RPA 202248 | RPA 203328[1] |
| sandy loam | 1.4/5.4 | 96/>360[2] | 977 |
| clay | 2.4/8.1 | 24/>360[2] | 289 |

[1] The reviewer was unable to calculate $DT_{50}$ values on the basis of submitted data for this product. Therefore, values presented were those reported by the registrant. The registrant did not report $DT_{90}$ values.

[2] At the end of the study, 25–30% of applied radioactivity remained as RPA 202248.

### 5.2.3 Anaerobic soil transformation

No data were submitted.

### 5.2.4 Field soil dissipation studies

The dissipation studies of isoxaflutole under field conditions were conducted at three corn-growing sites in Canada that differ with respect to soil texture as well as weather. The study sites were Springbank and Selkirk, Ontario (clay loam and clay soil, respectively) and Carman, Manitoba (sandy loam soil). The residues of isoxaflutole and its transformation products were detected almost exclusively within the top 15 cm soil depth. Residues were found below the 15 cm depth in only three samples, all near the method detection limit, MDL (0.005 ppm). No residues were detected below the 30 cm depth. The isoxaflutole and its transformation products, therefore, have low potential for contamination of groundwater. All residues were below the MDL at the 2-month sampling at both the Springbank and Carman sites and at the 4- to 5-month sampling at the Selkirk site. Isoxaflutole transformed quickly at all sites with a $DT_{50}$ ranging from 1.5 to seven days (Table 5.2). The $DT_{50}$ for RPA 202248 ranged from 11 days at the Springbank and Carman sites to 26 days at the Selkirk site. As RPA 203328 was forming

and transforming simultaneously, reliable estimates of the first-order degradation rate for this transformation product could not be determined. The estimated $DT_{50}$ for RPA 203328 was determined from the graph developed from the data collected at each site. The estimates ranged from nine to 73 days, with the longer $DT_{50}$ associated with the Selkirk site.

**Figure 2 Proposed environmental transformation pathway of isoxaflutole**

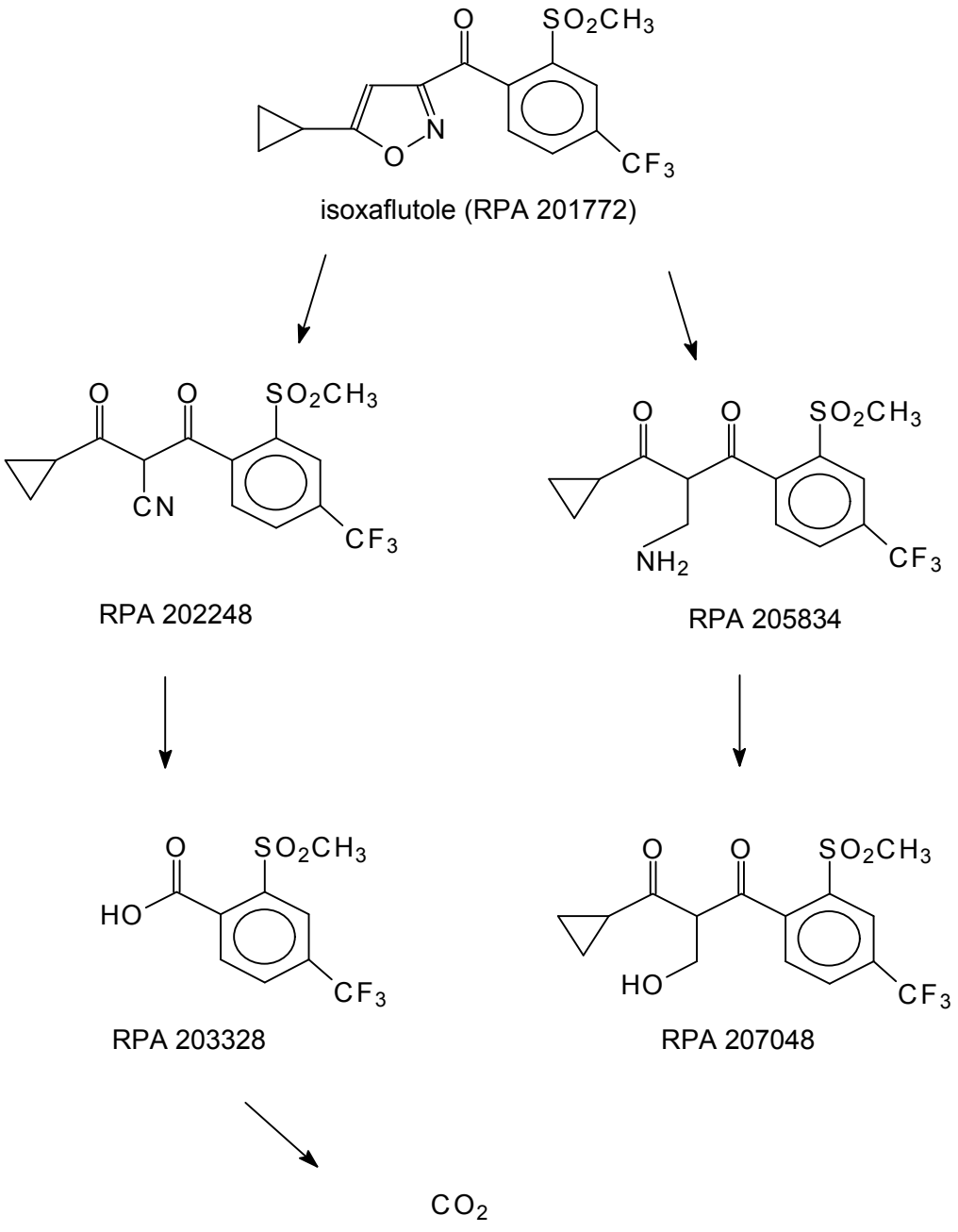


**Table 5.2 $DT_{50}$ for isoxaflutole and its transformation products in soil under field conditions**

| Compound | $DT_{50}$ (days) | | |
|---|---|---|---|
| | Springbank, Ontario | Selkirk, Ontario | Carman, Manitoba |
| Isoxaflutole | 1.5 | 7.04 | 3.07 |
| RPA 202248 | 10.97 | 26.05 | 11.2 |
| RPA 203328 | 11.75 | 72.95 | 8.9 |

In the United States, terrestrial field dissipation study were conducted at four sites in Nebraska, California, North Carolina and Washington. For the purpose of this review, only the study conducted at the Washington site, which is located in the same ecozone as British Columbia and Alberta, was reviewed. The Washington site was located in Ephrata, Grant County. The soil was classified as a Timmerman sandy loam soil. Isoxaflutole and its transformation products were nonpersistent in the Washington sandy loam soil, with $DT_{50}$ values of 2.2 and 13.1 days for isoxaflutole and RPA 202248, respectively. As RPA 203328 was forming and transforming simultaneously, reliable estimates of the first-order degradation rate for this transformation product could not be determined. The residues of isoxaflutole and its transformation products were detected almost exclusively within the top 15 cm soil depth. No residues were detected below the 30 cm depth.

### 5.2.5 Mobility: soil adsorption and desorption

Adsorption and desorption studies of isoxaflutole with one U.S. and three U.K. soils (and one sediment) indicated that isoxaflutole was moderately to highly mobile. The adsorption coefficient values, $K_{oc}$, for isoxaflutole were 131, 101, 93, 123 and 165 in sandy loam, sand, loam, silty clay and sediment, respectively.

Adsorption and desorption studies of transformation products, RPA 202248 and RPA 203328, indicated that they were highly to very highly mobile in four U.S. soils and one sediment. The $K_{oc}$ values for RPA 202248 were 94, 117, 159, 149 and 135 for clay, sand, loamy sand, silt loam and sediment, respectively. For RPA 203328, $K_{oc}$ values were 47, 82, 91, 100 and 23 for clay, sand, loamy sand, silt loam and sediment, respectively.

### 5.2.6 Mobility: soil column leaching

The leaching of isoxaflutole after aerobic incubation to $DT_{50}$ (5.5, 9.8, 13.5, 32.6 and 44.6 h for sand, clay loam, silty clay, loam and sandy loam, respectively) was conducted in four different soils and one sediment. Following incubation, the aged soils were transferred to leaching columns to a nominal depth of 36 cm of soil in each column. The soils were leached over a period of five to nine days with 1040 mL of 0.01 M aqueous

calcium chloride equivalent to 50.8 cm of rainfall. Leachate and soil extracts containing more than 5% of the applied radioactivity were analysed by HPLC and thin layer chromatography. Confirmation of the identity of isoxaflutole and its transformation products was done by liquid chromatography with MS or MS alone. In soils containing a low percentage of organic matter (3.4% or less), most of the applied radioactiviy (50.5–89.4%) was present in the leachate. Isoxaflutole was found only in the top 6 cm of soil. RPA 202248 was found in the leachate from all tested soils. The other transformation product, RPA 203328, was found only in the leachate from sandy loam soil (less than 10% of applied). RPA 202248 and RPA 203328 were both detected down to 18 and 24 cm in the high organic matter silty clay soil and loam sediment, respectively. The anaerobic transformation product, RPA 205834, was found in a small amount (<1%) in the loam sediment column.

### 5.2.7 Mobility: soil thin layer chromatography

No data were submitted.

### 5.2.8 Mobility: field leaching data

Studies conducted with soil columns under field conditions in Canada and the United States indicated that the leaching of isoxaflutole and its transformation products was minimal.

### 5.2.9 Expected environmental concentration in soil

According to the proposed label, the maximum application rate is 105 g a.i./ha. Assuming a soil bulk density of 1.5 g/cm$^3$ and a soil depth of 15 cm, an application at the maximum label rate would result in an expected environmental concentration (EEC) of 0.047 mg a.i./kg soil.

## 5.3 Fate and behaviour in aquatic systems

### 5.3.1 Hydrolysis

Isoxaflutole hydrolysed easily at pH 5, 7 and 9 by isoxazole ring opening, forming one transformation product, RPA 202248. Isoxaflutole hydrolysed, following pseudo-first-order kinetics, into RPA 202248. This transformation product did not transform further under the test conditions. The half-lives, calculated by linear regression, were 11.1 days, 20.1 h and 3.2 h for pH 5, 7 and 9, respectively, at 25EC.

### 5.3.2 Phototransformation in water

In aquatic system, isoxaflutole readily phototransformed with a $DT_{50}$ value of 40 h. In contrast, the parent compound was stable in the dark control solutions (>89% applied remained after 54 h). Phototransformation was, therefore, a significant route of

transformation of isoxaflutole in aquatic systems. Several transformation products were observed, but each of them represented less than 10% of the initial dose. Three transformation products were identified as RPA 202248, RPA 205834 and RPA 203328. In the dark controls, RPA 202248 was the only significant transformation product (5% of the initial dose).

### 5.3.3 Aquatic aerobic biotransformation

Isoxaflutole dissipated rapidly from two U.K. water and sediment systems under aerobic conditions. The $DT_{50}$ values of 0.5–0.6 days in water, and water and sediment systems at 20 ± 2EC indicated that isoxaflutole was not persistent in aquatic systems under aerobic conditions. Its major transformation products, however, were persistent under the study conditions (Table 5.3).

Partition of the radioactivity between water and sediment occurred more rapidly in the Manningtree system, in which radioactivity declined to 50% of applied in the surface water at day 14, than in River Roding system, in which it declined to 63%. At 100 DAT, radioactivity in the surface water declined to 22 and 41% of applied, and extractable residues in the sediments were 51 and 34% of applied in the Manningtree and River Roding systems, respectively. Unextractable residues increased with the time from ca. 1 and 2% at day 0 to ca. 23 and 19% of applied at 100 DAT, respectively, and were characterized as being primarily in the fulvic acid fraction. Isoxaflutole was observed only in the surface water of each system and was not detected after seven days. The major transformation products were identified as RPA 202248 and RPA 205834. RPA 202248 reached a maximum of 63 and 60% of applied radioactivity at 2 DAT in the Manningtree and River Roding systems, respectively. RPA 205834 reached a maximum of 24% at 2 DAT in the Manningtree system, and 26% at 7 DAT in the River Roding system. Two minor transformation products, RPA 203328 and RPA 207048, were observed in both systems. They did not exceed 5% of applied radioactivity in either system.

**Table 5.3 $DT_{50}$ and $DT_{90}$ values (days) from aerobic water and sediment study**

| System | Phase | Isoxaflutole | | RPA 202248 | | RPA 205834 | |
|---|---|---|---|---|---|---|---|
| | | $DT_{50}$ | $DT_{90}$ | $DT_{50}$ | $DT_{90}$ | $DT_{50}$ | $DT_{90}$ |
| Manningtree | whole system | 0.5 | 2 | 703 | 2335 | 97 | 322 |
| | water | 0.5 | 2 | 66 | 220 | 36 | 120 |
| River Roding | whole system | 0.6 | 2 | 255 | 846 | 52 | 173 |
| | water | 0.6 | 2 | 89 | 295 | 36 | 118 |

### 5.3.4 Aquatic anaerobic biotransformation

Under anaerobic aquatic conditions, isoxaflutole dissipated rapidly, with $DT_{50}$ values less than two hours. The dissipation of its transformation products was slower and did not follow the first-order kinetics. The results of the study indicated that isoxaflutole was not persistent in an anaerobic aquatic system. Its major transformation products, however, were persistent under the study conditions (Table 5.4).

There was a rapid transfer of radioactivity from the water to the sediment. At time 0, 2% of the applied radioactivity was found in the sediment and increased to 15% at 1 DAT. Equilibrium was achieved after 28 days with 73% of applied radioactivity found in the sediment and 26% in the water. Isoxaflutole was observed only in the surface water at time 0 and was not detected after two hours. Two major transformation products were identified as RPA 202248 and RPA 205834 (see Figure 1). At 14 DAT, RPA 202248 represented 80.0% of the applied radioactivity in the sediment and water system. In the water, the highest concentration of RPA 202248 was found after 6 h and represented 69% of the applied radioactivity. The concentration of RPA 202248 in the water declined with time to 23% at 365 DAT. Correspondingly, there was an increase of RPA 202248 concentration in the sediment from 3.9 to 57% of the applied at 183 DAT. RPA 205834 reached 28% of the applied at 6 h in the system (25% in the water and 3% in the sediment). There was again transfer from the water to the sediment with a decline from 25% to <1% of the applied in the water after 274 DAT. The sediment concentration increased from 1% of the applied at time 0 to 10% at 7 DAT. After 14 DAT, the amount of RPA 205834 declined to 3.1% of the applied at 365 DAT. Two minor transformation products, RPA 203328 and RPA 207048, were also observed. They did not exceed 1.5% of the applied radioactivity.

**Table 5.4 $DT_{50}$ values from the anaerobic aquatic study**

| | Isoxaflutole | RPA 202248 | RPA 205834 |
|---|---|---|---|
| **Water** | less than two hours | 316 days | 48 days |
| **Sediment** | not detected | could not be calculated | 236 days |
| **Whole system** | less than two hours | could not be calculated | 131 days |

### 5.3.5 Expected environmental concentration in water

Under the proposed use pattern, the potential exposure of surface water is through surface runoff, spray drift and accidental overspray on neighbouring water bodies. Assuming a scenario of 100% deposition, a direct overspray of isoxaflutole at the maximum recommended Canadian label rate of 105 mg a.i./ha would result in an EEC of 0.035 mg a.i./L in a 30-cm depth of water. The estimated seasonal losses from runoff following the application of a wettable granular formulation of isoxaflutole is expected to be 2–5% of the amount applied. Assuming 2–5% runoff, 30 cm depth of pond water and a

ratio of 100:1 of watershed area to pond area in the Prairies, the EEC of isoxaflutole would be 0.07–0.175 mg a.i./L. In the case of deeper water bodies in the Prairies, the EEC for human drinking water, on the basis of a 4000-$m^3$ dugout, a 100–2000 ha watershed and 2–5% runoff, would be 0.05–2.6 mg a.i./L.

### 5.4 Fate and behaviour in air

The vapour pressure of isoxaflutole is $1.0 \times 10^{-6}$ Pa at 25EC and the calculated Henry's Law Constant $1.87 \times 10^{-5}$ Pa $m^3$/mol ($1.85 \times 10^{-10}$ atm $m^3$/mol).

These values indicate that isoxaflutole is nonvolatile and the contamination of the atmosphere by isoxaflutole would be extremely low under the proposed use pattern.

## 6.0 Effects on nontarget species

### 6.1 Effects on terrestrial nontarget species

#### 6.1.1 Wild birds

Isoxaflutole was practically nontoxic to the bobwhite quail and the mallard duck on an acute oral basis with $LD_{50}$ values of >2150 mg a.i./kg bw, the highest dose tested (Appendix II, Table 1). The NOEL values were 2150 mg a.i./kg bw.

On a dietary basis also, isoxaflutole was practically nontoxic to the bobwhite quail and the mallard duck with $LC_{50}$ values of >5000, the highest dose tested. The no observable effect concentration (NOEC) values were 5000 mg a.i./kg bw.

#### 6.1.2 Wild mammals

Isoxaflutole was practically nontoxic to male and female rats on an acute oral basis with $LD_{50}$ values of >5000 mg a.i./kg (Appendix II, Table 1).

#### 6.1.3 Bees

Isoxaflutole was relatively nontoxic to honeybees (*Apis mellifera*) on acute oral and contact basis. The 48-h acute contact and oral $LD_{50}$ values were >100 and >168.7 Fg a.i./bee, respectively, the highest doses tested (Appendix II, Table 1). The corresponding NOECs were 100 and 168.7 Fg a.i./bee, respectively.

#### 6.1.4 Arthropod predators and parasites

No data were submitted.

### 6.1.5 Earthworms

Isoxaflutole was nontoxic to earthworms (*Eisenia foetida*). The NOEC and 14-day $LC_{50}$ values were 1000 and >1000 mg a.i./kg soil, respectively (Appendix II, Table 1).

### 6.1.6 Effects on soil micro-organisms

No data are required.

### 6.1.7 Terrestrial nontarget plants

The submitted phytotoxicity data revealed that all 10 tested species have some sensitivity to isoxaflutole. The degree of effect varied among species and among the different tests.

*Seed germination:* There were no treatment-related mortalities or morphological abnormalities observed. Except for soybean radicle length, the percentage germination and radicle length of all species were either greater than the pooled control, not significantly reduced compared with the pooled control or significantly reduced compared with the pooled control (but less than 25% reduced). Therefore, the NOEC values for these parameters were the highest application rate for each species (235.4 or 246.6 g a.i./ha) and the $EC_{25}$ values were empirically estimated to be greater than the highest application rate. A significant reduction (28%) in soybean radicle length was observed at 235.4 g a.i./ha. The NOEC for soybean radicle length was 109.8 g a.i./ha, and the $EC_{25}$ was 201.75 g a.i./ha.

*Seedling emergence:* Morphological abnormalities (e.g., chlorosis, necrosis, foliar lesions, leaf blotch) and mortalities were observed in all tested species at higher application rates.

*Vegetative vigour:* Morphological abnormalities (e.g., chlorosis, necrosis, foliar lesions, leaf blotch, leaf curl) were observed in all tested species at higher application rates. Mortalities were observed in lettuce, onion, perennial ryegrass, tomato and turnip.

## 6.2 Effects on aquatic nontarget species

Low solubility of technical isoxaflutole in water, resulting in precipitation, limited used concentration range in all aquatic toxicity study discussed below. Therefore, most end points are given as greater than the highest concentration measured.

### 6.2.1 Bioconcentration in fish

The octanol–water partition coefficient (log $K_{ow}$) for isoxaflutole was 2.3 at 20EC. This value indicated that isoxaflutole has a limited potential to bioaccumulate in organisms. As this value is less than the threshold of 3 at which a fish bioconcentration study is required, no data on bioaccumulation in fish were required.

### 6.2.2 Fish

Isoxaflutole was moderately toxic to rainbow trout, bluegill sunfish and sheepshead minnow on an acute basis with $LC_{50}$ values of >1.7, >4.5 and >6.4 mg a.i./L, respectively, the highest concentrations tested (Appendix II, Table 2). The corresponding NOEC values were 1.7, 4.5 and 6.4 mg a.i./L, respectively. Three transformation products were practically nontoxic to rainbow trout, with $LC_{50}$ values ranging from 33.8 to 160 mg a.i./L. In the early life-cycle toxicity study, the 28-day $LC_{50}$ was 0.19 mg a.i./L (NOEC, 0.1 mg a.i./L), indicating that isoxaflutole is toxic to juvenile rainbow trout.

### 6.2.3 Aquatic invertebrates

Isoxaflutole was practically nontoxic to daphnids on an acute basis with $EC_{50}$ and NOEC values of >1.5 and 1.5 mg a.i./L, respectively, the highest concentration tested (Appendix II, Table 2). Isoxaflutole did not significantly affect the reproductive performance, survival and growth of daphnids up to 102 mg a.i./L (NOEC). Isoxaflutole was very highly toxic to mysid shrimps (*Mysidopsis bahia*) on an acute basis with 96-h NOEC and $LC_{50}$ values of 5.1 and 18 Fg a.i./L, respectively. It was also very highly toxic to mysid shrimps in the chronic toxicity test, with the lowest observable effect concentration (LOEC) and NOEC values of 1.9 and 1.9 Fg a.i./L, respectively. Isoxaflutole was moderately toxic to eastern oyster (*Crassostrea virginica*), with 96-h NOEC and $LC_{50}$ values of 0.98 and 3.4 mg a.i./L, respectively.

### 6.2.4 Algae

Isoxaflutole was highly toxic to freshwater ($EC_{50}$, 0.12–0.38 mg a.i./L) and marine algae ($EC_{50}$, 0.11 mg a.i./L). Major transformation products of isoxaflutole were practically nontoxic to algae ($EC_{50}$ > 9.4–20 mg a.i./L).

### 6.2.5 Aquatic plants

The aquatic plant duckweed (*Lemna gibba*) was very sensitive to isoxaflutole with NOEC and $EC_{25}$ values of 0.0011 and 0.0014 mg a.i./L, respectively (Appendix II, Table 2). Isoxaflutole significantly reduced the frond production and increased the percentages of dead and chlorotic fronds when compared with the negative controls.

## 6.3 Effects on biological methods of sewage treatment

No data are required.

## 6.4 Environmental risk assessment

### 6.4.1 Terrestrial organisms

**Wild birds**

Concentrations of isoxaflutole residues in plants and other food sources were estimated using linear conversions of application rates on the basis of Hoerger and Kenaga (1972) and Kenega (1973). The maximum label application rate of 105 g a.i./ha was used to calculate the concentrations in different food sources to which wildlife may be exposed (Appendix II, Table 3).

Wild birds would not likely be exposed to isoxaflutole as a result of direct overspray. Birds could be exposed, however, to isoxaflutole drift or by consumption of sprayed vegetation or contaminated prey. Immediately after application, food sources such as seeds and small insects in a treated field could have isoxaflutole concentrations of 3.55 and 20.75 mg/kg dw, respectively (Appendix II, Table 3). Consideration of the large difference in magnitude between EECs and acute oral and dietary $LD_{50}$s (and NOECs) indicates that isoxaflutole would not be expected to present an acute and dietary risk to terrestrial birds through the consumption of contaminated food (Appendix II, Table 4).

Risk assessment for birds was done using NOELs for two bird species, i.e., bobwhite quail and mallard duck. The dietary intake (DI) of isoxaflutole was estimated from information on the food consumption (FC) and EEC of isoxaflutole in various foodstuffs ($DI = FC \times EEC$).

*Acute risk assessment:* Assuming bobwhite quail will consume 30% small insects and 70% grain (EPA 1993), the EEC in the diet would amount to 12.6 mg a.i./kg dw and the daily intake would be 0.2 mg a.i./individual/day. The maximum number of days of intake of isoxaflutole required that would have observable effects ($NOEL_{ind}$/EEC) would be 2150. This number indicated that birds are not at potential risk on an acute basis.

*Dietary risk assessment:* The NOEC for the bobwhite quail was 5000 mg a.i./kg dw and the EEC in the diet was 12.6 mg a.i./kg dw. The values of risk factor (EEC/NOEL = 0.0025) and margin of safety (NOEL/EEC = 397) for the dietary risk indicated that the environmental concentration is much lower than the NOEC and that ingestion of this compound at the indicated levels would not pose a dietary risk to birds.

**Wild mammals**

The available mammalian data indicate that isoxaflutole is nontoxic to small mammals on an acute oral basis. The $LD_{50}$ values for male and female rat are greater than 5000 mg a.i./kg.

Immediately after application of 105 g a.i./ha, food sources such as short grass, leafy crops and seeds in a treated field could have isoxaflutole concentrations ranging from 3.55 to 129.35 mg a.i./kg dw (Appendix II, Table 3). Consideration of the large difference in magnitude between the EECs and acute oral $LD_{50}$s and NOELs for the rat indicates that isoxaflutole would not present an acute risk to small mammals through the consumption of contaminated food (Appendix II, Table 4).

**Honeybee**s

The 48-h acute oral and contact NOEC values were 168.7 and 100 Fg a.i./bee, respectively. Under the proposed maximum application rate of isoxaflutole, the EEC in large insects was 3.55 mg a.i./kg dw (Appendix II, Table 3). Assuming an average bee weight of one gram, the EEC would be 3.55 Fg a.i./bee. The SFs for the acute oral and contact toxicity are 47.5 and 28.2, respectively (Appendix II, Table 4). An assessment of these values indicated that the bees were not at risk on an acute basis under the proposed maximum application rates.

**Earthworms**

The acute 14-day NOEC for earthworms was 1000 mg a.i./kg soil (Appendix II, Table 1). The EEC in soil at the proposed maximum application rate was 0.046 mg a.i./kg. The values of the risk ($4.6 \times 10^{-5}$) and safety ($2.2 \times 10^{4}$) factors indicated that the effect on earthworms of application of isoxaflutole at the proposed maximum application rate would be insignificant (Appendix II, Table 4).

### 6.4.2 Aquatic organisms

The exposure to nontarget aquatic organisms may occur through either runoff or direct overspray or spray drift. Isoxaflutole technical is moderately toxic to fish, nontoxic to freshwater invertebrates, moderately to very highly toxic to marine and estuarine invertebrates, toxic to algae and highly toxic to vascular plants (Appendix II, Table 2). Risk assessment to aquatic organisms was done using the most sensitive invertebrate, fish and nontarget plant species (Appendix II, Table 5). The EEC in a scenario of direct overspray (100% deposition) of isoxaflutole at the maximum application rate would be 0.035 mg a.i./L. The EEC in water owing to surface runoff in the Prairies would be 0.07–0.175 mg a.i./L.

Nontarget aquatic plants are susceptible to isoxaflutole. The EEC (0.035 mg a.i./L) in water under direct overspray at the maximum application rate is higher than NOEC values and would, therefore, adversely affect the nontarget aquatic plants. On the basis of the toxicity end point (NOEC = 0.0011 mg a.i./L) and EEC in water under direct overspray for the most sensitive species, giant duckweed, the buffer zone would be 22 m. It should be noted that this buffer zone will not protect against runoff, which would result in higher EEC values.

### 6.5 Environmental risk mitigation

An assessment of environmental safety with the use of isoxaflutole has identified the following concern:

- Isoxaflutole is toxic to aquatic plants. Under the proposed use pattern isoxaflutole would adversely affect the aquatic wildlife habitat.

To protect the sensitive nontarget aquatic plants, buffer zones between the last spray swath and the edge of the sensitive areas are required. These buffer zones were calculated using Nordby and Skuterud (1975) and Ganzelmeier (1995) models.

To protect the nontarget aquatic plant species from isoxaflutole injury, a buffer zone of 22 m should be observed between the last spray swath and the edge of sensitive aquatic areas such as wetlands and ponds.

To protect the nontarget aquatic plant species from isoxaflutole in runoff, the following label statement is required:

> "Do not spray if there is rain forecast for during or soon after application."

## 7.0 Efficacy data and information

### 7.1 Effectiveness

#### 7.1.1 Intended uses

Converge 75 WDG is a pre-emergent herbicide for control of several annual grass and broadleaf weeds in conventionally tilled field corn grown in eastern Canada. Application must be made after crop seeding but prior to emergence with ground equipment only, and is not to be applied on sandy and loamy sand soils or on soils with less than 2% organic matter.

Efficacy of Converge 75 WDG was assessed in numerous Canadian field trials conducted in Quebec and Ontario, and in U.S. trials conducted in northern sates. Fourteen of the 15 weed species for which a claim of control was proposed were supported by adequate data, but in conventionally tilled corn only (see bolded text, Appendix III, Table 1). A claim of green pigweed control and use in no-till field corn were not accepted because of insufficient data.

A tank mixture of Converge 75 WDG at 79–105 g a.i./ha plus atrazine at 800–1120 g a.i./ha was also proposed for use in conventional and no-till field corn for control of the above weeds plus lady's-thumb and wild buckwheat. In conventionally tilled field corn, 15 of the 17 proposed weed claims were supported by adequate data

(see bolded text, Appendix III, Table 2) but the value of use rates in excess of the minimum proposed was not demonstrated. Insufficient data was available to support use in no-till field corn and to support claims of green pigweed and wild buckwheat control.

In lieu of rotational crop studies, a rationale was submitted on the basis of the expected $DT_{50}$ of isoxaflutole and the metabolite RPA 202248, and the metabolism of the compounds in corn. While the available information supports field corn as an acceptable rotational crop, recropping studies generated in eastern Canada are required to establish the acceptability of other rotational crops.

### 7.1.2 Mode of action

Isoxaflutole is the first member of a new class of herbicides referred to as the isoxazoles. It is a systemic herbicide that is absorbed through shoots and roots of treated plants and translocated in the xylem and phloem. Isoxaflutole inhibits the enzyme *p*-hydroxy phenyl pyruvate dioxygenase, which converts *p*-hydroxy phenyl pyruvate to homogentisate. This conversion is a key step in plastoquinone biosynthesis and its inhibition in meristematic tissues gives rise to bleaching symptoms on new growth. These symptoms result from an indirect inhibition of carotenoid biosynthesis owing to the involvement of plastoquinone as a cofactor of phytoene desaturase. Emerging weeds are bleached as the herbicide is taken up by the root system. Under conditions of adequate soil moisture, weed seedlings of susceptible species either do not emerge or turn white upon emergence and then die.

Field corn tolerance appears to be due to its rapid metabolism via hydrolytic reactions, while sensitive weed species metabolize the product at much slower rates.

### 7.1.3 Crops

Field corn is the only crop on which data is presented and for which a label claim is made.

### 7.1.4 Effectiveness against pests

#### 7.1.4.1 Converge 75 WDG alone

Efficacy of Converge 75 WDG applied alone in conventionally tilled field corn was examined in trials conducted between 1995 and 1997. Several trials reported control with use rates below those proposed (i.e., 26, 52 and 79 g a.i./ha for barnyard grass and green foxtail; 26 and 52 g a.i./ha for other species). In general, a more consistent and higher level of control was reported for the proposed rates than for the lower rates that were examined. A summary of accepted weed claims follow.

**Barnyard grass (*Echinochloa crusgalli*):** Control of barnyard grass with Converge 75 WDG at 105 g a.i./ha was reported in 28 Canadian field trials conducted at 14 locations across Ontario and Quebec between 1995 and 1997. The Canadian data was supplemented by results from 15 U.S. trials performed in 1995 and 1996 at two locations, one each in Wisconsin and Ohio. Mean late season control in the Canadian trials was 92% at 30–93 DAT ($n$ = 28) and in the U.S. trials was 85% at 47–57 DAT ($n$ = 15). The data support a claim of barnyard grass control in conventionally tilled field corn with Converge 75 WDG at 105 g a.i./ha.

**Green foxtail (*Setaria viridis*):** Green foxtail control with Converge 75 WDG at 105 g a.i./ha was reported in 49 Canadian trials conducted over a three-year period at three locations in Quebec and 19 in Ontario. This data was supported by results from eight U.S. trials conducted in Wisconsin in 1995 and 1996. Mean reported control was 89% at 20–94 DAT ($n$ = 49) in the Canadian trials and 91% at 53–57 DAT ($n$ = 8) in the U.S. trials. The data support a claim of green foxtail control in conventionally tilled field corn following product application at 105 g a.i./ha.

**Witchgrass (*Panicum capillare*):** Control of witchgrass with Converge 75 WDG at 79 g a.i./ha was reported in 23 Canadian trials conducted between 1995 and 1997 at three Quebec and eight Ontario locations. Mean control of 90% was reported at 57–89 DAT ($n$ = 23). The data support a claim of witchgrass control in conventionally tilled field corn following application of Converge 75 WDG at 79 g a.i./ha.

**Large crabgrass (*Digitaria sanguinalis*):** Large crabgrass control following product application at 79 g a.i./ha was reported in seven Canadian and three U.S. field trials. Canadian trials were conducted in 1996 and 1997 at five locations, one in Quebec and four in Ontario, while U.S. trials were conducted in 1995 and 1996 in Wisconsin. Mean control of 92% at 29–82 DAT ($n$ = 7) was reported in the Canadian trials and 98% at 56–59 DAT ($n$ = 3) in the U.S. trials. The data support a claim of large crabgrass control in conventionally tilled field corn following product application at 79 g a.i./ha.

**Smooth crabgrass (*Digitaria ischaemum*):** Smooth crabgrass control with Converge 75 WDG at 79 g a.i./ha was reported in five Canadian field trials conducted in 1996 and 1997 at two Quebec and two Ontario locations. Two additional Canadian trials conducted in 1996 and one U.S. trial performed in 1995 reported control of crabgrass species and were considered in support of the proposed weed claim, as was data made available for the related species, large crabgrass. Reported control of smooth crabgrass was similar to that reported for the related species, large crabgrass, and for crabgrass species. A mean control of 95% at 30–80 DAT ($n$ = 5) was reported for smooth crabgrass and 98% at 56–79 DAT ($n$ = 3) for crabgrass species. The data support a claim of smooth crabgrass control in conventionally tilled field corn following application of Converge 75 WDG at 79 g a.i./ha.

**Lamb's-quarters (*Chenopodium album*):** Control of lamb's-quarters with Converge 75 WDG at 79 g a.i./ha was reported in 60 Canadian trials conducted between 1995 and 1997 at 30 locations across Ontario and Quebec. The Canadian data was supplemented by results from 19 U.S. trials performed at four locations in Wisconsin, Michigan and Indiana in 1995 and 1996. Mean reported control in the Canadian trials was 89% at 39–117 DAT ($n$ = 60) and in the U.S. trials was 98% at 38–66 DAT ($n$ = 19). The data support a claim of lamb's-quarters control in conventionally tilled field corn with Converge 75 WDG at 79 g a.i./ha.

**Redroot pigweed (*Amaranthus retroflexus*):** Redroot pigweed control with Converge 75 WDG at 79 g a.i./ha was reported in 42 Canadian field trials conducted over the three-year period of 1995–1997 at two locations in Quebec and 19 locations in Ontario. The Canadian data was supplemented by results from 14 U.S. trials conducted in 1995 and 1996 at four locations in Wisconsin, Ohio, Indiana and Michigan. Mean reported control in the Canadian trials was 88% at 33–109 DAT and in the U.S. trials was 97% at 28–62 DAT. The data support a claim of redroot pigweed control in conventionally tilled field corn following product application at 79 g a.i./ha.

**Common ragweed (*Ambrosia artemisiifolia*):** Common ragweed control with Converge 75 WDG at 79 g a.i./ha was reported in 33 Canadian field trials conducted between 1995 and 1997 at five locations in Quebec and 14 in Ontario. This data was supplemented by results from 28 U.S. trials conducted in 1995 and 1996 at four locations in Wisconsin, Indiana and Michigan. Mean reported control in the Canadian trials was 98% at 37–112 DAT, while mean control in the U.S. trials was 99% at 48–66 DAT. The data support a claim of common ragweed control in conventionally tilled field corn following a Converge 75 WDG application at 79 g a.i./ha.

**Eastern black nightshade (*Solanum ptycanthum*):** Control of eastern black nightshade with Converge 75 WDG at 79 g a.i./ha was reported in seven Canadian trials conducted in 1996 and 1997 at five locations in Ontario and in one U.S. trial conducted in 1996 in Michigan. Mean reported control in the Canadian trials was 98% at 41–82 DAT and 100% at 60 DAT in the U.S. trial. The data support a claim of eastern black nightshade control in conventionally tilled field corn following application of Converge 75 WDG at 79 g a.i./ha.

**Wormseed mustard (*Erysimum cheiranthoides*):** Control of wormseed mustard with Converge 75 WDG at 79 g a.i./ha was reported in six Canadian trials conducted in 1996 and 1997 at two locations in Quebec and three in Ontario. Mean reported control was 100% at 66–93 DAT ($n$ = 6). The data support a claim of wormseed mustard control in conventionally tilled field corn following product application at 79 g a.i./ha.

**Wild mustard (*Sinapis arvensis*):** Wild mustard control with Converge 75 WDG at 79 g a.i./ha was reported in seven Canadian field trials conducted in 1996 and 1997 at one Quebec and five Ontario locations. Mean reported control was 93% at 37–94 DAT. The data support a claim of wild mustard control in conventionally tilled field corn following application of Converge 75 WDG at 79 g a.i./ha.

**Velvetleaf (*Abutilon theophrasti*):** Velvetleaf control with Converge 75 WDG at 79 g a.i./ha was reported in 13 Canadian field trials conducted between 1995 and 1997 at six locations in southern Ontario and two in Quebec. The Canadian data was supplemented by results from 23 U.S. trials conducted in 1995 and 1996 at four locations in Wisconsin, Illinois, Indiana and Michigan. Mean reported control was 93% at 37–82 DAT in the Canadian trials and 99% at 38–66 DAT in the U.S. trials. The data support a claim of velvetleaf control in conventionally tilled field corn following a Converge 75 WDG application at 79 g a.i./ha.

**Broadleaf plantain (*Plantago major*) seedlings:** Control of broadleaf plantain seedlings with Converge 75 WDG at 79 g a.i./ha was reported in eight Canadian field trials conducted using conventional tillage practices. Although insufficient data was available to support use under no-till practices, results from the two no-till trials were considered in support of the proposed conventional tillage use. Trials were conducted between 1995 and 1997 at two locations in Quebec and four in Ontario. Overall, mean reported control was 97% at 56–82 DAT ($n$ = 10). The data support a claim of broadleaf plantain seedling control in conventionally tilled field corn following application of Converge 75 WDG at 79 g a.i./ha.

**Dandelion (*Taraxacum officinale*) seedlings:** Control of dandelion seedlings with Converge 75 WDG application at 79 g a.i./ha was reported in several trials; however, individual trial reports submitted to support the claim did not always clearly indicate if the target population emerged from seed or had established the previous year. Six conventionally tilled trials reported dandelion seedling control. Although insufficient data was available to support use under no-till practices, results from two additional trials conducted with this tillage regime were considered in support of the proposed conventional tillage use. Trials were conducted between 1995 and 1997 at two locations in Quebec and four locations in Ontario. Mean reported control was 91% at 23–132 DAT ($n$ = 8). The data support a claim of dandelion seedling control in conventionally tilled field corn following a Converge 75 WDG application at 79 g a.i./ha.

#### 7.1.4.2 Converge 75 WDG plus atrazine

Effectiveness of the proposed tank mixture of Converge 75 WDG plus atrazine in conventionally tilled field corn was examined in 28 Canadian field trials conducted in Ontario and Quebec in 1996 and 1997. The tank mixture was evaluated for annual grass and broadleaf weed control to ensure that weed control provided by Converge 75 WDG was not compromised by the addition of atrazine, and to evaluate control of lady's-thumb. A summary of accepted weed claims follow.

**Barnyard grass (*Echinochloa crusgalli*):** Eleven side-by-side trials reported control of barnyard grass following an application of Converge 75 WDG alone at 105 g a.i./ha and when tank mixed at 79 g a.i./ha with Aatrex Nine-0 at 800 g a.i./ha. Two trials were conducted in 1996 and nine in 1997 at three locations in Quebec and five in Ontario. Mean reported control for Converge 75 WDG alone was 92% and for the tank mixture was 95% at 37–70 DAT ($n$ = 11). The level of barnyard grass control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha, and was similar to that reported for Converge 75 WDG alone at the higher use rate of 105 g a.i./ha. The data support a claim of barnyard grass control in conventionally tilled field corn with Converge 75 WDG at 79 g a.i./ha plus atrazine at 800 g a.i./ha.

**Green foxtail (*Setaria viridis*):** Control of green foxtail was reported in 14 trials that allowed for direct comparisons of Converge 75 WDG alone at 105 g a.i./ha alone and in tank mix combination at 79 g a.i./ha with Aatrex Nine-0 at 800 g a.i./ha. Six trials were conducted in 1996 and nine in 1997 at one location in Quebec and nine in Ontario. Mean control reported for Converge 75 WDG alone was 91% and for the tank mixture was 92% at 28–58 DAT ($n$ = 14). The level of green foxtail control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha, and was similar to that reported for Converge 75 WDG alone at the higher use rate of 105 g a.i./ha. The data support a claim of green foxtail control in conventionally tilled field corn with Converge 75 WDG at 79 g a.i./ha plus atrazine at 800 g a.i./ha.

**Witchgrass (*Panicum capillare*):** Ten side-by-side trials, three conducted in 1996 and seven in 1997, reported control of witchgrass following an application of Converge 75 WDG alone at 79 g a.i./ha and in a tank mixture with Aatrex Nine-0 at 800 g a.i./ha. Two trials were located in Quebec at two locations and eight in Ontario at four locations. Mean control reported for Converge 75 WDG alone was 86% and for the tank mixture was 96% at 43–62 DAT ($n$ = 10). The level of witchgrass control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha, and in some instances was improved.

**Smooth crabgrass (*Digitaria ischaemum*):** Three side-by-side trials conducted in 1997, two in Quebec at two locations and one in Ontario, reported control of smooth crabgrass following an application of Converge 75 WDG at 79 g a.i./ha alone and in a tank mixture with Aatrex Nine-0 at 800 g a.i./ha. Mean control reported for Converge 75 WDG alone was 96% and for the tank mixture was 98% at 56–67 DAT ($n$ = 3). The level of control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha.

**Large crabgrass (*Digitaria sanguinalis*):** Two side-by-side trials conducted in Ontario in 1997 reported control of large crabgrass following an application of Converge 75 WDG at 79 g a.i./ha alone and in a tank mixture with Aatrex Nine-0 at 800 g a.i./ha. Mean control reported for Converge 75 WDG alone was 80% and for the tank mix was 99% at 29–62 DAT ($n$ = 2). The available data, in conjunction with that

provided for the related species smooth crabgrass, suggest that the level of large crabgrass control provided by Converge 75 WDG is not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha.

**Lamb's-quarters (*Chenopodium album*):** Twenty-three side-by-side trials conducted in 1996 and 1997 reported control of lamb's-quarters following an application of Converge 75 WDG at 79 g a.i./ha alone and in a tank mixture with Aatrex Nine-0 at 800 g a.i./ha. Five trials were located in Quebec at four locations and 19 in Ontario at 11 locations. Mean control reported for Converge 75 WDG alone was 83% and for the tank mix was 93% at 28–82 DAT ($n$ = 23). The level of lamb's-quarters control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha and in some instances was improved.

**Redroot pigweed (*Amaranthus retroflexus*):** Control of redroot pigweed was reported in 18 trials conducted in 1996 and 1997 that allowed for direct comparisons of Converge 75 WDG at 79 g a.i./ha alone and in tank mix combination with Aatrex Nine-0 at 800 g a.i./ha. Three trials were located in Quebec at two locations and 15 in Ontario at 10 locations. Mean control reported for Converge 75 WDG alone was 81% and for the tank mixture was 93% at 28–64 DAT ($n$ = 18). The data support a claim of redroot pigweed control in conventionally tilled field corn with Converge 75 WDG at 79 g a.i./ha plus atrazine at 800 g a.i./ha. The level of redroot pigweed control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha and in some instances was improved.

**Common ragweed (*Ambrosia artemisiifolia*):** Sixteen side-by-side trials conducted in 1996 and 1997 reported control of common ragweed following an application of Converge 75 WDG at 79 g a.i./ha alone and in tank mix combination with Aatrex Nine-0 at 800 g a.i./ha. Three trials were located in Quebec at three locations and 13 in Ontario at 11 locations. Mean control reported for Converge 75 WDG alone was 94% and for the tank mixture was 96% at 28–64 DAT ($n$ = 16). The data support a claim of common ragweed control in conventionally tilled field corn with Converge 75 WDG at 79 g a.i./ha plus atrazine at 800 g a.i./ha. The level of common ragweed control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha.

**Eastern black nightshade (*Solanum ptycanthum*):** Two side-by-side trials conducted at two locations in Ontario in 1997 reported control of eastern black nightshade following an application of Converge 75 WDG at 79 g a.i./ha alone and in a tank mixture with Aatrex Nine-0 at 800 g a.i./ha. Mean control reported for both Converge 75 WDG alone and for the tank mixture was 100% at 56–67 DAT ($n$ = 2). The level of common eastern black nightshade control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha.

**Wild mustard (*Sinapis arvensis*):** Four side-by-side trials, one conducted in 1996 and three in 1997, reported control of wild mustard following an application of Converge 75 WDG at 79 g a.i./ha alone and in tank mix combination with Aatrex Nine-0 at 800 g a.i./ha. One trial was located in Quebec and three in Ontario at three locations. Mean control reported for Converge 75 WDG alone was 74% and for the tank mix was 97% at 37–64 DAT ($n$ = 4). The level of wild mustard control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha.

**Velvetleaf (*Abutilon theophrasti*):** Six side-by-side trials, of which one was conducted in 1996 and the remainder in 1997, reported control of velvetleaf following an application of Converge 75 WDG at 79 g a.i./ha plus Aatrex Nine-0 at 800 g a.i./ha. Two trials were located in Quebec at two sites and four in Ontario at two locations. Mean control reported for Converge 75 WDG alone was 90% and for the tank mixture was 87% at 37–77 DAT ($n$ = 6). The level of velvetleaf control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha.

**Broadleaf plantain (*Plantago major*) seedlings:** Control of broadleaf plantain was reported in two trials that allowed for direct comparisons between Converge 75 WDG at 79 g a.i./ha alone and in tank mix combination with Aatrex Nine-0 at 800 g a.i./ha. Both trials were conducted in Ontario at two locations in 1996 and 1997. Mean control reported for both Converge 75 WDG alone and the tank mixture was 100% at 43 and 77 DAT ($n$ = 2), respectively. The level of broadleaf plantain (seedlings) control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha.

**Dandelion (*Taraxacum officinale*) seedlings:** Two side-by-side trials conducted in 1996 and 1997 reported control of dandelion following an application of Converge 75 WDG at 79 g a.i./ha alone and in a tank mixture with Aatrex Nine-0 at 800 g a.i./ha. The trials were conducted at two Ontario locations. Mean control reported for Converge 75 WDG alone was 96% and for the tank mixture was 97% at 50–132 DAT ($n$ = 2). The level of dandelion (seedlings) control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha.

**Wormseed mustard (*Erysimum cheiranthoides*):** One side-by-side trial conducted in Ontario in 1997 reported control of wormseed mustard following an application of Converge 75 WDG at 79 g a.i./ha alone and in a tank mixture with Aatrex Nine-0 at 800 g a.i./ha. Mean control reported for both Converge 75 WDG alone tank mixed with Aatrex Nine-0 was 98% at 43 DAT ($n$ = 1). The level of wormseed mustard control provided by Converge 75 WDG was not compromised when tank mixed with Aatrex Nine-0 at 800 g a.i./ha.

**Lady's-thumb (*Polygonum persicaria*):** Control of lady's-thumb with the tank mixture of Converge 75 WDG at 79 g a.i./ha plus Aatrex Nine-0 at 800 g a.i./ha was reported in nine trials conducted in 1996 and 1997 at six locations in Ontario. These same trials also reported control following application of Converge 75 WDG alone at 79 g a.i./ha. Mean control reported for the tank mixture was 87%, while for Converge 75 WDG alone was 53% at 43–62 DAT ($n$ = 9). The data support a claim of lady's-thumb control in conventionally tilled field corn with Converge 75 WDG at 79 g a.i./ha plus atrazine at 800 g a.i./ha.

**Use of other atrazine formulations:** Five trials included a treatment of the proposed tank mixture with Aatrex 480. All trials were conducted in 1997 at five locations in Ontario. The trials included treatments of Converge 75 WDG at 79 g a.i./ha in tank mixes with Aatrex Nine-0 and with Aatrex 480, each at 800 g a.i./ha. Direct comparisons were available for 10 weed species. Similar levels of weed control were reported across the treatments (Appendix III, Table 3). The data made available for Aatrex Nine-0 and Aatrex 480 support the use of a Converge 75 WDG plus atrazine tank mixture.

#### 7.1.4.3 Use of liquid fertilizer as a carrier

The use of nitrogen solution (28–0–0) as a carrier for application of Converge 75 WDG alone or in tank mix with atrazine was supported by data from a total of four trials conducted in 1997 at four locations in Ontario. All trials included treatments of Converge 75 WDG applied alone at 79 and 105 g a.i./ha and a tank mix of Converge 75 WDG at 105 g/ha plus Aatrex Nine-0 at 800 g a.i./ha. Reported levels of weed control were similar to those observed for product or tank mix use with water as a carrier (Appendix III, Table 4). The efficacy data made available for review supports the use of nitrogen fertilizer as a carrier for Converge 75 WDG when applied alone at 79 and 105 g a.i./ha, and when applied at 79 g a.i./ha with atrazine at 800 g a.i./ha.

### 7.2 Information on the occurrence or possible occurrence of the development of resistance

To address the issue of development of herbicide resistance, the following information will be included on the Converge 75 WDG label:

> "Converge 75 WDG is a Group 28 herbicide. Any weed population may contain plants naturally resistant to Converge 75 WDG and other Group 28 herbicides. The resistant individuals can eventually dominate the weed population if these herbicides are used repeatedly. These resistant weeds will not be controlled by Converge 75 WDG or other Group 28 herbicides.
> To delay herbicide resistance:
>
> - Avoid the exclusive, repeated use of Converge 75 WDG or other herbicides in the same herbicide group.

- Rotate with herbicides from a different herbicide group that control the same weeds as Converge 75 WDG.

- Use tankmixes with herbicides from a different group when such a use is permitted.

- Integrate tillage or other mechanical cultural control methods into weed control programs whenever practical.

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

- Keep accurate records of crop rotation and herbicides used for each of your fields.

For further information, contact your local Rhône-Poulenc representative."

## 7.3 Effects on the yield of treated plants or plant products in terms of quantity and quality

**Converge 75 WDG alone:** Forty-two conventionally tilled trials reported field corn yield following application of Converge 75 WDG at the maximum requested use rate of 105 g a.i./ha, while nineteen reported yield following application of the product at 210 g a.i./ha (2× the maximum requested rate). Mean reported yields for the 1× and 2× rates, expressed as a percentage of the untreated checks, was 202 ($n$ = 42) and 178% ($n$ = 19), respectively. Twelve trials reported field corn yield relative to a weed-free check. Mean yield of field corn treated with Converge 75 WDG at the 1× and 2× rates was reported as 96 and 97% ($n$ = 12), respectively.

**Converge 75 WDG + atrazine:** Sixteen trials reported yield of conventionally tilled field corn following application of Converge 75 WDG alone at 79 g a.i./ha and when tank mixed with Aatrex Nine-0 at 800 g a.i./ha. Expressed as a percentage of the untreated checks, reported yield for the Converge 75 WDG plus Aatrex Nine-0 tank mixture was 209% ($n$ = 16), while reported yield for field corn treated with Converge 75 WDG alone was 188% ($n$ = 16). Three side-by-side trials reported yield of the tank mixture following application of Converge 75 WDG at 79 g a.i./ha plus Aatrex Nine-0 and Aatrex 480 at 800 g a.i./ha. Mean reported yield with Aatrex Nine-0 as the atrazine source was 163% and with Aatrex 480 was 166% ($n$ = 3) of the untreated checks. Four trials reported yield of Converge 75 WDG plus Aatrex Nine-0 treated field corn relative to a weed-free control. Mean reported yield following application of Converge 75 WDG at 79 g a.i./ha plus Aatrex Nine-0 at 800 g a.i./ha was 101% ($n$ = 4) of the weed-free check.

## 7.4 Phytotoxicity to target plants (including different varieties) or target plant products

**Converge 75 WDG at 105 g a.i./ha**

Tolerance of conventionally tilled field corn to the maximum proposed rate of Converge 75 WDG was evaluated in 53 Canadian field trials conducted over the three-year period of 1995–1997 and represented 23 field corn hybrids ranging in corn heat unit requirements of <2500 to approximately 3100. Five trials were located in Quebec at three locations and 48 in Ontario at 18 locations. These data were supplemented by results from 32 U.S. trials also conducted over the three-year period of 1995–1997. U.S. trials were conducted in Indiana, Ohio and Wisconsin at three locations. Tolerance was assessed visually relative to an untreated check.

Tolerance differences between soil types proposed for product use (i.e., excluding sand and loamy sand soils and coarse textured soils with less than 2% organic matter) and cultivar selection were not detected. The product label includes a statement advising that under certain conditions, including cold weather, excessive moisture and compacted soils, temporary yellowing of some leaves may occur when plants are in the seedling stage. The label also states that these symptoms are more visible where excessive rates have been applied, such as sprayer overlaps. Data submitted for review support these statements.

Mean reported visual injury at 28 DAT or fewer over 49 Canadian and 43 U.S. observations following application of Converge 75 WDG at the proposed maximum use rate of 105 g a.i./ha was 1.1% and 0.4%, respectively. Visual injury reported at more than 28 DAT averaged 1.2% over 25 Canadian observations and 0.2% across 16 U.S. observations. At twice the proposed maximum rate (280 g/ha) mean reported injury in the Canadian trials was 7.0% at 28 DAT or fewer over 17 trials and 3.0% at more than 28 DAT over 13 trials.

**Converge 75 WDG at 79 g a.i./ha + atrazine at 800 g a.i./ha**

Results of 22 Canadian field trials, six conducted in 1996 and 16 in 1997, reported tolerance of conventionally tilled field corn to application of Converge 75 WDG at 79 g a.i./ha plus Aatrex Nine-0 or Aatrex 480 at 800 g a.i./ha. Two trials were conducted in Quebec at two locations and 20 in Ontario at 13 sites. Fourteen corn hybrids with corn heat units requirements of <2500 to approximately 3100 were represented in these trials.

There was no discernable difference in tolerance between requested soil types (i.e., excluding sand and loamy sand soils or coarse textured soils with less than 2% organic matter) or cultivar selection.

Mean reported visual injury with Converge 75 WDG at 79 g a.i./ha plus Aatrex Nine-0 at 800 g a.i./ha was 1.1% at 28 DAT or fewer across 21 trials and 0.7% at more than 28 DAT over 13 trials. Visual injury following application at the same use rates of active, but with Aatrex 480 as the atrazine source, was 1% at 28 DAT or fewer over five trials and 0% at more than 28 DAT in one trial. As there was no data generated with the 2× rate

of the proposed tank mixture, it is not possible to assess the potential impact of a spray overlap on crop tolerance.

**Use of nitrogen solution as a carrier**
The use of nitrogen solution (28–0–0) as a carrier for application of Converge 75 WDG alone or in tank mix with atrazine was supported by data from a total of three trials conducted in 1997 at three locations in Ontario. All trials included treatments of Converge 75 WDG at 79 and 105 g a.i./ha and a tank mix of Converge 75 WDG at 79 g a.i./ha plus Aatrex Nine-0 at 800 g a.i./ha. One trial also included the Converge 75 WDG plus Aatrex 480 tank mix at 79 g a.i./ha and 800 g a.i./ha, respectively. No visual injury was reported in any of the trials.

## 7.5 Observation on undesirable or unintended side effects

### 7.5.1 Impact on succeeding crops

In lieu of rotational crop studies, a rationale on the basis of the expected $DT_{50}$ of isoxaflutole and the metabolite RPA 202248, and the metabolism of the compounds in corn was submitted. On the basis of the soil dissipation and metabolism data, the rationale suggested that it is highly unlikely that any quantifiable isoxaflutole or RPA 202248 would remain in the soil after the time required for growing of the initial corn crop. The rationale was considered acceptable to support field corn as a rotational crop. As isoxaflutole is a soil residual herbicide that represents chemistry for which there is no previous Canadian experience, the submitted rationale was not considered sufficient for other rotational crops. Field studies generated in eastern Canada are required to assess the possible impact of residues resulting from product use on other major rotational crops. In the interim, the product label must carry a statement advising that a bioassay must be conducted prior to seeding any rotational crop other than field corn.

## 7.6 Economics

Corn is eastern Canada's most important grain crop and ranks third nationally behind wheat and barley. Canadian production is primarily in central Canada. In 1997, grain corn was grown in Ontario on 0.73 million ha and in Quebec on 0.33 million ha, representing 94% of the Canadian acreage. Approximately 200 000 ha of silage corn are also grown for feed purposes. The value of Canadian corn production in 1993 was 417 million dollars and contributed to 3.8% of Quebec's total farm receipts and 4.5% of Ontario's.

The majority of Canadian produced corn is used domestically, with imports exceeding exports to the United States and other countries. The 1997 Canadian production of 297 million bushels of grain corn was supplemented by 31.3 million bushels of imported grain, while only 12.9 and 1.7 million bushels were exported to the United States and overseas, respectively. Canadian industry utilized 56.2 million bushels, while the majority of production, 247.8 million bushels, was used for livestock feed.

Weed control is essential for successful field corn production. Unchecked weed growth can reduce corn growth and yield owing to competition for nutrients, water and light. Crop loss as a result of weed competition is directly related to weed pressure. Light weed populations may reduce yields by 10–15%, while severe infestations may reduce yields by more than 50%. Harvest operations can also be more difficult and costly because of weed presence.

Data submitted for the use of Converge 75 WDG has demonstrated that acceptable control of many weeds common to corn producing areas of eastern Canada will be provided by the product when used according to label directions. The product will provide corn producers with another chemical alternative for the pre-emergent control of several important weed species that could reduce yield and quality of field corn, and contribute to increased harvest costs.

## 7.7 Sustainability

### 7.7.1 Survey of alternatives

Many pre-emergent herbicides that may be used alone or in various tank mix combinations are registered for weed control in field corn. Such products include dimethenamid, *s*-metolachlor, pendimethalin, atrazine, dicamba, diflufenzopyr, flumetsulam–clopyralid and linuron. Converge 75 WDG (isoxaflutole) represents a new mode of action for control of several annual grass and broadleaf weeds common to the corn producing areas of eastern Canada. Use of Converge 75 WDG at 79 g a.i./ha in a tank mixture with atrazine at 800 g a.i./ha increases the spectrum of weeds controlled.

While imazethapyr is also registered the pre-emergent control of several grass and broadleaf weed species, application can only be made on imazethapyr tolerant varieties. Converge 75 WDG has no varietal restrictions.

### 7.7.2 Compatibility with current management practices including integrated pest management

Application of Converge 75 WDG would not exclude the sequential use of other herbicides with different modes of action for control of annual and perennial species not controlled by the product alone or when tank mixed with atrazine.

Nonchemical means of weed control include cultivation and crop rotation. The pre-emergent use of Converge 75 WDG on conventionally tilled field corn would not exclude the use of cultivation. Recropping data is required with which to determine the possible impact of product residues on rotational crops.

### 7.7.3 Contribution to risk reduction

Converge 75 WDG alone will provide a broad spectrum of weed control in field corn. The same spectrum of weed control may be attained with other pre-emergent herbicides, but often tank mix combinations are required. Product use could thus reduce the need for tank mixing and the associated increase in mixer, handler and applicator exposure.

Used in tank mix combination with atrazine, the spectrum of weeds controlled by Converge 75 WDG is expanded, while the rate of application is restricted to the minimum labelled rate of 79 g a.i./ha. The rate of atrazine required is also reduced by 20–46.5% of that recommended for product use alone.

## 7.8 Conclusion

The data made available for review indicate that, when used according to label directions, a pre-emergent application of Converge 75 WDG at 79–105 g a.i./ha can be made to conventionally tilled field corn for the control of specific grass and broadleaf weeds. Converge 75 WDG at 79 g a.i./ha may be tank mixed with atrazine at 800 g a.i./ha to provide additional broadleaf control. Until data for commonly grown rotational crops can be generated and appropriate recropping intervals established, the product label must include a bioassay statement for all rotational crops other than field corn.

### 7.8.1 Summary

| | |
|---|---|
| Crop: | field corn (*Zea mays*), conventionally tilled |
| Hybrids: | all (no restriction) |
| Product: | Converge 75 WDG |
| Application timing: | pre-emergent to field corn and weeds |
| Application method: | ground equipment only<br>Do not apply by air |
| Number of applications per year: | one |
| Rates of application: | 105 g/ha (79 g a.i./ha)<br>140 g/ha (105 g a.i./ha) |
| Spray volume: | minimum 200 L/ha |
| Spray pressure: | 138–275 kPa |

| | |
|---|---|
| Weed species controlled: | **At 79 g a.i./ha:**<br>witchgrass (*Panicum capillare*)<br>smooth crabgrass (*Digitaria ischaemum*)<br>large crabgrass (*Digitaria sanguinalis*)<br>common ragweed (*Ambrosia artemisiifolia*)[1]<br>redroot pigweed (*Amaranthus retroflexus*)[1]<br>lamb's-quarters (*Chenopodium album*)[1]<br>velvetleaf (*Abutilon theophrasti*)<br>eastern black nightshade (*Solanum ptycanthum*)<br>wild mustard (*Sinapis arvensis*)<br>wormseed mustard (*Erysimum cheiranthoides*)<br>dandelion (*Taraxacum officinale*) seedlings<br>broadleaf plantain (*Plantago major*) seedlings<br><br>**At 105 g a.i./ha:**<br>barnyard grass (*Echinochloa crusgalli*)<br>green foxtail (*Setaria viridis*) |
| Tank mixture option: | Converge 75 WDG at 79 g a.i./ha + atrazine at 800 g a.i./ha |
| Rotational crop: | Field corn |

[1] includes triazine and ALS resistant biotypes

## 8.0 Toxic substances management policy

During the review of Isoxaflutole Technical and Converge 75 WDG, the PMRA has considered the implications of the federal Toxic Substances Management Policy (TSMP) and the PMRA Regulatory Directive DIR99-03 (*The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*) and has concluded the following:

- Isoxaflutole does not meet the criteria for persistence. Its values for half-lives in water (<1 day) and soil (<10 days) are below the TSMP Track-1 cut-off criteria for water (≥182 days) and soil (≥182 days). Although a half-life in air was not submitted, isoxaflutole is non-volatile from moist soil and water surfaces, on the basis of values for vapour pressure and Henry's Law Constant.

- Isoxaflutole is not bioaccumulative. Studies have shown that the log $K_{ow}$ is 2.3, which is below the TSMP Track-1 cut-off criterion of 5.0 or higher.

- The toxicity of isoxaflutole is described in detail in chapters 3–6 of this document.

- Isoxaflutole forms three major transformation products. One of these, RPA 202248, is persistent in water (under anaerobic conditions) and in aerobic water and sediment systems with half-lives of 316 and 703 days, respectively.

- Isoxaflutole technical grade does not contain any by-products that meet the TSMP Track-1 criteria. Microcontaminants of toxicological concern identified in Section 2.13.4 of DIR98-04, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*, are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

The formulated product does not contain any formulants that are known to be TSMP Track-1 substances.

## 9.0 Overall conclusions

Isoxaflutole provides commercially acceptable crop tolerance to conventionally tilled field corn when applied according to label directions at rates of 79 and 105 g a.i./ha (Converge 75 WDG at 105 and 140 g/ha). Converge 75 WDG at 79 g a.i./ha will control common lamb's-quarters, redroot pigweed, common ragweed, velvetleaf, wild mustard, wormseed mustard, eastern black nightshade, plantain (seedling), dandelion (seedling), witchgrass, smooth crabgrass and large crabgrass. Application at 105 g a.i./ha will provide additional control of barnyard grass and green foxtail. Converge 75 WDG may be applied at 79 g a.i./ha in tank mix combination with atrazine at 800 g a.i./ha for control of all species controlled by Converge 75 WDG alone at 79 and 105 g a.i./ha, plus lady's-thumb. Converge 75 WDG may be applied alone or in a tank mixture with atrazine using either water or a nitrogen fertilizer (28–0–0) as the carrier.

Technical isoxaflutole and Converge 75 WDG herbicide were of low acute toxicity via the oral and inhalation routes of exposure in rats and via the dermal route of exposure in rabbits. In rabbits, technical isoxaflutole was minimally irritating to the eyes and nonirritating to the skin. In rabbits, Converge 75 WDG was minimally irritating to the eyes and slightly irritating to the skin. Neither induced dermal sensitization in guinea pigs.

In short-term and chronic toxicity and oncogenicity studies, toxicologically significant effects included liver toxicity (mouse, rat or dog), thyroid toxicity (rat) and ocular toxicity (rat). Hepatocellular adenomas and carcinomas were observed in both male and female mice and rats. Thyroid follicular cell adenomas were observed in male rats. Isoxaflutole was, however, nongenotoxic in a range of in vitro mammalian and bacterial cell assays and in an in vivo mouse assay. Thyroid tumours were considered secondary to microsomal enzyme induction in the liver that produced alterations in thyroid–pituitary hormonal feedback mechanisms with a concomitant hormonal imbalance. The liver tumours were attributed to a nongenotoxic mechanism triggered by marked microsomal enzyme induction. Mechanistic studies suggest that a threshold may exist for the

induction of liver tumours in rodents; however, the evidence was not conclusive. The weight of evidence suggests that isoxaflutole be characterized as "likely" to be carcinogenic to humans by all routes of exposure on the basis of the increased incidence of liver tumours in two rodent species (both sexes) and thyroid tumours in male rats in adequate long-term studies.

Isoxaflutole is not considered to be teratogenic nor did it impair reproductive capacity of adult rats. In the rat and rabbit developmental studies, developmental effects were observed at doses that were not maternally toxic, indicating an increased sensitivity in rat and rabbit fetuses. On the basis of the maternal and developmental NOELs in a two-generation reproductive toxicity study in rat, no increased susceptibility of pups was demonstrated. Isoxaflutole was not considered to be neurotoxic.

The recommended ADI was 0.005 mg/kg bw/day, on the basis of the most appropriate NOEL of 0.5 mg/kg bw/day established in the 104-week dietary study in rat (on the basis of an increased incidence of ocular toxicity at the higher doses) using a SF of 100.

The following precautionary statements replaced those on the draft label:

> "Wear coveralls over long sleeved shirt and pants and rubber boots during all activities. Wear chemical resistant gloves and protective eyewear during mixing, loading, clean-up and repair."

The nature of the residue in plants and animals is adequately understood. The ROC was defined as the parent compound isoxaflutole and its metabolites, RPA 202248 and RPA 203328.

The confined crop rotation studies for lettuce, radish, wheat and sorghum indicated that residues of isoxaflutole were only in trace amounts for certain 34-day RACs. The metabolites decreased as a function of time (34, 123 and 365 DAT). These data indicated that no crop rotational restrictions were required for secondary crops when isoxaflutole was applied to corn at the proposed maximum labelled rate.

Livestock and poultry feeding studies indicated, that at the highest feeding level, residues of isoxaflutole were less than 0.05 ppm (LOQ) in liver, kidney, muscle, skin, fat, eggs and milk. At the lowest feeding level, the metabolite RPA 202248 was less than 0.05 ppm (LOQ) in eggs, muscle, skin (+ fat) and fat and 0.02 ppm in milk (41 DAT). Residues of the metabolite RPA 202248, however, were observed in poultry liver (0.14 ppm), cattle liver (0.62 ppm) and cattle kidney (0.14 ppm). Therefore, MRLs will be established in tissues, milk and eggs to cover the potential residues of isoxaflutole and its metabolite RPA 202248.

The proposed method for data gathering and enforcement purposes in plant commodities was a common moiety method that involved hydrolysis of the isoxazole ring to form the cyclopropyl propan-1,3-dione moiety (RPA 202248), conversion to the trifluoromethyl

benzoic acid moiety (RPA 203328). Residues of RPA 203328 were derivatized to a methyl ester and quantified by GC–MS. The LOQ of the method was 0.01 ppm for isoxaflutole and its metabolites in field corn matrices. In animal commodities, a common moiety method was used that involved base hydrolysis of isoxaflutole to form RPA 202248. Residues of RPA 202248 were quantified by HPLC–UV. The LOQs for isoxaflutole and its metabolites were 0.01 ppm (milk and eggs), 0.4 ppm (beef and poultry liver), 0.2 ppm (beef and poultry muscle and fat) and 0.2 ppm (beef kidney). These methods were validated, in the range of expected residues, for accuracy and precision. The recoveries obtained from a large number of spiked samples were acceptable. These methods were successfully validated by an independent laboratory. Adequate enforcement methodology is available to enforce the established MRLs.

Isoxaflutole and its metabolites were stable (–10EC) in raw corn and its processed fractions for up to 15 months and three months, respectively. The parent isoxaflutole degraded in stored milk samples (after 85–127 days), with no degradation of the metabolites. Isoxaflutole immediately converted to RPA 202248 in the egg matrix; however, RPA 202248 was found to be stable for up to 129 days. Isoxaflutole and its metabolites were stable in muscle (85 days), liver (130 days) and kidneys and fat (115 days). Therefore, there was no degradation of isoxaflutole and its metabolites in tissues, milk and eggs during the conditions of the study.

Supervised field trials were conducted in Canada and the U.S. as a pre-emergence application of isoxaflutole to field corn. The results of the Canadian field trials demonstrated that residues of isoxaflutole and its metabolites were below the LOQ (0.01 ppm). Residues up to 0.11 ppm were observed in the U.S. field trials. As field corn and its processed fractions are fed to livestock, the transfer of residues into edible commodities was examined. After consideration of the data submitted, Canada will establish MRLs of 0.5 ppm (liver), 0.3 ppm (poultry liver), 0.2 ppm (in or on field corn and meat), 0.1 ppm (meat by-products), 0.02 ppm (milk) and 0.01 ppm (eggs) to cover potential residues of isoxaflutole and its metabolites. The proposed MRLs are the same as the established tolerances in the U.S. CODEX has not established MRLs for isoxaflutole.

The chronic dietary risk assessment indicated that the PDI was less than 48% of the ADI for infants or children and adults. Using $Q_1$* and a linear dose–response approach, the dietary risk was estimated to be in the range of $1 \times 10^{-7}$ to $9.8 \times 10^{-8}$ mg/kg bw for all population subgroups, including infants and children. This linear risk estimate was below the level of concern for life-time cancer risk. The acute dietary risk assessment conducted on all females 13+ years indicated that the PDI was 25% of the ARD. Therefore, the proposed domestic use of isoxaflutole as a pre-emergent treatment in field corn does not pose an unacceptable chronic, life-time cancer or acute dietary risk.

Isoxaflutole is not persistent in soils under field conditions. Although the laboratory studies indicate that isoxaflutole and its transformation products, RPA 202248 and RPA 203328, are highly mobile in soils, they have a low potential to contaminate the groundwater under field conditions.

Isoxaflutole is toxic to fish and highly toxic to nontarget aquatic plants and aquatic invertebrates. The proposed use pattern has a potential to significantly affect the aquatic habitat because of spray drift and runoff. To protect aquatic habitat, a buffer zone of 22 m is required between the last spray swath and the edge of the sensitive areas such as wetlands, ponds, lakes and rivers. The following label statement is required to protect the nontarget aquatic organisms from isoxaflutole runoff:

> "Do not spray if there is a forecast for rain during or soon after application."

## 10.0 Regulatory decision

The Pest Management Regulatory Agency has granted temporary registrations for the active ingredient Isoxaflutole and Converge 75WDG for the control of specific annual grass and broadleaf weeds in field corn, pursuant to PCP Regulations Section 17 subject to the generation and review of the following:

- rotational crop studies

## List of Abbreviations

| | |
|---|---|
| ADI | acceptable daily intake |
| a.i. | active ingredient |
| ALAT | alanine aminotransferase |
| ALS | acetolactate synthase |
| AP | alkaline phosphatase |
| ARD | acute reference dose |
| ASAT | aspartate aminotransferase |
| BROD | benzoxyresorufin *O*-debenzylase |
| bw | body weight |
| CAS | Chemical Abstracts Service |
| Ci | curie (measure of radioactivity) |
| CODEX | Codex Alimentarius Commission, Food and Agriculture Organization, United Nations |
| DAT | days after treatment |
| DI | dietary intake |
| $DT_{50}$ | dissipation time (50%) |
| $DT_{90}$ | dissipation time (90%) |
| dw | dry weight |
| $EC_{25}$ | effect concentration (25%) |
| $EC_{50}$ | effect concentration (50%) |
| EEC | expected environmental concentration |
| EROD | ethoxyresorufin *O*-deethylase |
| 5'-NT | 5'-nucleotidase |
| 4-HPLA | 4-hydroxyphenyl lactate |
| 4-HPP | 4-hydroxyphenyl pyruvate |
| 4-HPPDase | 4-hydroxyphenyl pyruvate dioxygenase |
| FC | food consumption |
| FCA | Freunds Complete Adjuvant |
| $F_0$ | parental animals |
| $F_1$ | first generation offspring |
| $F_2$ | second generation offspring |
| FOB | functional observational battery |
| GC | gas chromatography |
| GSD | geometric standard deviation |
| (-GT | (-glutamyltransferase |
| h | hour |
| Hb | hemoglobin |
| Hct | hematocrit |
| HPLC | high performance liquid chromatography |
| HPPD | *p*-hydroxy phenyl pyruvate dioxygenase |
| $K_d$ | adsorption coefficient (ratio of concentration in the soil phase to that in the aqueous phase, under test conditions) |
| $K_{oc}$ | adsorption coefficient (relates $K_d$ to the organic carbon content of the soil sample) |

| | |
|---|---|
| $K_{ow}$ | octanol–water partition coefficient |
| $LC_{50}$ | lethal concentration (50%) |
| $LD_{50}$ | lethal dose (50%) |
| LOAEL | lowest observed adverse effect level |
| LOEC | lowest observed effect concentration |
| LOEL | lowest observed effect level |
| LOQ | limit of quantitation |
| MAS | maximum average score (at 24, 48 and 72 h) |
| MDL | method detection limit |
| MIS | maximum irritation score |
| MMAD | mass median aerodynamic diameter |
| MOE | margin of exposure |
| MRL | maximum residue limit |
| MROD | methoxyresorufin *O*-demethylase |
| MSD | mass spectrometry detection |
| *n* | number of trials |
| nm | nanometres |
| NOAEL | no observed adverse effect level |
| NOEC | no observed effect concentration |
| NOEL | no observed effect level |
| NTBC | 2-(2-nitro-4-trifluromethylbenzoyl)cyclohexane-1,3-dione |
| NZW | New Zealand white |
| Pa | pascal |
| PAI | pure active ingredient |
| PDI | potential daily intake |
| PG | propylene glycol |
| PHED | pesticide handler exposure database |
| PHI | preharvest interval |
| p$K_a$ | dissociation constant |
| ppm | parts per million |
| PROD | pentoxyresorufin *O*-depentylase |
| $Q_1$* | linear default value (cancer estimate risk number) |
| QA | quality assurance |
| RAC | raw agricultural commodity |
| RBC | red blood cells |
| ROC | residue of concern |
| S9 | metabolic activation system prepared from Aroclor 1254 induced rat livers |
| SD | Sprague–Dawley |
| SF | safety factor |
| $T_{½}$ | half-life |
| $T_3$ | tri-iodothyronine |
| $T_4$ | thyroxine |
| TBC | thyroxine binding capacity |
| TGAI | technical grade active ingredient |
| TS | test substances |
| TSMP | Toxic Substances Management Policy |

| | |
|---|---|
| UDPGT | uridine 5'-diphosphate-glucuronyltransferase |
| v/v | volume per volume |
| w/v | weight per volume |

# Appendix I Summary of the toxicity studies with isoxaflutole (RPA 201772)

**Metabolism**

Rate and extent of absorption and excretion: rapid absorption at both 1.0 and 100 mg/kg bw. The maximal whole blood concentration was achieved within one hour at both dose levels. On the basis of available urinary excretion data (radioactivity detected in urine, cage washes and tissues), the mean estimated proportion of the administered dose absorbed was approximately 39, 73 and 75% for the high-, low- and repeat-dose groups, respectively. Elimination was rapid and dose dependent. The major route of elimination in the high-dose group was via the feces (approximately 55–63% of the administered dose) and in the single and repeat low dose groups was via the urine (68–74% of the administered dose). The majority of the activity was eliminated within 24 and 48 h post-dosing for the low- and high-dose groups, respectively. The terminal elimination phase $T_{½}$ was about 60 h in both sexes at both dose levels. Higher fecal elimination at the high dose may be due to saturation of absorption, resulting in elimination of unchanged parent compound. Mean recovery of radioactivity in the tissues at 168 h post-dosing was low, indicating that there was most likely a good systemic clearance of the test substance with little potential for accumulation. The absorption, distribution, metabolism and excretion were not influenced by repeat oral administration.
Distribution and target organ(s): tissue distribution of radioactivity between the sexes appeared to be similar. In the high-dose group, the highest levels in both sexes were found in the blood and plasma and to a lesser extent in the liver and kidneys of males and in the liver, kidneys, lungs and heart of females. In the single and repeat low-dose groups, higher tissue concentrations were found in the liver and kidneys.
Toxicologically significant compound(s): RPA 201772 was rapidly and extensively metabolized. The major metabolite was the diketonitrile RPA 202248 (70–85% of the administered dose). Minor metabolites included RPA 203328 (0.6–3.6% of the administered dose), RPA 207048, RPA 205834 and RPA 205568. The parent compound, RPA 201772, was detected only in fecal extracts in the single high-dose group during the first 24 h. Data suggest that only Phase I reactions occurred; there was no indication of any metabolites resulting from Phase II (conjugation) reactions.

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| **Acute studies: technical isoxaflutole (RPA 201772)** | | | |
| Oral (limit test) | SD albino rats (five animals/sex), dose level: 5000 mg/kg bw | $LD_{50}$ > 5000 mg/kg bw | No clinical or gross pathological observations; no treatment-related effects on body weight<br>Low toxicity |
| Dermal (limit test) | NZW rabbits (five animals/sex), dose level: 2000 mg/kg bw | $LD_{50}$ > 2000 mg/kg bw | No clinical or gross pathological observations; no treatment-related effects on body weight<br>Low toxicity |
| Inhalation (4-h, whole-body) | SD rats (five animals/sex), nominal dose: 15.5 mg/L, analytical dose: 5.23 ± 0.50 mg/L | $LC_{50}$ > 5.23 mg/L | No clinical observations; no treatment-related effects on body weight; one females exhibited slightly congested lungs<br>(mass median aerodynamic diameter [MMAD] = 3.1 Fm, geometric standard deviation [GSD] = 1.95)<br>Low toxicity |
| Skin irritation | NZW rabbit (five animals/sex), dose level: 0.5 g of test substances (TS) in 0.5 mL of 0.5% volume per volume (v/v) carboxymethyl cellulose | MIS: 0.17/8 at one hour<br>MAS: 0/8 | Nonirritating |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| Eye irritation | NZW rabbits (three animals/sex), dose level: 0.1 g TS | MIS: 5.83/110 at one hour<br>MAS: 0/110 | Minimally irritating |
| Skin sensitization (modified Buehler method) | Dunkin–Hartley albino guinea pigs (10 animals/sex in test group and five animals/sex in control group), induction treatment (left flank) 0.25 mL of 50% w/v TS in propylene glycol (PG), challenge treatment (right flank) site 1: 0.25 mL of PG, site 2: 0.25 mL of 10% w/v TS in PG, site 3: 0.25 mL of 50% w/v TS in PG | No dermal reactions observed at 24 or 48 h after challenge treatment.<br>Positive control produced sensitization, demonstrating responsiveness of assay. | Not a skin sensitizer |
| Skin sensitization (maximization test) | Dunkin–Hartley albino guinea pigs (10 animals/sex in test group and five animals/sex in control group), intradermal induction site 1: 0.1 mL 50% v/v Freunds Complete Adjuvant (FCA), site 2: 0.1 mL of 10% w/v TS in PG, site 3: 0.1 mL of 10% w/v TS in PG in FCA, topical induction: 0.6 mL of 50% w/v TS in PG, challenge treatment left flank: 0.03 mL of PG, right flank (two sites) site 1: 0.03 mL of 50% w/v TS in PG, site 2: 0.03 mL of 10% w/v TS in PG | No dermal reactions observed at 24 or 48 h after challenge treatment.<br>Positive control produced sensitization, demonstrating responsiveness of assay. | Not a skin sensitizer |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| **Acute studies: Converge 75 WDG herbicide formulation** | | | |
| Oral (limit test) | SD albino rats (five animals/sex), dose level: 5000 mg/kg bw | $LD_{50}$ > 5000 mg/kg bw | Clinical signs included diarrhea and peri-anal staining of fur, no gross pathological findings and no treatment-related effect on body weight.<br>Low toxicity<br>No labelling recommendations |
| Dermal (limit test) | NZW rabbits (five animals/sex), dose level: 2000 mg/kg bw | $LD_{50}$ > 2000 mg/kg bw | No treatment-related clinical or gross pathological findings and no treatment-related effect on body weight<br>Low toxicity<br>No labelling recommendations |
| Inhalation (4-h whole-body) | SD albino rats (five animals/sex), nominal dose: 21.0 mg/L, actual dose: 5.26 mg/L | $LC_{50}$ > 5.26 mg/L | No treatment-related clinical or gross pathological findings and no treatment-related effect on body weight<br>(MMAD = 2.30 Fm, GSD = 2.5)<br>Low toxicity<br>No labelling recommendations |
| Primary eye irritation | NZW rabbits (three animals/sex), dose level: 0.1 mL (approximately 80 mg TS) | MIS: 13.5/110 at one hour<br>MAS: 6.89/110 | Minimally irritating<br>No labelling recommendations |
| Primary dermal irritation | NZW rabbits (three animals/sex), dose level: 0.5 g in 0.2 mL water | MIS: 0.83/8 at one hour<br>MAS: 0.56/8 | Minimally irritating<br>No labelling recommendations |
| Dermal sensitization (Buehler method) | Dunkin–Hartley albino guinea pigs (five animals/sex) in both the test and control groups, dose level: 0.3 mL of 40% w/v test substance in 0.25% (w/v) aqueous methyl cellulose solution used for both induction (left scapular and lumbosacral region) and challenge (right scapular region) treatment | At 24 h after challenge treatment slight patchy erythema (grade 0.5) was observed in 2/10 test animals and 3/10 control animals. At 48 h after challenge treatment slight patchy erythema was observed in 1/10 test animals and 2/10 control animals. | Not a skin sensitizer<br>No labelling recommendations |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| **Short term studies** | | | |
| 28-day dietary | 10 CD-1 mice/sex/dose, dose levels: 0, 175, 700, 2800 or 7000 ppm (equal to 0, 29, 121, 475 or 1140 mg/kg bw/day in males and 0, 35, 143, 534 or 1347 mg/kg bw/day in females) | NOAEL: 175 ppm (equal to 29 mg/kg bw/day in males and 35 mg/kg bw/day in females) | **175 ppm:** increased liver weight (males and females)<br>**700 ppm:** increased ALAT levels (females), increased liver weight (males and females), enlarged liver (males), centrilobular hepatocellular hypertrophy (males and females) and hepatocellular necrosis (males)<br>**2800 ppm:** increased ALAT (males and females) and ASAT (males) levels, increased liver weight (males and females), enlarged liver (males and females), centrilobular hepatocellular hypertrophy (males and females) and hepatocellular necrosis (males and females)<br>**7000 ppm (males and females):** increased ALAT and ASAT levels, increased liver weight, enlarged liver, white striations on liver, centrilobular hepatocellular hypertrophy, hepatocellular necrosis and extramedullary hematopoiesis in the spleen |
| 90-day dietary | 12 CD-1 mice/sex/dose, dose levels: 0, 50, 1000 or 2000 ppm (equal to 0, 7.6, 170 or 324 mg/kg bw/day in males and 0, 8.7, 81 or 376 mg/kg bw/day in females) | NOAEL: 50 ppm (equal to 7.6 mg/kg bw/day in males and 8.7 mg/kg bw/day in females) | **50 ppm:** males exhibited increased absolute liver weight<br>**1000 ppm:** males exhibited increased liver weight and increased incidence of periacinar hypertrophy<br>**2000 ppm:** males and females exhibited increased ASAT and ALAT levels, increased liver weight and periacinar hepatocytic hypertrophy<br>**Control terminal (week 13) body weight:** males 41.6 g; females 30.6 g<br>**Control terminal (week 13) daily food consumption:** males 5.2 g/mouse; females 5.7 g/mouse |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| 90-day dietary (six weeks dose, seven weeks recovery) | 10 CD rats/sex/dose, dose levels: 25, 100, 400 or 1000 mg/kg bw/day | No NOEL or NOAEL identified | **Significant findings:** decreased bw gain and food efficiency at 400 (females) and 1000 (males and females) mg/kg bw/day, decreased food consumption at 1000 mg/kg bw/day (males)<br>Clinical and ophthalmoscopic findings: increased incidence of opaque eyes and corneal opacity all dose levels (except females at 25 mg/kg bw/day) with associated keratitis (males at $100 mg/kg bw/day) and vascularization (males and females at $100 mg/kg bw/day); occurrence not dose related, males more susceptible<br>Histopathological findings<br>**Eye (cornea):** generalized thickening of the epithelium, subepithelial fibroblastic reaction and vascularization of the stroma (males and females at $100 mg/kg bw/day) Treatment-related signs were reversed after seven-week recovery period. |
| 90-day dietary | 10 CD rats/sex/dose, dose levels: 0, 1, 3, 10 or 100 mg/kg bw/day | NOEL:<br>3 mg/kg bw/day | **Clinical findings:** increased incidence of opaque eyes at 10 (males) and 100 (males and females) mg/kg bw/day<br>**Ophthalmoscopic findings:** increased incidence of corneal opacity at 10 (males) and 100 (males and females) mg/kg bw/day with associated vascularization (males at $10 mg/kg bw/day, females at 100 mg/kg bw/day), keratinization (males at 100 mg/kg bw/day) and iritis (males at $10 mg/kg bw/day and females at 100 mg/kg bw/day)<br>**Histopathological findings**<br>**Eye:** superficial exfoliated epithelial cells (males and females at 100 mg/kg bw/day), generalized thickening of epithelial cells (males at 100 mg/kg bw/day), focal epithelial thickening (males at 100 mg/kg bw/day), vacuolation of epithelial cells (males at $10 mg/kg bw/day and females at 100 mg/kg bw/day), epithelial inflammation (males and females at 100 mg/kg bw/day), subepithelial fibroblastic reaction (males and females at 100 mg/kg bw/day) and vascularization of the stroma (males at $10 mg/kg bw/day and females at 100 mg/kg bw/day) |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| 90-day dietary (continued) | 10 CD rats/sex/dose, dose levels: 0, 1, 3, 10 or 100 mg/kg bw/day | NOEL: 3 mg/kg bw/day | Corneal effects were considered reversible on the basis of the previous 90-day rat study (six weeks treatment, seven weeks recovery). **Liver:** increased liver weight (males at 100 mg/kg bw/day), increased incidence of periacinar hepatocytic hypertrophy (males at 100 mg/kg bw/day) **Control terminal (week 13) body weight:** males 497 g, females 312 g **Control terminal (week 13) daily food consumption:** males 28.6 g/rat, females 20.2 g/rat |
| Six weeks capsule and two weeks dietary | One male and one female beagle dog, dose levels capsule: 1000 mg/kg bw/day, dietary: 25 000 ppm (approximately 1000 mg/kg bw/day) | No NOEL or NOAEL identified | Increased liver weight in both animals |
| 52-week dietary | Five beagle dogs/sex/dose, dose levels: 0, 240, 1200, 12 000 or 30 000 ppm (equal to 0, 8.41, 45.33, 498 or 1254 mg/kg bw/day in males and 0, 8.56, 44.81, 453 or 1265 mg/kg bw/day in females) | NOEL: 1200 ppm (equal to 45.3 mg/kg bw/day in males and 44.8 mg/kg bw/day in females) LOEL: 12 000 ppm equal to 453 mg/kg bw/day in males and 498 mg/kg bw/day in females) | Decreased bw gain in females at 12 000 ppm and males and females at 30 000 ppm Regenerative hemolytic anemia in females at 12 000 ppm and males and females at 30 000 ppm (characterized by decreased RBC, Hct and Hb, increased PCEs and extramedullary hematopoiesis) At $12 000 ppm (males and females) increased liver weight, AP, ALAT, ASAT, 5'-NT and (-GT activity, hepatocellular swelling, centrilobular swelling and margination of cytoplasmic staining, centrilobular necrosis and fibrosis, vacuolated hepatocytes and centrilobular glycogen depletion; no neoplastic tissue observed in either the treated or the control animals |
| 21-day dermal | Eight CD rats/sex/dose, dose levels: 0, 10, 100 or 1000 mg/kg bw/day (eight hours/day semi-occlusive wrapping) | NOAEL: 1000 mg/kg bw/day | Increased liver weight at 1000 mg/kg bw/day (both sexes) |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| **Chronic toxicity and oncogenicity** | | | |
| 78-week dietary (oncogenicity) | 52 CD-1 mice/sex/dose, dose levels: 0, 25, 500 or 7000 ppm (equal to 0, 3.2, 63.5 or 977.3 mg/kg bw/day in males and 0, 4.0, 77.9 or 1161.1 mg/kg bw/day in females) | Chronic effects NOEL: 25 ppm (equal to 3.2 mg/kg bw/day in males and 4.0 mg/kg bw/day in females) Oncogenicity Females hepatocellular adenomas and carcinomas NOEL: 500 ppm (equal to 78 mg/kg bw/day) Males hepatocellular adenomas NOEL: 500 ppm in males (equal to 64 mg/kg bw/day), hepatocellular carcinomas NOEL: 25 ppm (equal to 3.2 mg/kg bw/day) | **500 ppm:** decreased bw and body weight gain (males), increased incidence of periacinar hepatocytic hypertrophy (males), necrosis of individual hepatocytes (males) and hepatocellular carcinomas (males) **7000 ppm:** decreased bw, bw gain and food efficiency (males and females), increased incidence of distended abdomen (males) and cyanosis in the ventral abdomen (males and females), increased liver weight (males and females), increased incidence of liver masses (males and females), enlarged or swollen livers (males), liver "areas of change" (males), abdominal distension (males), periacinar hepatocytic hypertrophy (males and females), necrosis of individual hepatocytes (males), erythrocytes in hepatocytes (males and females), pigment laden hepatocytes and Kupffer cells (males), periacinar hepatocytic fatty vacuolation (females), basophilic foci and increased ploidy (males) and extramedullary hematopoiesis in the spleen (males) increased incidence of hepatocellular adenomas, carcinomas and adenomas and carcinomas combined (males and females) Hepatocellular adenomas appeared at approximately one year in males at all dose levels and at approximately 77–78 weeks in females at all dose level. In males, there appeared to be a dose-related trend in appearance of hepatocellular carcinomas (at 78, 71, 52 and 47 weeks at 0, 25, 500 and 7000 ppm, respectively) Hepatocellular carcinomas first appeared in females at week 60 at 7000 ppm |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| 104-week dietary (chronic toxicity) | 75 SD rats/sex/dose, dose levels: 0, 0.5, 2.0, 20 or 500 mg/kg bw/day<br>An additional 20 rats/sex/dose treated for 52 weeks after which 10 rats/sex/dose were sacrificed and 10 rats/sex/dose were sacrificed after an eight-week recovery period | Chronic effects NOEL: males 0.5 mg/kg bw/day, females 2 mg/kg bw/day<br>LOEL: males 2 mg/kg bw/day, females 20 mg/kg bw/day<br>Oncogenicity Hepatocellular adenomas and carcinomas NOEL: 20 mg/kg bw/day for both sexes<br>Thyroid follicular adenomas NOEL: 20 mg/kg bw/day for males | **500 mg/kg bw/day:** decreased bw gain (males and females), food consumption (females) and food efficiency (males and females), increased liver (males and females) and thyroid weights (males) increased incidence of thin body build, abnormal gait, limited use of limbs and corneal opacity in males and females increased incidence of swollen livers (males), "areas of change" (males) and masses (males and females) in the liver, dark enlarged thyroids with masses (males), periacinar hepatocytic hypertrophy (males and females), focal cystic degeneration (males), midzonal foamy hepatocytes (males and females), portal tract senile changes in bile duct (males and females), basophilic and clear cell foci (females), pigment laden hepatocytes (females), eye lesions in males (including keratitis, vascularization of the stroma, epithelial thickening and superficial exfoliated epithelial cells), thyroid cystic follicular hyperplasia (males and females), axonal and myelin sciatic nerve degeneration (males and females), and focal degeneration and inflammation of the thigh muscle (males and females), increased incidence of hepatocellular adenomas, carcinomas and adenomas and carcinomas combined (males and females) and thyroid follicular cell adenomas (males)<br>**20 mg/kg bw/day:** increased liver (males) and thyroid weights (males), increased incidence of corneal opacity (males), swollen livers (males), dark enlarged thyroids with masses (males), eye lesions (males), periacinar hepatocytic hypertrophy (males and females), focal cystic degeneration (males), midzonal foamy hepatocytes (males), portal tract senile changes in bile duct (males and females), thyroid cystic follicular hyperplasia (males), axonal and myelin sciatic nerve degeneration (males) and focal degeneration and inflammation of the thigh muscle (males) |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| 104-week dietary (chronic toxicity) (continued) | | | **2.0 mg/kg bw/day:** increased incidence of keratitis (males)<br>Hepatocellular adenomas were 1st observed at 365 days in **%** at 500 mg/kg bw/d & at 427 days in **&** at 500 mg/kg bw/d compared to 728 days in **%**/**&** control groups. Hepatocellular carcinomas were 1st observed at 646 days in **%** at 500 mg/kg bw/d compared to 594 days in the control group & at 426 days in **&** at 500 mg/kg bw/d compared to 728 days in the control group.<br>Thyroid follicular cell adenomas were 1st observed at 612 days in **%** at 500 mg/kg bw/d compared to 647 days in the control group. groups. Hepatocellular carcinomas were first observed at 646 days in males at 500 mg/kg bw/day compared with 594 days in the control group and at 426 days in females at 500 mg/kg bw/day compared with 728 days in the control group. Thyroid follicular cell adenomas were first observed at 612 days in males at 500 mg/kg bw/day compared with 647 days in the control group. |
| **Reproduction and developmental toxicity** | | | |
| Multigenerational dietary | 30 CD rats/sex/dose, target dose: 0, 0.5, 2, 20 or 500 mg/kg bw/day, actual dose males: 0, 0.45, 1.76, 17.4 or 414 mg/kg bw/day, females: 0, 0.46, 1.79, 17.7 or 437 mg/kg bw/day | NOEL<br>Systemic toxicity: 2.0 mg/kg bw/day<br>Reproductive toxicity: 2.0 mg/kg bw/day | **Systemic toxicity**<br>**Adults:** decreased bw, bw gain and food consumption in $F_0$ and $F_1$ adults (males and females) at 500 mg/kg bw/day<br>increased liver weight, centrilobular hepatocellular hypertrophy in $F_0$ and $F_1$ adults (males and females) at 20 and 500 mg/kg bw/day<br>Hepatocellular vacuolation in $F_0$ and $F_1$ males at 500 mg/kg bw/day and in $F_1$ males at 20 mg/kg bw/day<br>increased incidence of chronic keratitis and unilateral and bilateral subacute corneal inflammation in $F_1$ adults (males and females) at 500 mg/kg bw/day<br>Pups and weanlings: increased incidence of chronic keratitis in $F_2$ pups and weanlings at 500 mg/kg bw/day (males and females) |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| Multigenerational dietary (continued) | 30 CD rats/sex/dose, target dose: 0, 0.5, 2, 20 or 500 mg/kg bw/day, actual dose males: 0, 0.45, 1.76, 17.4 or 414 mg/kg bw/day, females: 0, 0.46, 1.79, 17.7 or 437 mg/kg bw/day | NOEL<br>Systemic toxicity: 2.0 mg/kg bw/day<br>Reproductive toxicity: 2.0 mg/kg bw/day | **Reproductive and developmental toxicity:** increased number of females in $F_0$ generation with stillborn pups at 500 mg/kg bw/day, increased number of stillborn pups in $F_1$ pups at 20 and 500 mg/kg bw/day, decreased bw and underdeveloped renal papilla in $F_1$ and $F_2$ pups at 500 mg/kg bw/day (males and females), decreased viability index in $F_1$ and $F_2$ pups at 500 mg/kg bw/day and in $F_1$ pups at 20 mg/kg bw/day, decreased bw and absence of milk in stomach in $F_1$ and $F_2$ pups at 500 mg/kg bw/day (males and females) |
| Teratogenicity | 25 mated female SD rats/dose, dose levels: 0, 10, 100 or 500 mg/kg bw/day | NOEL<br>Maternal toxicity: 100 mg/kg bw/day<br>NOAEL<br>Developmental toxicity: 10 mg/kg bw/day<br>NOEL<br>Teratology:<br>500 mg/kg bw/day, not considered to be teratogenic | **Maternal toxicity:** decreased bw, bw gain and food consumption at 500 mg/kg bw/day<br>**Developmental toxicity**<br>**500 mg/kg bw/day:** decreased 13/13 ribs, increased incidence of 13/14 and 14/14 ribs and enlargement of 14th rib/ribs, increased incidence of subcutaneous edema<br>**100 and 500 mg/kg bw/day:** decreased fetal weight at with an associated increased in number of small fetuses and decreased in number of large fetuses, growth retardation (decreased ossification of the 3rd, 4th and 5th sternebrae, caudal vertebrae, metacarpals and metatarsals, pubic bones, 1st thoracic vertebral centrum), decreased incidence of 4/4 metacarpals and metatarsals and increased 3/4 metacarpals and metatarsals, increased incidence of subcutaneous hemorrhage<br>**10 mg/kg bw/day:** increased incidence of incomplete ossification of the 3rd sternebra, decreased incidence of 4/4 metacarpals and metatarsals and increased 3/4 metacarpals and metatarsals |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| | 25 mated female NZW rabbits/dose, dose levels: 0, 5, 20 or 100 mg/kg bw/day | NOEL<br>Maternal toxicity:<br>20 mg/kg bw/day<br>NOAEL<br>Developmental toxicity: 5 mg/kg bw/day<br>NOEL<br>Teratology:<br>100 mg/kg bw/day, not considered to be teratogenic | **Maternal toxicity:** decreased bw gain, food consumption and fecal output at 100 mg/kg bw/day. increased number of late resorptions with an associated increased post-implantation loss and slight decreased number viable pups/litter at 100 mg/kg bw/day<br>**Developmental toxicity:**<br>**100 mg/kg bw/day:** increased incidence of rudimentary 1st rib/ribs, decreased ossification of pubic bones and increased incidence of incisors not erupted<br>**20 and 100 mg/kg bw/day:** increased incidence of 27th presacral vertebrae, increased incidence of 13/13 ribs, decreased incidence of 12/12 ribs and decreased ossification of heads of limb long-bones and metacarpals and phalanges<br>**5 mg/kg bw/day:** increased incidence of 27th presacral vertebrae |
| **Mutagenicity** | | | |
| *Salmonella typhimurium* (Ames Test) | *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 | RPA 201772 at 0, 25, 50, 100, 250, 500, 1000, 2500 or 5000 Fg/plate<br>± S9 metabolic activation | Negative |
| *Salmonella typhimurium* (Ames Test) | *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 | RPA 202248 (metabolite of RPA 201772) at 0, 100, 250, 500, 1000, 2500 or 5000 Fg/plate<br>± S9 metabolic activation | Negative<br>Minimal cytotoxicity at 5000 Fg/plate in presence of S9 mix (plate incorporation method) and absence of S9 mix (preincubation method) |
| *Salmonella typhimurium* (Ames Test) | *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 | RPA 203328 (a metabolite of RPA 201772) at 0, 100, 250, 500, 1000, 2500 and 5000<br>± S9 metabolic activation | Negative<br>Cytotoxicity observed at $2500 Fg/plate ± S9 mix |
| In vitro mammalian cell gene mutation test | L5178Y TK ± mouse lymphoma cells | RPA 201772 at 0, 37.5, 75, 150, 300 and 600 Fg/mL<br>± S9 metabolic activation | Negative |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| In vitro mammalian cell gene mutation test | Chinese hamster V79 lung cells | RPA 201772 at 0, 6.25, 12.5, 25, 50 or 100 Fg/mL ± S9 metabolic activation | Negative |
| In vitro mammalian cytogenetic test | Human lymphocytes | RPA 201772 at 0, 75, 150, 300 or 500 Fg/mL ± S9 metabolic activation | Negative |
| In vitro mammalian cytogenetic test | Human lymphocytes | RPA 201772 at 0, 75, 300 or 600 Fg/mL ± S9 metabolic activation | Negative |
| Mouse micronucleus test | Mouse bone marrow cells | RPA 201772 at 0, 200, 1000 or 5000 mg/kg bw | Negative |
| **Special studies** | | | |
| Acute neurotoxicity | Male and female CD rats (10 animals/sex/dose) | Dose levels: 0, 125, 500 or 2000 mg/kg bw | NOEL<br>**Systemic and neurotoxicity:**<br>2000 mg/kg bw<br>Decreased landing foot splay measurement on day 15 in males at 500 and 2000 mg/kg bw, although values were comparable to pretest values |
| Subchronic neurotoxicity | Male and female SD rats (10 animals/sex/dose) | Dose levels: 0, 25, 250 or 750 mg/kg bw/day | NOEL<br>**Systemic toxicity:** 250 mg/kg bw/day<br>**Neurotoxicity:** 750 mg/kg bw/day<br>decreased bw and bw gain males at 750 mg/kg bw/day<br>No significant treatment-related neurotoxicity observations |
| Assessment of thyroid tumours in male rat | Male SD rats (10 rats/group) | Dose level: 0 or 500 mg/kg bw/day<br>Positive control:<br>80 mg/kg bw/day sodium phenobarbital | Decreased $T_4$ with little or no change in $T_3$<br>increased liver and thyroid weights, enlarged livers, increased concentration and total weight of hepatic microsomal protein and increased microsomal cytochrome $P_{450}$ concentration<br>increased Phase I PROD and Phase II UDPGT activity, increased systemic clearance of $^{125}$I-thyroxine with concomitant decreased $T_4$ concentration and $T_{½}$, increased thyroid iodine uptake |

| Study | Species or strain and doses | NOEL, NOAEL and LOEL (mg/kg bw/day) | Target organ and significant effects with comments |
|---|---|---|---|
| 14-day dietary administration effect on liver enzymes in male CD-1 mice | CD-1 mice (25 animals/dose level) hepatic microsomes | Dose levels: 0, 175, 700, 2800 or 7000 ppm | No NOEL<br>Increased liver weights at 700 ppm and above, increased total cytochrome $P_{450}$ concentration at 700 ppm and above, increased absolute and relative PROD activity at 175 ppm and above and 700 ppm and above, respectively, increased absolute and relative BROD activity at 175 ppm and above, no significant induction of other $P_{450}$ isoenzymes (EROD or MROD) or increased in peroxisome proliferation (lauric acid 11- and 12-hydroxylase activity)<br>Overall, isoxaflutole appears to induce cytochrome $P_{450}$ enzymes similar to phenobarbital. |
| 14-day dietary administration effect on liver enzymes in male SD rats | SD rats (five animals/dose level) | Dose levels: 0, 10, 100 or 400 mg/kg bw/day | No NOEL<br>Increased liver weights at all dose levels increased absolute and relative PROD and BROD activity at all dose levels, no significant induction of other $P_{450}$ isoenzymes (EROD or MROD) or increased in peroxisome proliferation (lauric acid 11- and 12-hydroxylase activity)<br>Overall, isoxaflutole appears to induce cytochrome $P_{450}$ enzymes similar to phenobarbital. |

# Appendix II Effects on nontarget species

## Table 1 Summary of toxicity of isoxaflutole to nontarget terrestrial organisms

| Group | Organism | Effect | NOEL or NOEC (mg a.i./kg) | $LC_{50}$ or $LD_{50}$ (mg a.i./kg) | Classification |
|---|---|---|---|---|---|
| Wild birds | bobwhite quail (*Colinus virginanus*) | acute oral | 2150 | >2150 | nontoxic |
| | | dietary | 5000<br>5200[1] | >5000<br>>5200[1] | nontoxic |
| | mallard duck (*Anas platyrhynchos*) | acute oral | 2150 | >2150 | nontoxic |
| | | dietary | 5000 | >5000 | nontoxic |
| Wild mammals | rat | acute oral | — | >5000 | nontoxic |
| Invertebrates | honeybee (*Apis mellifera*) | acute contact | 100 Fg a.i./bee | >100 Fg a.i./bee | nontoxic |
| | | acute oral | 168.7 Fg a.i./bee | >168.7 Fg a.i./bee | nontoxic |
| | earthworm (*Eisenia foetida*) | acute | 1000 | >1000 | no-effect |
| Plants | seed germination | soybean[2], radicle length[3] | 109.8 g a.i/ha | 201.75 g a.i./ha ($EC_{25}$) | |
| | seedling emergence | turnip[2], shoot length[3] | 0.3 g a.i./ha | 0.44 g a.i./ha ($EC_{25}$) | toxic |
| | vegetative vigour | turnip[2], root weight[3] | 0.095 g a.i./ha | 0.13 g a.i./ha ($EC_{25}$) | toxic |

1 RPA 202248
2 most sensitive species
3 parameter

## Table 2 Summary of toxicity of isoxaflutole to nontarget aquatic organisms

| Group | Organism | Effect | NOEC (mg a.i./L) | $EC_{50}$ or $LC_{50}$[1] (mg a.i./L) | Classification |
|---|---|---|---|---|---|
| Invertebrates | daphnia (*Daphnia magna*) | acute | 1.5<br>59.6[2]<br>150.0[3]<br>59.6[4] | >1.5<br>>59.6<br>>150.0<br>>59.6 | nontoxic |
| | | chronic | 0.35 | 0.67 (LOEC) | nontoxic |
| | mysid shrimp (*Mysidopsis bahia*) | acute | 0.005<br>0.83[2] | 0.018<br>3.7 | very highly toxic<br>moderately toxic |
| | eastern oyster (*Crassostrea virginica*) | shell growth | 0.98 | 3.4 | moderately toxic |
| Fish | rainbow trout (*Oncorhynchus mykiss*) | acute | 1.7<br>33.8[2]<br>130.0[3]<br>77.1[4] | >1.7<br>>33.8<br>160.0[3]<br>>77.1 | moderately toxic<br>slightly toxic<br>nontoxic<br>slightly toxic |
| | bluegill sunfish (*Lepomis macrochirus*) | acute | 4.5 | >4.5 | moderately toxic |
| | sheepshead minnow (*Cyprinodon variegatus*) | acute | 6.4 | >6.4 | moderately toxic |
| | rainbow trout (*Oncorhynchus mykiss*) | chronic (early life cycle) | 0.1 | 0.19 | toxic |
| Algae | *Selenastrum capricornutum* | biomass | 0.016<br>2.4[3] | 0.12<br>>9.4 | highly toxic<br>slightly toxic |
| | *Anabena flos-aquae* | biomass | 0.0086 | 0.17 | highly toxic |
| | *Navicula pelliculosa* | biomass | 0.0031 | 0.38 | highly toxic |
| | *Scenedesmus subspicatus* | biomass | 2011532 | >20.0<br>>15.0<br>10.5 | nontoxic<br>nontoxic<br>nontoxic |
| | *Skeletonema costatum* | biomass | 0.0022 | 0.11 | highly toxic |
| Plants | duckweed (*Lemna gibba*) | biomass | 0.0011 | 0.0032 | very highly toxic |

[1] Low solubility of technical isoxaflutole in water, resulting in precipitation, limited the concentration range used in all aquatic toxicity studies; therefore, most end points are given as greater than the highest concentration measured.

[2] RPA 202248

[3] RPA 203328

[4] RPA 205834

**Table 3 The maximum expected environmental concentrations of isoxaflutole on vegetation immediately after application of 105 g a.i./ha**

| Environmental compartment | Concentration of fresh weight[1] [mg/kg] | Fresh to dry weight (dw) ratio[2] | Concentration of dw [mg/kg] |
|---|---|---|---|
| short range grass | 22.47 | 3.3 | 74.15 |
| leaves and leafy crops | 11.77 | 19.0 | 129.36 |
| long grass | 10.3 | 4.4 | 45.28 |
| forage crops | 5.46 | 5.4 | 29.48 |
| small insects | 5.46 | 3.8 | 20.75 |
| pods with seeds | 1.12 | 3.9 | 4.38 |
| large insects | 0.94 | 3.8 | 3.55 |
| grains and seeds | 0.94 | 3.8 | 3.55 |
| fruit | 0.65 | 7.6 | 4.95 |

[1] On the basis of correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)
[2] Fresh to dry weight ratios from Harris (1975) and Spector (1956)

**Table 4 Summary of risk assessment to terrestrial organisms**

| Organism | Effect | NOEL or NOEC (mg a.i./kg) | EEC (mg a.i./kg) | Risk factor | Safety factor | Risk | Mitigatory measures |
|---|---|---|---|---|---|---|---|
| mallard duck | acute oral | 2150 | | 11 727 days to NOEL | | no | not required |
| | dietary | >5000 | 3.6 | | 1390 | no | not required |
| bobwhite quail | acute oral | 2150 | | 2150 days to NOEL | | no | not required |
| | dietary | 500 052 001 | 12.6 | | 397 413 | no | not required |
| mammals (rat) | acute oral | 500 (1/10 of $LD_{50}$) | | 1268 days to NOEL | | no | not required |
| earthworm | acute | 1000 | 0.046 | $4.6 \times 10^{-5}$ | $2.2 \times 10^{4}$ | no | not required |
| honeybee | acute contact | 100 Fg/bee | 3.55 Fg/bee | 0.035 | 28.2 | no | not required |
| | acute oral | 168.7 Fg/bee | 3.55 Fg/bee | 0.02 | 47.5 | no | not required |

[1] RPA 202248

**Table 5 Summary of risk assessment to aquatic organisms**

| Organism | Effect | NOEC (mg a.i./L) | EEC (mg a.i./L) | Risk factor | Safety factor | Risk | Mitigatory measures |
|---|---|---|---|---|---|---|---|
| mysid shrimp | acute | 0.005 | 0.035 | 7 | 0.14 | risk | 7-m buffer zone |
| rainbow trout | acute | 1.7 | 0.035 | 0.02 | 48 | no risk | not required |
| *Anabena flosaque* | acute | 0.0086 | 0.035 | 4 | 0.25 | risk | 4-m buffer zone |
| *Navicula pelliculosa* | acute | 0.0022 | 0.035 | 16 | 0.06 | risk | 15-m buffer zone |
| *Lemna gibba* | acute | 0.0011 | 0.035 | 32 | 0.03 | risk | 22-m buffer zone |

# Appendix III Efficacy Tables

**Table 1 Proposed and accepted weed claims for Converge 75 WDG following pre-emergent application in field corn**

| Weed species | Proposed rate (g a.i./ha) | Accepted rate (g a.i./ha)[1] |
|---|---|---|
| **Barnyard grass (*Echinochloa crusgalli*)** | 105 | 105 |
| **Green foxtail (*Seteria viridis*)** | 105 | 105 |
| **Witchgrass (*Panicum capillare*)** | 79 | 79 |
| **Large crabgrass (*Digitaria sanguinalis*)** | 79 | 79 |
| **Smooth crabgrass (*Digitaria ischemum*)** | 79 | 79 |
| **Lamb's-quarters (*Chenopodium album*)** | 79 | 79 |
| **Redroot pigweed (*Amaranthus retroflexus*)** | 79 | 79 |
| Green pigweed (*Amaranthus powellii*) | 79 | |
| **Common ragweed (*Ambrosia artemisiifolia*)** | 79 | 79 |
| **Eastern black nightshade (*Solanum ptycanthum*)** | 79 | 79 |
| **Wormseed mustard (*Erysimum cheiranthoides*)** | 79 | 79 |
| **Wild mustard (*Sinapis arvensis*)** | 79 | 79 |
| **Velvetleaf (*Abutilon theophrasti*)** | 79 | 79 |
| **Broadleaf plantain (*Plantago major*) seedlings** | 79 | 79 |
| **Dandelion (*Taraxacum officinale*) seedlings** | 79 | 79 |

[1] accepted for use in conventionally tilled field corn only

**Table 2 Proposed and accepted weed claims for Converge 75 WDG plus atrazine following pre-emergent application in field corn**

| Weed species | Proposed rate Converge 75 WDG + atrazine (g a.i./ha) | Accepted rate Converge 75 WDG + atrazine (g a.i./ha)[1] |
|---|---|---|
| **Barnyard grass (*Echinochloa crusgalli*)** | 79–105 + 800–1063 | 79 + 800 |
| **Green foxtail (*Seteria viridis*)** | 79–105 + 800–1063 | 79 + 800 |
| **Witchgrass (*Panicum capillare*)** | 79–105 + 800–1063 | 79 + 800 |
| **Large crabgrass (*Digitaria sanguinalis*)** | 79–105 + 800–1063 | 79 + 800 |
| **Smooth crabgrass (*Digitaria ischemum*)** | 79–105 + 800–1063 | 79 + 800 |
| **Lamb's-quarters (*Chenopodium album*)** | 79–105 + 800–1063 | 79 + 800 |
| **Redroot pigweed (*Amaranthus retroflexus*)** | 79–105 + 800–1063 | 79 + 800 |
| Green pigweed (*Amaranthus powellii*) | 79–105 + 800–1063 | |
| **Common ragweed (*Ambrosia artemisiifolia*)** | 79–105 + 800–1063 | 79 + 800 |
| **Eastern black nightshade (*Solanum ptycanthum*)** | 79–105 + 800–1063 | 79 + 800 |
| **Wormseed mustard (*Erysimum cheiranthoides*)** | 79–105 + 800–1063 | 79 + 800 |
| **Wild mustard (*Sinapis arvensis*)** | 79–105 + 800–1063 | 79 + 800 |
| **Velvetleaf (*Abutilon theophrasti*)** | 79–105 + 800–1063 | 79 + 800 |
| **Broadleaf plantain (*Plantago major*) seedlings** | 79–105 + 800–1063 | 79 + 800 |
| **Dandelion (*Taraxacum officinale*) seedlings** | 79–105 + 800–1063 | 79 + 800 |
| **Lady's-thumb (*Polygonum persicaria*)** | 79–105 + 800–1063 | 79 + 800 |
| Wild buckwheat (*Polygonum convolvulus*) | 79–105 + 800–1063 | |

[1] accepted for use in conventionally tilled field corn only

**Table 3 Side-by-side efficacy comparisons of Converge 75 WDG + Aatrex Nine-0 and Converge 75 WDG + Aatrex 480**

| Weed species | No. of trials | Converge 75 WDG at 79 g a.i./ha +Aatrex Nine-0 at 800 g a.i./ha | Converge 75 WDG at 79 g a.i./ha +Aatrex 480 at 800 g a.i./ha |
|---|---|---|---|
| Barnyard grass | 1 | 100% | 100% |
| Green foxtail | 4 | 92% | 98% |
| Large crabgrass | 1 | 99% | 99% |
| Witch grass | 4 | 95% | 85% |
| Common ragweed | 4 | 100% | 100% |
| Redroot pigweed | 5 | 100% | 97% |
| Eastern black nightshade | 1 | 100% | 100% |
| Lamb's-quarters | 4 | 99% | 98% |
| Wild mustard | 1 | 100% | 100% |
| Velvetleaf | 1 | 100% | 100% |

**Table 4 Efficacy at 43–57 DAT of Converge 75 WDG alone and Converge 75 WDG + Aatrex Nine-0 with liquid nitrogen (28–0–0) as a carrier**

| Weed species | No. of trials | Converge 75 WDG at 79 g a.i./ha | Converge 75 WDG at 105 g a.i./ha | Converge 75 WDG at 79 g a.i./ha +Aatrex 480 at 800 g a.i./ha |
|---|---|---|---|---|
| Barnyard grass | 1 | | 96% | 94% |
| Green foxtail | 2 | | 97% | 97% |
| Witch grass | 1 | 91% | | 95% |
| Common ragweed | 2 | 100% | | 100% |
| Redroot pigweed | 2 | 97% | | 82% |
| Lamb's-quarters | 2 | 94% | | 89% |
| Wormseed mustard | 1 | 98% | | 98% |
| Lady's-thumb | 1 | | | 92% |