Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision Document PRDD2005-02

Imiprothrin

The active ingredient (a.i.) imiprothrin and the associated manufacturing concentrate Pralle® Manufacturing Use Product (both from Sumitomo Chemical Company Limited) as well as the manufacturing concentrate Multicide® Intermediate 2734 and the end-use product Multicide® Pressurized Roach Spray 27341 (both from McLaughlin Gormley King Company) are proposed for full registration under the Pest Control Products Regulations.

The end-use product Multicide® Pressurized Roach Spray 27341 is intended for domestic use to control cockroaches, ants and other household pests.

This Proposed Regulatory Decision Document provides a summary of data received and the rationale for the proposed full registration of these products. The Pest Management Regulatory Agency (PMRA) will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications at the address below.

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Foreword

Health Canada's PMRA has reviewed the submissions for full registration of Imiprothrin® Technical Grade and Pralle® Manufacturing Use Product (both manufactured by Sumitomo Chemical Company Limited) as well as manufacturing concentrate Multicide® Intermediate 2734 and end-use product Multicide® Pressurized Roach Spray 27341 (both produced by the McLaughlin Gormley King Company) for the control of cockroaches, ants and other household pests.

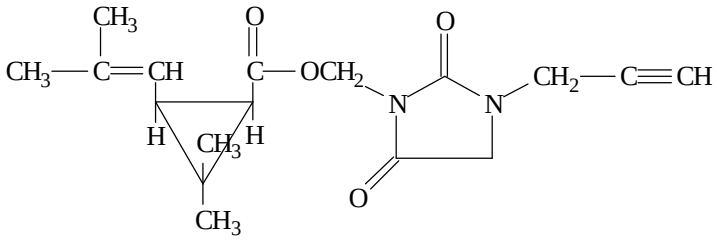
The PMRA has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value of Imiprothrin® Technical Grade and Pralle® Manufacturing Use Product, Multicide® Intermediate 2734 and Multicide® Pressurized Roach Spray 27341. The Agency has concluded that the use of Imiprothrin® Technical Grade, Pralle® Manufacturing Use Product, Multicide® Intermediate 2734 and Multicide® Pressurized Roach Spray 27341 in accordance with the label has merit and value consistent with the Pest Control Products Regulations and does not entail an unacceptable risk of harm. Therefore, based on the considerations outlined above, the use of Imiprothrin® Technical Grade, Pralle® Manufacturing Use Product, Multicide® Intermediate 2734 and Multicide® Pressurized Roach Spray 27341 for the control of cockroaches, ants and other household pests is proposed for full registration, pursuant to the Pest Control Products Regulations.

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

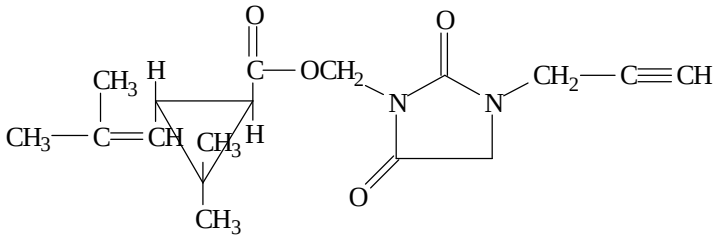
Table of Contents

1.0 The Active Substance, its Properties, Uses, Proposed Classification and Labelling

1.1 Identity of the Active Substance and Preparation Containing It

Common name	Imiprothrin
Function	Insecticide
Chemical name	
IUPAC	2,5-dioxo-3-prop-2-ynylimidazolidin-1-ylmethyl(1R)-*cis*,*trans*-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate
CAS	[2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl]methyl)2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate
CAS number	72963-72-5
Molecular formula	$C_{17}H_{22}N_2O_4$
Molecular weight	318.37
Structural formula	

(1R,3S)- or (1R)-cis- isomer of imiprothrin



(1R,3R)- or (1R)-trans- isomer of imiprothrin

Nominal purity of active	92.2%
Identity of relevant impurities of toxicological, environmental or other significance	The technical grade imiprothrin does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances.

1.2 Physical and Chemical Properties of the Active Substance

Technical Product: Imiprothrin® Technical Grade

Property	Result	Comments
Colour and physical state	Amber, viscous liquid	
Odour	Slightly sweet	
Melting point or range	Not applicable	
Boiling point or range	Degradation of the technical material occurs before a boiling point is reached.	
Specific gravity	1.122	
Vapour pressure at 25°C	1.86×10^{-6} Pa	Non-volatile
Henry's Law constant at 20°C	6.25×10^{-6} Pa	Non-volatile
UV or visible spectrum	No absorbance observed in the UV or visible range of spectrum	Low potential for phototransformation
Solubility (mg/L) in water at 20°C	**pH** 6.5 **mg/L** 93.5	Soluble
Solubility (g/L) in organic solvents	**Solvent** / **Solubility** *n*-octanol: soluble methanol: soluble acetonitrile: soluble acetone: soluble hexane: 6.2 g/L	
n-Octanol–water partition coefficient (log K_{ow})	**pH** 6.2–6.6 **log K_{ow}** 2.9	Potential for bioconcentration or bioaccumulation
Dissociation constant	Not applicable Compound does not dissociate	

Property	Result	Comments
Stability (temperature, metal)	Stable for 14 days at 54°C Stable when in contact with resin-coated steel and uncoated steel	

Manufacturing Concentrate: Pralle® Manufacturing Use Product

Guarantee (expressed as nominal value):

imiprothrin	50.5%

Manufacturing Concentrate: Multicide® Intermediate 2734

Guarantee (expressed as nominal value):

imiprothrin	8.0%
d-phenothrin	10.0%
N-Octyl bicycloheptene dicarboximide (MGK®264)	20.0%

End-use Product: Multicide® Pressurized Roach Spray 27341

Property	Result
Colour	Opaque white
Odour	Petroleum distillate
Physical state	Liquid
Formulation type	Pressurized spray
Guarantee (expressed as nominal values)	Imiprothrin 0.40% *d*-Phenothrin 0.50% N-Octyl bicycloheptene dicarboximide (MGK®264) 1.00%
Container material and description	Lined, metal aerosol container
Specific gravity	0.900 at 20°C
pH of 1% dispersion in water	6.7
Oxidizing or reducing action	Not an oxidizing or reducing agent
Storage stability	Chemically stable for 12 months at 37.8°C (100°F)
Explodability	Not applicable

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Substance as Manufactured

A gas chromatographic (GC) method was used for the determination of the active substance and two GC methods were used to determine the significant structurally related impurities (content $\geq$ 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 GC method was used for the determination of active substance in the formulation. The method has been shown to have satisfactory specificity, linearity, precision and accuracy and is suitable for use as an enforcement analytical method.

Conclusion: the product chemistry data for Imiprothrin® Technical Grade, the manufacturing intermediates Pralle® Manufacturing Use Product and Multicide® Intermediate 2734 as well as the end-use product Multicide® Pressurized Roach Spray 27341 are complete. The technical material was fully characterized and the specifications were supported by the analysis of seven batches for active ingredient and impurities using specific and validated methods of analysis. The technical material is not expected to contain any impurities or microcontaminants known to be TSMP Track 1 substances. The required chemical and physical properties of the technical material, intermediate products and the end-use product were determined using acceptable methods. A fully validated GC method for the determination of the active ingredient in the formulation was provided.

3.0 Impact on Human and Animal 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

Appendix I of this document contains a summary table of the toxicity studies with imiprothrin.

Toxicokinetic studies in rats with the cis and trans isomers of imiprothrin revealed rapid absorption with excretion primarily in urine, coupled with smaller amounts excreted in feces and expired air. There was no apparent sex difference in rate and extent of absorption and excretion, although administration of the trans isomer resulted in higher blood concentrations than the cis isomer. Imiprothrin was widely and relatively evenly distributed to the tissues, with the highest proportion observed in the liver. No apparent sex differences were noted in tissue distribution or metabolite profile. Imiprothrin was extensively metabolized, with up to 11 different urinary metabolites and up to 15 different

fecal metabolites detected after administration of the cis isomer. Administration of the trans isomer resulted in the detection of 11 urinary and 12 fecal metabolites. The main metabolic reactions included cleavage of the ester linkage and dehydroxymethylation of the resultant alcohols, hydroxylation of the imidazolidine ring, dealkylation of the 2-propynyl group and oxidation at the ω-*trans*-methyl group in the isobutenyl side chain.

Imiprothrin is moderately toxic via the oral route of exposure, slightly toxic via the inhalation route and of low toxicity via the dermal route of exposure. It is non-irritating to eyes and minimally irritating to skin. Imiprothrin is considered to possess sensitization potential. Clinical signs of toxicity were observed following oral and inhalation exposure and included, but were not limited to, ataxia, irregular respiration, urinary incontinence, tiptoe gait and tremors.

Acute toxicity studies with Pralle® Manufacturing Use Product (50.5% imiprothrin) revealed low toxicity via the oral, dermal and inhalation routes of exposure. Clinical signs of toxicity following oral and inhalation exposure were similar to those reported for technical imiprothrin. Pralle® Manufacturing Use Product was non-irritating to skin and minimally irritating to eyes. Skin sensitization testing failed to elicit a positive response using the same test methods as those employed to assess the sensitization potential of the technical active ingredient.

The acute toxicity profile of Multicide® Intermediate 2734 (8% imiprothrin plus other active ingredients) indicated low toxicity via the oral, dermal and inhalation routes of exposure. Although no mortality was observed in the acute dermal study, a decrease in hind limb function was observed in the test species (rabbit). The only clinical sign of toxicity was inactivity observed in the acute inhalation study. Multicide® Intermediate 2734 was non-irritating to skin and minimally irritating to eyes. The product was considered a potential skin sensitizer.

Multicide® Pressurized Roach Spray 27341 (0.4% imiprothrin) was determined to be of low acute toxicity following oral, dermal and inhalation toxicity testing. The profile of clinical signs was essentially identical to that observed for Multicide® Intermediate 2734. The product was minimally irritating to eyes and produced moderate irritation to skin. It produced a positive response following skin sensitization testing.

Repeated-dose studies were performed via the oral (rats, mice), dermal (rats) and inhalation (rats) routes of exposure. Systemic toxicity following short-term dermal dosing was limited to effects on body-weight gains. Following oral and inhalation exposure, however, the primary toxic effects were manifested as changes on red blood cell (RBC) parameters that suggested a regenerative anemia (increased reticulocyte counts, decreased RBC counts, hemoglobin [Hb] and hematocrit [Hct]). Treatment-related clinical signs of toxicity were restricted to the short-term inhalation study and were consistent with those observed following acute oral and inhalation exposure. Notable effects resulting from repeated administration of imiprothrin included changes in body weight, body-weight

gain, liver, salivary gland and spleen effects (increased weights, pathology) as well as hair loss or whisker defect (the latter finding observed in the mouse oncogenicity study). There did not appear to be any differences between the sexes or among the species in terms of sensitivity to most toxic effects. Increasing the length of dosing from short-term to chronic administration did not appear to significantly increase the toxicity of imiprothrin. A one-year study in the dog (not submitted to the PMRA, but for which an executive summary from a California Department of Pesticide Registration evaluation was made available) revealed a toxicity profile similar to that noted above as well as a comparable no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) for the primary toxic effects.

There was no evidence in the database to suggest that imiprothrin has any adverse effects on the endocrine system of mammals or that there was any increased sensitivity in the young. Imiprothrin was not teratogenic to rats or rabbits, although some developmental effects (skeletal variations) were observed at dose levels associated with maternal toxicity. Decreased pup body weight and increased incidence of variations (rib or lumbar) as well as indication of parental systemic toxicity were recorded in a multigeneration reproduction study. However, no effects on reproductive capacity of the parental animals were observed.

In genotoxicity testing, the overall weight of evidence from the battery of in vitro and in vivo tests indicated that imiprothrin is not genotoxic. However, positive results were observed in the presence of exogenous metabolic activation in an in vitro chromosomal aberration assay using Chinese hamster lung cells.

There was no demonstration of oncogenic potential in rats and mice following chronic dosing.

Several studies investigated the neurotoxicity of imiprothrin following single oral dosing in rats. Neurotoxicity findings consisted of repetitive flicking of forelimbs, decreased locomotor activity, salivation, urinary staining, tremors, convulsions and diarrhea. Although there were no treatment-related effects on brain weight or structural changes in nervous system tissue, a NOAEL for neurotoxic effects was not demonstrated. The resulting LOAELs were 100 mg/kg body weight (bw) in females and 200 mg/kg bw in males. In a subchronic neurotoxicity study, treatment-related effects such as a decrease in body weight, body-weight gain, food consumption and clinical signs were noted. The recorded clinical signs consisted of reduction in arousal, slight reduction in motor activity and reduced hindlimb grip strength. In the absence of any changes in quantitative measures in motor activities as well as any neuropathology, these clinical signs were considered to reflect generalized, systemic toxicity.

3.2 Toxicology Endpoint Selection for Handler and Bystander Risk Assessment

The end-use product, Multicide® Pressurized Roach Spray 27341, was determined to be of low acute toxicity following oral, dermal and inhalation toxicity testing, minimally irritating to eyes and moderately irritating to skin. It produced a positive response following skin sensitization testing.

As handler exposure would be intermittent, NOAELs from the 21-day dermal and 28-day inhalation studies were considered to be the most appropriate to reflect the anticipated routes and duration of exposure to handlers. In the 21-day dermal study, the primary systemic effect was decreased body weight, while in the 28-day inhalation study, clinical signs indicative of neurotoxicity were noted.

Given the time between applications (i.e., the product is not to be applied more than once per week) and the fact that imiprothrin is rapidly metabolized and excreted, it was also considered appropriate to view each application as an acute exposure. On this basis, the LOAEL of 100 mg/kg bw/day from the acute neurotoxicity study was deemed the most appropriate as the lowest effect level for clinical signs of neurotoxicity reported in this study. Further, in view of the fact that no NOAEL was established for this study, an additional uncertainty factor of three was considered appropriate in the risk assessment for this endpoint.

Postapplication exposure would be of intermediate duration and via the dermal (adults, children) and oral (children) routes. Inhalation exposure would be very low. The most appropriate endpoints for use in the postapplication risk assessment are the NOAEL of 300 mg/kg bw/day from the 21-day dermal study for the dermal route and the NOAEL of 6 mg/kg bw/day from the 90-day rat study for the oral route. In each instance, the target margin of exposure would be 100.

3.3 Impact on Human and Animal Health Arising from Exposure to the Active Substance or to Impurities Contained in It

3.3.1 Handler Exposure Assessment

Multicide® Pressurized Roach Spray 27341 is a ready-to-use aerosol formulation proposed for crack and crevice application in residences. The proposed end-use formulation contains the new active ingredient imiprothrin (0.4%).

The Pesticide Handlers Exposure Database (PHED Version 1.1) was used to derive an estimate of exposure to homeowners applying Multicide® Pressurized Roach Spray 27341. The PHED subsets meet North American Free Trade Agreement criteria for PHED estimates and, therefore, provide an adequate basis for estimating handler exposure for the proposed use.

Based on the PHED output, exposure would be predominantly dermal (<1% inhalation). Exposure resulting from dermal deposition would be 0.0233 mg a.i/kg bw/day (best fit measure of central tendency). Exposure resulting from inhalation would be 0.000 137 mg a.i./kg bw/day (best fit). Total exposure (dermal deposition and inhalation), assuming equivalent absorption via the oral and dermal routes, would be 0.0231 mg a.i./kg bw/day (best fit). Based on the proposed use pattern, exposure could occur intermittently throughout the year (i.e., brief exposures, typically not more than once per week).

For the homeowner spraying Multicide® Pressurized Roach Spray 27341, route-specific MOEs for systemic toxicity endpoints were based on the following:

- the NOAEL of 5 mg/kg bw/day in the 28-day inhalation study in rats on the basis of increased incidence of clinical signs at the next dose level; and
- the NOAEL of 300 mg/kg bw/day in the 21-day dermal study in rats based on decreased body-weight gain at the next dose level.

For the dermal route, the MOE is >12 000. For the inhalation route, the MOE is 36 500. In addition, a MOE of 4300 exists for the LOAEL of 100 mg/kg bw/day in the single oral dosing neurotoxicity study. These MOEs are considered adequate.

3.3.2 Bystanders

Given the limited use pattern proposed (i.e., crack and crevice only) and the low vapour pressure of imiprothrin (i.e., 1.86×10^{-6} Pa at 25°C), inhalation exposure to occupants (including the adult applying the product) was considered to be very low. Output from the United States Environmental Protection Agency's (USEPA) Multichamber Concentration and Exposure Model supports this conclusion.

Dermal and non-dietary ingestion exposure to occupants is considered to be low following crack and crevice applications. Tier one exposure and risk assessment approaches demonstrated adequate MOEs for postapplication exposure (adults and children exposure) following crack and crevice application. To minimize postapplication exposure potential, the product must be marketed with a nozzle tip adaptor to streamline spray (e.g., straw-like device) and the directions for use must be modified to provide instruction on use of the nozzle tip adaptor.

3.3.3 Workers

Not applicable, as the product is proposed for residential use.

4.0 Residue

Not applicable.

5.0 Fate and Behaviour in the Environment

5.1 Summary of the Fate and Behaviour of Imiprothrin in the Environment

5.1.1 Transformation

Imiprothrin was found to be stable with respect to hydrolysis at pH 5. The dissipation time 50% (DT_{50}) of imiprothrin was 58.6 days at pH 7 and 17.9 hours at pH 9. The hydrolysis of imiprothrin was base-catalysed. The major positively identified transformation product was N-carbamoyl-N-propargylglycine; it came from a study using imiprothrin labelled in the imidazolidine ring. No hydrolysis studies were submitted using imiprothrin labelled on the cyclopropanecarboxylic moiety of the molecule. However, published papers were submitted clearly showing that this moiety produces the hydrolytic product 2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxilic acid (CRA) that accounts for over 70% of the applied radioactivity and shows no indications of transformation after 30 days. These results indicate that imiprothrin would be persistent in water at pH 5, but would not be persistent at levels greater than pH 7.

Biotransformation rates in soils and aquatic systems were not measured because the use pattern is limited to indoor use.

5.1.2 Mobility

Values of the Freundlich adsorption coefficient (K_d) and the organic carbon adsorption coefficient (K_{oc}) were not measured because the use pattern is limited to indoor use. Imiprothrin is soluble in water and non-volatile. The solubility, volatility and hydrolysis rates of imiprothrin indicate that this chemical may have the potential to leach into groundwater or to run off into surface water if released into the environment.

5.1.3 Transformation products

The major positively identified transformation product in the hydrolysis study was CPG (N-carbamoyl-N-propargylglycine) (24.26% of total recovery at pH 7 on day 30; 87.28% of total recovery at pH 9 at hour 122.66); PGH (1-propargylimidazolidine-2,4-dione) (1.81% of total recovery at pH 7 on day 30; 4.26% of total recovery at pH 9 at hour 122.66) was a minor transformation product. There was also an unidentified peak observed (1.67% of total recovery at pH 7 on day 30; 5.07% of total recovery at pH 9 at hour 122.66). Submitted literature also indicates that CRA (2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxilic acid) will probably be the major transformation product from the cyclopropanecarboxylic moiety. The total CO_2 and volatile compounds were not determined.

5.2 Expected Environmental Concentrations

Expected environmental concentrations in soil and water as well as on vegetation were not calculated.

6.0 Effects on Non-target Species

6.1 Terrestrial Species

No data were required.

6.2 Aquatic Species

No data were required.

6.3 Environmental Risk Assessment

Imiprothrin is soluble in water and non-volatile. Hydrolysis is not expected to be a route of transformation in acidic and neutral waters, but will be a route of transformation in alkaline waters. Biotransformation rates and values of K_d and K_{oc} were not measured because the use pattern is limited to indoor use. Although the solubility, volatility and hydrolysis rates of the compound indicate that this chemical may have the potential to leach into groundwater or to run off into surface water if released into the environment, this risk could not be quantified. The log K_{ow} for imiprothrin was reported as 2.9, indicating that imiprothrin has the potential to bioconcentrate or bioaccumulate.

6.4 Mitigative Measures

Extreme caution is advised to ensure that products containing imiprothrin are disposed of in accordance with the label recommendations.

7.0 Integrated Efficacy Summary

7.1 Effectiveness Against Household Pests

Laboratory studies assessing the efficacy of imiprothrin against cockroaches as well as the efficacy of Multicide® Pressurized Roach Spray 27341 (0.4% imiprothrin, 0.5% *d*-phenothrin, and 1.0% N-octyl bicycloheptene dicarboximide) against various household pests has been reviewed in support of the application from McLaughlin Gormley King Company, Minnesota, to register Multicide® Pressurized Roach Spray 27341.

The imiprothrin laboratory trial demonstrated that a 0.4% imiprothrin product, applied as an aerosol at a rate of 180 mg a.i./m^2, resulted in a 40% mortality of German cockroaches

after 48 h, confirming that imiprothrin has insecticidal properties and can be recognized as an active ingredient. In addition, the 0.4% imiprothrin aerosol application provided fast knock-down (100% in <40 s) of German cockroaches, whether by itself, in combination with 1% N-octyl bicycloheptene dicarboximide (MGK®264) or as a component of Multicide® Pressurized Roach Spray 27341 (i.e., with 0.5% *d*-phenothrin in addition to imiprothrin and MGK®264).

Laboratory studies on the efficacy of Multicide® Pressurized Roach Spray 27341 in controlling cockroaches, black carpenter ants, house crickets, sowbugs, spiders, brown dog ticks and stored product pests (i.e., sawtoothed grain beetle, confused flour beetle, rice weevil) have been reviewed. Multicide® Pressurized Roach Spray 27341 was found to provide acceptable control (>95%) of the German cockroach at application levels of 899 mg a.i./m^2 (189 mg imiprothrin/m^2) or more. Acceptable control of American and Oriental cockroaches (100 and 88% mortality, respectively) was evident when the product was applied at a rate of approximately 3000 mg a.i./m^2 (626–638 mg imiprothrin/m^2). Multicide® Pressurized Roach Spray 27341 also provided adequate control (88–100%) of black carpenter ants, house crickets, sowbugs, spiders, brown dog ticks and stored product pests when applied at rates of 277–2371 mg a.i./m^2 (58–500 mg a.i./m^2). Where 100% mortality occurred, minimum effective rates were not determined.

On the basis of these data, the registration of Multicide® Pressurized Roach Spray 27341 can be supported as per label directions, i.e., that the product is to be applied at a rate of 5 seconds per linear metre from a height of 15 cm. For crack and crevice treatments, this results in an application rate of approximately 3498 mg a.i./m^2 (733 mg imiprothrin, 910 mg *d*-phenothrin and 1855 mg N-octyl bicycloheptene dicarboximide) in the 3-cm portion of the total band width (i.e., 8 cm) where the spray is concentrated.

7.2 Integrated Pest Management and the Development of Imiprothrin Resistance

The use of Multicide® Pressurized Roach Spray 27341 would not be incompatible with current pest management practices. The registration of this product would add another synthetic pyrethroid and synergist combination formulation to the domestic class market.

Imiprothrin is a new active ingredient, and its potential to induce resistance in the arthropods listed on the proposed draft label is not yet known. However, because its mode of action is equivalent to the other synthetic pyrethroids currently registered for this domestic class, the premise treatment use is not seen as having the potential to contribute to any resistance management strategy.

8.0 Toxic Substances Management Policy

8.1 Active Ingredient

During the review of imiprothrin, the PMRA has considered the implications of the federal TSMP and its Regulatory Directive DIR99-03 and has concluded that the log K_{ow} of imiprothrin is 2.9, which is below the TSMP Track 1 cut-off criterion of $\geq$5.0. On this basis, the PMRA concluded that imiprothrin does not meet TSMP Track 1 criteria.

8.2 Transformation Products

Insufficient data were submitted to determine whether the transformation products of imiprothrin meet the TSMP Track 1 criteria. However, imiprothrin is intended for indoor use only; therefore, it will have minimal environmental impact.

8.3 End-use Formulations

The formulated products do not contain any formulants that are known to be TSMP Track 1 substances. It is noted, however, that one end-use product (Multicide® Pressurized Roach Spray 27341) contains petroleum distillate (CAS no. 64742-47-8) as a solvent. This compound is a USEPA List 2 inert compound. Compounds on this list are potential toxins and are slated for high priority testing in the United States.

8.4 Microcontaminants

Imiprothrin® Technical Grade does not contain any impurities of toxicological concern or any TSMP Track 1 microcontaminants.

9.0 Regulatory Decision

Imiprothrin® Technical Grade, Pralle® Manufacturing Use Product, Multicide® Intermediate 2734 and Multicide® Pressurized Roach Spray 27341 can be granted full registrations.

List of Abbreviations

a.i.	active ingredient
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bw	body weight
CAS	Chemical Abstracts Service
d	day
DT_{50}	dissipation time 50%
F_1	first filial generation
F_2	second filial generation
FOB	functional observation battery
GC	gas chromatography
GGT	gamma glutamyl transferase
h	hour
Hb	hemoglobin
Hct	hematocrit
IUPAC	International Union of Pure and Applied Chemistry
K_d	Freundlich adsorption coefficient
K_{oc}	organic carbon adsorption coefficient
K_{ow}	*n*-octanol–water partition coefficient
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
MAS	maximum average score
MCCEM	Multichamber Concentration and Exposure Model
MCH	mean cell hemoglobin
MCV	mean cell volume
MIS	maximum irritation score
NOAEL	no observed adverse effect level
NZW	New Zealand white
P_1	parental generation
Pa	Pascal(s)
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RBC	red blood cells
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency

Appendix I Summary Table of the Toxicity Studies with Imiprothrin

Metabolism

Rate and extent of absorption and excretion: rapidly absorbed, peak blood levels reached within 1–9 h of dosing, blood levels remained high until approximately 12 h, followed by rapid elimination. Biological half-lives of elimination ranged from 6 to 12 h. No apparent sex difference; however, administration of the trans isomer resulted in higher blood concentrations than the cis isomer. Rapidly excreted, approximately 78–85% of the cis isomer excreted in the urine and 4–15% in the feces within 24 h, approximately 1–3% of the administered dose was excreted in expired air. Approximately 90–93% of the trans isomer was excreted in the urine within 24 h, with 4–7% in the feces and 0.3–0.6% in expired air.

Distribution and target organ(s): after oral administration of either isomer, imiprothrin was widely and relatively evenly distributed to the tissues. Peak tissue concentrations were reached within 3 h after administration of the low dose and within 6 h after administration of the high dose. The highest proportions were observed in liver, while skin and hair, blood, blood cells, bone and kidney were also relatively high. After seven days, tissue residues were all very low. The rate of elimination from the tissues was slower following administration of the cis isomer. There were no apparent sex differences observed.

Metabolites: parent S-41311 was not detected in blood or urine, and only small quantities were detected in feces. Up to 11 different urinary metabolites and 15 different fecal metabolites were detected after administration of the cis isomer. Up to 11 different urinary metabolites and 12 different fecal metabolites were detected after administration of the trans isomer. The main metabolic reactions included cleavage of the ester linkage and dehydroxymethylation of the resultant alcohols, hydroxylation of the imidazolidine ring, dealkylation of the 2-propynyl group and oxidation at the ω-*trans*-methyl group in the isobutenyl side chain.

Study	Species or Strain and Doses	NOAEL and LOAEL	Target Organ and Significant Effects and Comments
Acute Studies: Technical Product (95.3% a.i.)			
Oral	Rats, Crj:CD 0, 500, 700 (females only), 1000, 1400, 2000, 2800 or 4000 (males only) mg/kg	Lethal dose 50% (LD_{50}): 900 mg/kg (females), 1800 mg/kg (males)	Moderately toxic, mortalities at ≥ 700 mg/kg in females and ≥ 1000 mg/kg in males; all deaths within 0.5–1 h post-dosing; clinical signs observed at these dose levels in both sexes included decreased spontaneous activity, prone position, lateral position, tremor, ataxic gait, irregular respiration, urinary incontinence and stained fur
Dermal	Rats, Crj:CD 2000 mg/kg	LD_{50} > 2000 mg/kg	Low toxicity, no mortality, no adverse clinical signs and no effect on body weight

Study	Species or Strain and Doses	NOAEL and LOAEL	Target Organ and Significant Effects and Comments
Inhalation	Rats, Sprague–Dawley 0.418 or 1.20 mg/L (actual)	Lethal concentration 50% (LC_{50}) > 1.20 mg/L	Slightly toxic, no mortality; clinical signs in both sexes included irregular respiration, tiptoe gait, urinary incontinence and rough coat at ≥0.418 mg/L noted at 1 h post-exposure; additional signs noted at 1.20 mg/L in males and females included hypersensitivity, ataxic gait and hair loss; these signs absent by day 9 with the exception of hair loss, which improved after day 13; body-weight gain lower in males at 0.418 mg/L on day 3 and at 1.20 mg/L on day 7; although no mortality, testing performed to 1.20 mg/L only; hence, the product classified as slightly toxic
Eye irritation	Rabbits, New Zealand White (NZW) 0.1 mL	Maximum average score (MAS): 0.56 Maximum irritation score (MIS): 3.7 (1 h)	Minimally irritating, slight redness and very slight chemosis of the conjunctiva were observed at 1 h; all signs of irritation absent at 48 h
Skin irritation	Rabbits, NZW 0.5 mL	MAS: 0 MIS: 0	Non-irritating, no signs of irritation in any of the animals tested
Skin sensitization (maximization test)	Guinea pigs, Hartley (males only)	Potential dermal sensitizer	"Mild" sensitizer, very slight erythema observed in 3 of 20 sensitized animals, with moderate to severe erythema in positive controls and no reactions in non-sensitized groups
Skin sensitization (Buehler method)	Guinea pigs, Hartley (males only)	Non-sensitizing	Non-sensitizing, no evidence of sensitization
Acute Studies: Pralle® Manufacturing Use Product (50.5% a.i.)			
Oral	Rats, Crj:CD (SD) 1000, 2000, 2600 (females only), 3200, 4000, 5000 (males only) mg/kg	LD_{50}: 2400 mg/kg (females), 4500 mg/kg (males)	Low toxicity, deaths at ≥2000 mg/kg in females and ≥4000 mg/kg in males within 24 h of dosing; clinical signs in both sexes at ≥2000 mg/kg included decrease in spontaneous activity, tremor, clonic convulsion, ataxic gait, prone position, lateral position, irregular respiration, urinary incontinence and blotted fur; body-weight gain transiently affected in both sexes at ≥2000 mg/kg from day 1 to day 5
Dermal	Rats, Crj:CD 2000 mg/kg	LD_{50} > 2000 mg/kg	Low toxicity, no mortality and no clinical signs and no effect on body weight

Study	Species or Strain and Doses	NOAEL and LOAEL	Target Organ and Significant Effects and Comments
Inhalation	Rats, Sprague–Dawley 2.81, 3.62 or 4.43 mg/L	LC_{50} > 2.81 mg/L	Low toxicity, mortality at all dose levels within 24 h of dosing; clinical signs noted in both sexes within 0.5 h after initiation of exposure included ataxic gait, tiptoe gait and ocular discharge; hypersensitivity and tremor also noted at 3.62 mg/L; all signs absent by day 7; body-weight gain transiently affected in both sexes at ≥2.81 mg/L
Eye irritation	Rabbits, NZW 0.1 mL	MAS: 0 MIS: 1.3 (1 h)	Minimally irritating, slight redness and very slight chemosis of the conjunctiva observed at 1 h; all signs of irritation absent at 24 h
Skin irritation	Rabbits, NZW 0.5 mL	MAS: 0 MIS: 0	Non-irritating, no signs of irritation in any of the animals tested
Skin sensitization (maximization test)	Guinea pigs, Hartley (males only)	Non-sensitizing	Non-sensitizing, no evidence of sensitization
Skin sensitization (Buehler test)	Guinea pigs, Hartley (males only)	Non-sensitizing	Non-sensitizing, no evidence of sensitization
Acute Studies: Multicide® Intermediate 2734 (8% a.i. plus other active ingredients)			
Oral	Rats, CrL:CD (SD) BR 5000 mg/kg	LD_{50} > 5000 mg/kg	Low toxicity, no mortality and no clinical signs and no effect on body weight
Dermal	Rabbits, Hra:(NZW)SPF 2000 mg/kg	LD_{50} > 2000 mg/kg	Low toxicity, no mortality and no effect on body weight; decrease in hind limb function to day 2; signs of dermal irritation observed to day 14 included erythema, edema, atonia and desquamation
Inhalation	Rats, Sprague–Dawley 2.69 mg/L	LC_{50} > 2.69 mg/L	Low toxicity, no mortality and no effect on body weight; inactivity of animals throughout exposure period
Eye irritation	Rabbits, NZW 0.1 mL	MAS: 1.3 MIS: 8.3 (1 h)	Minimally irritating, redness, chemosis and discharge of the conjunctiva observed at 1 h; all signs of irritation absent at 72 h
Skin irritation	Rabbits, NZW 0.5 mL	MAS: 0 MIS: 0	Non-irritating, no signs of irritation in any of the animals tested
Skin sensitization (Buehler test)	Guinea pigs, Crl:(HA)BR (males only)	Potential dermal sensitizer	Sensitizer, faint to strong erythema reactions following challenge

Study	Species or Strain and Doses	NOAEL and LOAEL	Target Organ and Significant Effects and Comments
Acute Studies: Multicide® Pressurized Roach Spray 27341 (0.4% a.i.)			
Oral	Rats, CrL:CD (SD) BR 5000 mg/kg	LD_{50} > 5000 mg/kg	Low toxicity, no mortality and no clinical signs and no effect on body weight
Dermal	Rabbits, Hra: (NZW) SPF 2000 mg/kg	LD_{50} > 2000 mg/kg	Low toxicity, no mortality and no effect on body weight; decrease in hind limb function to day 2; signs of dermal irritation observed to day 14 included erythema, edema, atonia, desquamation, coriaceousness and fissuring
Inhalation	Rats, Sprague–Dawley 3.82 mg/L	LC_{50} > 3.82 mg/L	Low toxicity, no mortality and no effect on body weight; inactivity of animals throughout exposure period
Eye irritation	Rabbits, NZW One-second spray	MAS: 1.8 MIS: 5.7 (1h)	Minimally irritating, redness, chemosis and discharge of the conjunctiva were observed at 1 h, all signs of irritation absent at 72 h
Skin irritation	Rabbits, NZW 0.5 mL	MAS: 3.8 MIS: 4.5	Moderately irritating, blanching and fissuring observed in all animals, erythema and edema observed from day 1 to day 7, all signs of irritation absent at day 14
Skin sensitization (Buehler test)	Guinea pigs, Crl:(HA)BR (males only)	Potential dermal sensitizer	Sensitizer, very faint to moderate erythema reactions following challenge
Short-term Toxicity			
21-day dermal	Rats, Sprague–Dawley 5/sex/dose at 0, 100, 300 or 1000 mg/kg bw/day in corn oil	Systemic NOAEL: 300 mg/kg/ bw/day LOAEL: 1000 mg/kg bw/day Dermal effects NOAEL: 1000 mg/kg bw/day (males and females)	**Systemic:** decrease in body-weight gain at 1000 mg/kg bw/day **Dermal effects:** slight increases in the incidence and severity of acanthosis and hyperkeratosis of the skin at 1000 mg/kg bw/day in both sexes, but not considered adverse

Study	Species or Strain and Doses	NOAEL and LOAEL	Target Organ and Significant Effects and Comments
28-day inhalation	Rats, Sprague–Dawley 10/sex/dose at 0, 0.0024, 0.022 or 0.186 mg/L in corn oil 4 h/day continuously for 28 days (male) or 29 days (female)	NOAEL: 0.022 mg/L (males and females) (5.0 mg/kg bw/day males; 6.0 mg/kg bw/day females) LOAEL: 0.186 mg/L (males and females) (approximately 50 mg/kg bw)	**0.186 mg/L:** increase in the incidence of clinical signs including irregular respiration, reduced spontaneous activity, salivation, tiptoe gait, nasal discharge and urinary incontinence (in both sexes), jumping, hyperactivity and tremor (in females); majority of clinical signs observed beginning day 1 during the 4-h exposure; decreased body-weight gain in males and in females, increased reticulocyte count and decreased Hb and Hct (in both sexes), decreased mean cell volume (MCV) and mean cell hemoglobin (MCH) (in males), decreased erythrocyte count (in females), increased relative liver weights, dark liver, increased absolute and relative salivary gland weights and hyperplasia of acinous cells of salivary glands (in both sexes)
90-day dietary	Rats, Crj:CD (SD) 12/sex/dose at 0, 100, 3000, 6000 or 10 000 ppm (0, 5.9, 179, 350 or 611 mg/kg bw/day males; 0, 6.7, 197, 399 or 657 mg/kg bw/day females)	NOAEL: 100 ppm (5.9 mg/kg bw/day males; 6.7 mg/kg bw/day females) LOAEL: 3000 ppm (179 mg/kg bw/day males; 197 mg/kg bw/day females)	**3000 ppm and above:** decreased body-weight gain and food consumption, decreased Hb and Hct (both sexes); increased α_2-globulin, cholesterol, phospholipids, decreased triglycerides (males); increased reticulocytes (females) **6000 ppm and above:** increased albumin, total protein, leucocytes, lymphocytes and basophils, extended prothrombin time and activated thromboplastin time (males) **10 000 ppm:** decreased γ-globulin and increased reticulocytes and neutrophils (males); decreased RBC, increased hepatocellular hypertrophy and eosinophilic hepatocytes (both sexes)

Study	Species or Strain and Doses	NOAEL and LOAEL	Target Organ and Significant Effects and Comments
90-day dietary	Mice, Crj:CD-1 12/sex/dose at 0, 1000, 3000, 5000 or 7000 ppm (0, 130, 371, 643 or 884 mg/kg bw/day males; 0, 150, 435, 803 or 1239 mg/kg bw/day females)	NOAEL not determined LOAEL: 1000 ppm (130 mg/kg bw/day males; 150 mg/kg bw/day females)	**1000 ppm and above:** decreased erythrocyte counts (males), increased reticulocyte counts (males), increased absolute and relative liver weights (males and females) **3000 ppm and above:** decreased erythrocyte counts (females), decreased Hb concentration and Hct (males and females) **5000 ppm and above:** increased absolute and relative spleen weights (males), decreased absolute ovary weight **7000 ppm:** increased reticulocyte counts (females), slight increase in leukocyte and lymphocyte counts (males), slight hepatocellular hypertrophy (males), increased extramedullary hematopoesis in the spleen (males and females)
Chronic Toxicity and Oncogenicity			
104-week feeding	Rats, Crj:CD (SD) 50/sex/dose at 0, 50, 250, 2500 or 5000 ppm (0, 1.8, 8.7, 90 or 180 mg/kg bw/day males; 0, 2.2, 10.7, 109 or 219 mg/kg bw/day females) Satellite group (14 rats/sex/group) for interim sacrifice at 52 weeks	Chronic toxicity NOAEL: 250 ppm (8.7 mg/kg bw/day males; 10.7 mg/kg bw/day females) LOAEL: 2500 ppm (90 mg/kg bw/day males; 109 mg/kg bw/day females)	**Non-neoplastic** **2500 ppm and above:** altered hematology (decreased Hct, MCV, MCH), increased liver enzyme parameters (ALT, AST, GGT) in males at 5000 ppm, increased liver and salivary gland weights, enlargement of the liver in males at 2500 ppm and both sexes at 5000 ppm, enlargement of the salivary gland observed in males only at 5000 ppm, increased incidence of acinar cell hypertrophy in the submandibular salivary gland in both sexes, increased incidence of hemosiderosis of the spleen in females at 2500 and 5000 ppm at week 52, much reduced by week 104, increased incidence of foci of cellular alteration in liver and bile duct hyperplasia in females at ≥2500 ppm **Oncogenicity** No oncogenic potential identified for rats at the highest dose in the study

Study	Species or Strain and Doses	NOAEL and LOAEL	Target Organ and Significant Effects and Comments
78-week feeding	Mice, Crj:CD-1 51/sex/dose at 0, 100, 3500 or 7000 ppm (0, 10, 354 or 702 mg/kg bw/day males; 0, 12, 409 or 814 mg/kg bw/day females) An extra 15/sex/group at 52 weeks	**Chronic toxicity** NOAEL: 100 ppm (10.2 mg/kg bw/day males, 11.8 mg/kg bw/day females) LOAEL: 3500 ppm (354 mg/kg bw/day males, 409 mg/kg bw/day females)	**Non-neoplastic** **3500 ppm and above:** increased mortality in females; decreased body weight and body-weight gain in both sexes; increased absolute and relative liver weights in both sexes at 52 weeks and in females only at 78 weeks; increased incidence of black discolouration of the liver in both sexes in interim sacrifice animals and main group animals **Liver effects:** increased incidence of hepatocellular hypertrophy in both sexes, foci of cellular alteration in males **7000 ppm:** increased mortality in females, increased incidence of hair loss and whisker defect in both sexes; decreased body weight and body-weight gain and decreased food consumption in both sexes, increased absolute and relative liver weight in both sexes at interim and 78 weeks with increased incidence of black discolouration of liver, hepatocellular hypertrophy and foci of cellular alteration in liver of both sexes At 52 weeks, hematological parameters in males affected: decreased RBC, Hb and Hct and increased reticulocytes, slight regenerative anemia No apparent effect on bone marrow and no signs of anemia at week 78 **Neoplastic** **7000 ppm:** increased incidence of alveolar adenocarcinoma in males and combined alveolar adenoma and adenocarcinoma in both sexes were considered incidental and spurious Increased incidence of hepatocellular tumours (adenoma and carcinoma) in males was without a dose response or statistical significance

Study	Species or Strain and Doses	NOAEL and LOAEL	Target Organ and Significant Effects and Comments
Reproduction and Developmental Toxicity			
Multigeneration reproduction	Rats, Crl:CD BR VAF/Plus (Sprague–Dawley) 30/sex/dose 0, 200, 2000 or 6000 ppm (0, 12, 126 or 369 mg/kg bw/day males, pre-mating; 0, 15, 144 or 423 mg/kg bw/day females, pre-mating)	**Parental toxicity** NOAEL = 200 ppm (15 mg/kg bw/day) (females); 2000 ppm (126 mg/kg bw/day) (males) LOAEL = 2000 ppm (144 mg/kg bw/day) (females) LOAEL = 6000 ppm (369 mg/kg bw/day) (males) **Reproductive toxicity** NOAEL = 6000 ppm (369 mg/kg bw/day males; 423 mg/kg bw/day females) **Offspring toxicity** NOAEL = 2000 ppm (126 mg/kg bw/day males; 144 mg/kg bw/day females) LOAEL = 6000 ppm (369 mg/kg bw/day males; 423 mg/kg bw/day females)	**Parental toxicity** **2000 ppm and above:** increased severity of hemosiderosis of the spleen in P_1 parental females **6000 ppm**: increased liver weights (females both generations; males P_1 only), decreased body-weight gain and food consumption in both sexes of both generations, increased incidence of hemosiderosis of the spleen in both sexes of both generations **Reproductive toxicity** No treatment-related effects reported **Offspring toxicity** **6000 ppm:** decreased pup body weight in F_1 and F_2, increased incidence of rib pairs, 14^{th} ribs, increased ossification site in thoracic vertebrae and decreased ossification site in lumbar vertebrae (variations)
Range finding developmental toxicity	Rats, Sprague–Dawley 10 pregnant females/dose at 0, 400, 600, 800 or 1000 mg/kg bw/day days 6–17 of gestation	**Maternal toxicity** NOAEL = 400 mg/kg bw/day LOAEL (maternal): 600 mg/kg bw/day **Developmental toxicity** NOAEL = 600 mg/kg bw/day LOAEL = 800 mg/kg bw/day	**Maternal toxicity** **600 mg/kg bw/day and above:** decreased mean food consumption during the early part of administration, clinical signs of toxicity within 10 min of dosing (clonic convulsion, exophthalmos, urinary incontinence and prone position) **800 mg/kg bw/day and above:** maternal deaths, reduced body-weight gain **Developmental toxicity** **800 mg/kg bw/day and above:** decreased fetal body weights **No evidence of teratogenicity**

Study	Species or Strain and Doses	NOAEL and LOAEL	Target Organ and Significant Effects and Comments
Developmental toxicity	Rats, Sprague–Dawley Crj:CD, 36 females/dose at 0, 50, 200 or 600 mg/kg bw/day days 6–17 of gestation (24 designated to developmental toxicity, 12 retained for reproductive phase with no further administration of test material)	**Maternal toxicity** NOAEL = 50 mg/kg bw/day LOAEL = 200 mg/kg bw/day **Developmental toxicity** NOAEL= 50 mg/kg bw/day LOAEL = 200 mg/kg bw/day	**Maternal toxicity** **200 mg/kg bw/day and above:** decreased body-weight gain and food consumption during the dosing period **600 mg/kg bw/day:** two deaths attributed to treatment, clinical signs including tremor, clonic convulsion, exophthalmos, prone position, staggering gait and urinary incontinence **Developmental toxicity** **200 mg/kg bw/day and above:** increased incidence of skeletal variations (lumbar rib) **600 mg/kg bw/day:** increased incidence of visceral anomaly (thymic remnant in the neck), data from reproductive phase confirmed lumbar rib observation and indicated that maturation, behaviour and learning abilities of F_1 remain unaffected **No evidence of teratogenicity**
Developmental toxicity	Rabbits, JW-NIBS Phase I: 15–17 pregnant females/dose at 0, 30, 100 or 300 mg/kg bw/day, days 6–18 of gestation Phase II: 20 pregnant females/dose at 0, 3, 10 or 30 mg/kg bw/day, days 6–18 of gestation	**Maternal toxicity** NOAEL = 30 mg/kg bw/day LOAEL = 100 mg/kg bw/day **Developmental toxicity** NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day	**Maternal toxicity** **100 mg/kg bw/day and above:** decreased body-weight gain and food consumption **300 mg/kg bw/day:** mortality, weight loss, abortions, pale red urine **Developmental toxicity** **300 mg/kg bw/day:** decreased mean fetal body weights, fusion of nasal bones, hypoplasia of the frontal bone **No evidence of teratogenicity**
Study	**Species or Strain or Cell Type and Concentrations or Doses Employed**		**Results**
Genotoxicity			
Gene mutations in bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538; *Escherichia coli* WP2uvrA 156–5000 µg/plate, with and without activation		Negative
Gene mutations in mammalian cells in vitro	Chinese hamster cells V79 44.4–150 µg/mL without activation 50–200 µg/mL with activation		Negative

Study	Species or Strain or Cell Type and Concentrations or Doses Employed		Results
Unscheduled DNA synthesis	Primary rat hepatocytes, harvested from Sprague–Dawley rats 250, 500 or 1000 mg/kg (gavage)		Negative. The study was considered supplemental owing to lack of gross nuclear grain counts and cytoplasmic grain counts; study upgradeable if missing information submitted
Chromosome aberrations	Chinese hamster lung cells CHL/IU 50–200 or 75–300 µg/mL without activation 25–100 µg/mL with activation		Positive results seen with activation at 75 and 100 µg/mL; clastogenic activity manifested as chromatid breaks and exchanges
Micronucleus assay (in vivo)	Male and female CD-1 ICR mice 19, 38 or 75 mg/kg (interperitoneal)		Negative; overt toxicity in the 75 mg/kg dose group included two deaths and tremor, clonic convulsions, prone position, ataxic gait and urinary incontinence
Study	**Species or Strain and Doses**	**NOAEL and LOAEL**	**Target Organ and Significant Effects and Comments**
Neurotoxicity			
Peak behavioural effects (supplemental study only)	Crl:CD (SD) BR rats 2/sex/dose; single oral dose (0, 500, 1000, 2000 mg/kg bw males; 0, 250, 500, 1000 mg/kg bw females)		**Peak behavioural effects for FOB:** 1.25–1.5 h post-dosing for males; 0.5–0.75 h post-dosing for females **Peak behavioural effects for motor activity:** 2–2.25 h post-dosing for males; 0.75–1 h post-dosing for females Neurotoxic findings (repetitive flicking of forelimbs, decreased average locomotor activity, salivation, urinary staining) noted at lowest doses tested (250 mg/kg bw for females; 500 mg/kg bw for males)
Acute oral benchmark (supplemental study only)	Crl:CD (SD) BR rats 2/sex/dose 0, 250, 500, 1000 or 2000 mg/kg bw	Highest non-lethal dose: 1000 mg/kg bw/day females; 2000 mg/kg bw/day males	**2000 mg/kg bw:** tremors, convulsions, transient decrease in body-weight gain (males); single mortality (females) **1000 mg/kg bw:** convulsions (females) **500 mg/kg bw:** no significant clinical signs noted in males or females

Study	Species or Strain and Doses	NOAEL and LOAEL	Target Organ and Significant Effects and Comments
Neurotoxicity			
Neurotoxicity screening battery (accepted for acute neurotoxicity study, with exception that no neurochemical analysis is done)	Crl:CD (SD) rats 12/sex/dose, single oral dose 0, 200, 600 or 1000 mg/kg bw males; 0, 100, 300 or 1000 mg/kg bw females	NOAEL not established LOAEL: 200 mg/kg bw/day males; 100 mg/kg bw/day females	**1000 mg/kg bw:** severe tremors, significantly decreased average total motor activity counts, two deaths, urinary staining and flicking of forelimbs (females); slight tremor in one animal, flicking of forelimbs, urinary staining, diarrhea (males) **600 mg/kg bw:** flicking of forelimbs, urinary staining, diarrhea (males) **300 mg/kg bw:** increased salivation; urinary staining and flicking of forelimbs (females) **200 mg/kg bw:** flicking of forelimbs, urinary staining, diarrhea (males) **100 mg/kg bw:** urinary staining and flicking of forelimbs (females) None of the above clinical signs observed in control animals; no treatment-related effects on body weight, absolute brain weight or gross pathology No structural changes in nervous system tissue noted during the neuropathology assessment
Subchronic neurotoxicity study	Sprague-Dawley rats 12/sex/dose 0, 1000, 3000, 10 000 ppm (0, 62, 191, 648 mg/kg bw/day males and 0, 74, 219, 722 mg/kg bw/day females) in diet	NOAEL: 3000 ppm (191 mg/kg bw/day males; 219 mg/kg bw/day females) LOAEL: 10 000 ppm (648 mg/kg bw/day males; 719 mg/kg bw/day females)	**10 000 ppm**: decreased body weight, body-weight gain, food consumption (males and females); reduced arousal, slight reduction in motor activity, reduced hindlimb grip strength (males) No treatment-related effects on brain weight, gross and histologic pathology or neuropathology