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Proposed Registration Decision

PRD2023-10

Paclobutrazol and TRIMMIT

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Overview

Proposed registration decision for paclobutrazol

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Paclobutrazol Technical and TRIMMIT, containing the technical grade active ingredient paclobutrazol, for use on turfgrass on golf courses to slow the growth of turfgrass and suppress *Poa annua*.

Paclobutrazol is currently registered as a plant growth regulator for use on container grown ornamental bedding plants and plugs in greenhouses. For details, see Proposed Re-evaluation Decision PRVD2013-04, *Paclobutrazol*, and Re-evaluation Decision RVD2014-06, *Paclobutrazol*.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

This Overview describes the key points of the evaluation, while the Science evaluation provides detailed technical information on the human health, environmental and value assessments of paclobutrazol and TRIMMIT.

What does Health Canada consider when making a registration decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to individuals and the environment from the use of pest control products. Health or environmental risk is considered acceptable¹ if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value² when used according to the label directions. Conditions of registration may include precautionary measures on the product label to further reduce risk.

To reach its decisions, Health Canada's PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children). They also consider the unique characteristics of organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of the Canada.ca website.

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

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

Before making a final registration decision on paclobutrazol and TRIMMIT, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.³ Health Canada will then publish a Registration Decision⁴ on paclobutrazol and TRIMMIT, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

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

What is paclobutrazol?

Paclobutrazol is a plant growth regulator which reduces internode growth, resulting in shorter and stouter stems. It is absorbed by plant roots and translocated to the growing tissues.

Health considerations

Can approved uses of paclobutrazol affect human health?

TRIMMIT plant growth regulator, containing paclobutrazol, is unlikely to affect your health when used accordingly to proposed label directions.

Potential exposure to paclobutrazol may occur through the diet (drinking water only), when handling and applying the end-use product, or when entering an area that has been treated with the product. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are selected to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

In laboratory animals, the technical grade active ingredient paclobutrazol was of moderate acute toxicity by the oral route and was mildly irritating to the eyes; consequently, the signal word "WARNING" and hazard statements "POISON" and "EYE IRRITANT" are required on the label. It was of low acute toxicity by the dermal and inhalation routes. It was minimally irritating to the skin and did not cause an allergic skin reaction.

³ "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

⁴ "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The acute toxicity of the end-use product TRIMMIT, containing paclobutrazol, was low via the oral, dermal and inhalation routes of exposure. It was non-irritating to the eyes and skin and did not cause an allergic skin reaction.

Guideline and supplemental short- and long-term (lifetime) animal toxicity tests were assessed for the potential of paclobutrazol to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. There was no evidence of tumourigenicity. The most sensitive endpoints for risk assessment were effects on activity level, body weight, fetal bone development, and the liver. There was an indication that the young were more sensitive than the adult animal.

The risk assessment protects against the effects noted above and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

Residues in water and food

Dietary risks from drinking water are not of health concern.

No food residue data are required to support the registration of paclobutrazol for use on golf course turf in Canada. There are no food or feed uses associated with paclobutrazol, with either the registered uses on nursery and greenhouse ornamentals, or with the proposed use on golf course turf. However, there is the potential for residues to enter drinking water sources as a result of the proposed use on golf course turf.

The proposed use of TRIMMIT on golf course turf in Canada does not constitute a health risk of concern for acute or chronic dietary exposure to residues of paclobutrazol in drinking water to any segment of the population, including infants, children, adults and seniors.

Acute dietary (drinking water alone) intake estimates indicated that all population subgroups, including females 13–49 years old, are exposed to less than or equal to 16% of the acute reference dose (ARfD), and therefore are not of health concern.

Chronic dietary (drinking water alone) intake estimates indicated that the general population and all population subgroups are exposed to less than 30% of the acceptable daily intake (ADI), and therefore are not a health concern.

As no food residue data are required to support the registration of paclobutrazol for use on golf course turf in Canada, maximum residue limits (MRLs) are not required for this proposed use.

Occupational risks from handling TRIMMIT

Occupational risks are not of health concern when TRIMMIT is used according to the proposed label directions, which include protective measures.

Workers mixing, loading or applying TRIMMIT, and workers entering recently treated golf courses can be exposed to paclobutrazol residues through direct skin contact or through

inhalation. Therefore, the label specifies that anyone mixing, loading and applying TRIMMIT must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Gloves are not required during application within a closed cab.

The label also requires that workers do not enter or be allowed on treated golf courses until sprays have dried. Taking into consideration the label statements, the number of applications and the duration of exposure for handlers and postapplication workers, the risks to these individuals from exposure to TRIMMIT are not of health concern when the end-use product is used according to the proposed label directions.

Health risks in residential and other non-occupational environments

Risks in residential and other non-occupational environments are not of health concern when TRIMMIT is used according to the proposed label directions and restricted-entry interval (REI) is observed.

Adults, youth and children golfing can come into direct contact with paclobutrazol residues from treated turf. Therefore, the label requires that individuals do not enter treated golf courses until sprays have dried. Taking into consideration the label statements, the number of applications and the duration of exposure, the risks to individuals golfing from exposure to TRIMMIT are not of health concern when the end-use product is used according to the proposed label directions.

Health risks to bystanders

Bystander risks are not of health concern when TRIMMIT is used according to the proposed label directions and spray drift restrictions are observed.

A standard label statement to protect against drift during application is on the label. Therefore, health risks to bystanders are not of concern when the end-use product is used according to the proposed label directions.

Environmental considerations

What happens when paclobutrazol is introduced into the Environment?

When used according to the proposed label directions, environmental risks associated with paclobutrazol and its end-use product, TRIMMIT, are acceptable.

Paclobutrazol enters the environment when TRIMMIT is used on golf courses to slow turfgrass growth and to suppress the growth of grassy weeds. Paclobutrazol is not expected to break down by reacting with water or light, or to be found in air. On land, paclobutrazol can be broken down by microorganisms in the soil to form two main breakdown products. Paclobutrazol and its breakdown products may move through soil to reach groundwater. Paclobutrazol and its breakdown products are unlikely to carry over between growing seasons.

Paclobutrazol may move from the treatment area in runoff to reach surface water. In aquatic habitats, paclobutrazol is expected to be persistent and move quickly from water to sediment. It is not likely to build up in aquatic organisms.

Use restrictions and hazard statements on the TRIMMIT label are required to reduce risks to non-target terrestrial plants and some aquatic organisms. When TRIMMIT is used according to the proposed label directions, paclobutrazol and its breakdown products pose acceptable risk to terrestrial and aquatic organisms.

Value considerations

What is the value of TRIMMIT?

TRIMMIT, formulated with the active ingredient paclobutrazol, reduces the frequency of mowing by slowing down turfgrass growth and suppressing *Poa annua* on golf courses.

TRIMMIT can be applied at 0.45–1.12 L/ha once, or multiple times with an interval of 7–21 days, and at a maximum annual rate of 4.05 L/ha in water volumes of 400–800 L/ha. TRIMMIT slows turfgrass growth, reduces the frequency of mowing by up to 50%, and suppresses *Poa annua*.

Measures to minimize risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Paclobutrazol Technical and TRIMMIT to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

To reduce the potential exposure of workers to paclobutrazol through direct skin contact or inhalation of sprays, workers mixing, loading and applying TRIMMIT and performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Gloves are not required during application within a closed cab. The label also requires that workers do not enter or allow others to enter treated areas until sprays have dried.

Furthermore, a standard label statement to protect against drift during application is present on the label.

Environment

- Standard precautionary label statements to inform users of:
 - Toxicity to aquatic organisms and non-target terrestrial plants,
 - The potential for leaching of paclobutrazol residues to groundwater.

- Spray buffer zones of up to 5 metres to protect sensitive aquatic and non-target terrestrial habitats
- Standard runoff label statements to reduce the risks to aquatic organisms

Next steps

Before making a final registration decision on paclobutrazol and TRIMMIT, Health Canada's PMRA will consider any written comments received from the public in response to this consultation document up to 45 days from the date of publication (by 31 December 2023) of this document. Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other information

When Health Canada makes its registration decision, it will publish a Registration Decision on paclobutrazol and TRIMMIT (based on the Science evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's [Pest Management Information Service](#).

Science evaluation

Paclobutrazol and TRIMMIT

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance Paclobutrazol

Function Plant Growth Regulator

Chemical name

1. International Union of Pure and Applied Chemistry (IUPAC) (2*RS*,3*RS*)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1*H*-1,2,4-triazol-1-yl)pentan-3-ol

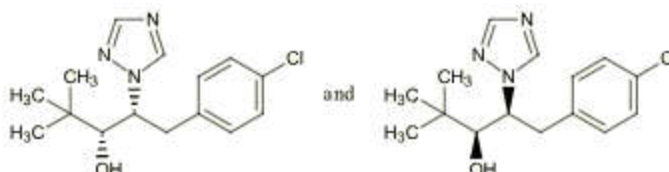
2. Chemical Abstracts Service (CAS) (α *R*, β *R*)-*rel*- β -[(4-chlorophenyl)methyl]- α -(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol

CAS number 76738-62-0

Molecular formula C₁₅H₂₀ClN₃O

Molecular weight 293.8

Structural formula



Purity of the active ingredient 98.8%

1.2 Physical and chemical properties of the active ingredient and end-use product

Technical product—Paclobutrazol Technical

Property	Result
Colour and physical state	Beige granule
Odour	Odourless
Melting point	159°C
Boiling point	384°C

Property	Result	
Density	1.23 g/cm ³	
Vapour pressure at 20°C	0.0019 mPa	
Ultraviolet (UV)-visible spectrum	$\lambda_{\text{max}} = 221 \text{ nm}$	
Solubility in water at 20°C	22.9 mg/L	
Solubility in organic solvents at 20°C	Solvent	Solubility (g/L)
	n-heptane	0.199
	xylene	5.67
	n-octanol	24.9
	ethyl acetate	45.1
	1,2-dichloroethane	51.9
	acetone	72.4
	methanol	115
<i>n</i> -Octanol-water partition coefficient (K_{ow})	pH	$\log K_{ow}$
	7	3.11
Dissociation constant (pK_a)	Does not dissociate in environmental pH range.	
Stability (temperature, metal)	Stable for more than 2 years at 20 °C, and more than 6 months at 50°C. Stable to hydrolysis (pH 4–9), and not degraded by UV light (pH 7, 10 days).	

End-use product—TRIMMIT

Property	Result
Colour	Tan
Odour	Aromatic odour
Physical state	Liquid
Formulation type	Suspension
Label concentration	247 g/L
Container material and description	Plastic jug (0.5L to bulk)
Density	1.06 g/mL at 20°C
pH of 1% dispersion in water	9.5
Oxidizing or reducing action	Not oxidizing or reducing
Storage stability	Stable for 14 days at 54°C
Corrosion characteristics	Not corrosive to non-fluorinated packaging
Explosibility	Not explosive

1.3 Directions for use

TRIMMIT is used for slowing turfgrass growth for up to two months after each application and reducing the frequency of mowing by up to 50% during that time. TRIMMIT also suppresses *Poa annua* in turfgrass.

TRIMMIT can be applied at 0.45–1.12 L/ha once, or multiple times with an interval of 7–21 days and at a maximum annual rate of 4.05 L/ha. Use the low rate and more frequent applications if turf discoloration cannot be tolerated. Apply TRIMMIT in water volumes of 400–800 L/ha, to ensure thorough coverage.

For best results, irrigate TRIMMIT into the soil but not to the point of runoff, prior to rain or within 24 hours after application to limit soil surface movement. For best residual activity, remove TRIMMIT from the leaf surface by irrigation or rainfall prior to mowing.

For growth suppression, apply in spring after green-up and turfgrass has been mowed once or twice or at least one month before onset of high air temperatures. In late summer/early fall, apply at least one month before anticipated first killing frost.

For *Poa annua* suppression, apply when *Poa annua* is actively growing. In climates with a prolonged winter dormancy, a fall application can be made up to one month prior to anticipated first killing frost.

1.4 Mode of action

Paclobutrazol acts in two ways in the target plant. First, it inhibits the plant's ability to produce gibberellic acid, which reduces the plant's cell elongation. Second, it decreases the destruction of abscisic acid, which makes the plant grow slowly and lose less water, helping the plant stay shorter and stouter. The application of paclobutrazol on turfgrass results in stouter stems by reducing internodal growth and increasing root growth.

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

The methods provided for the characterization of the technical product have been validated and assessed to be acceptable.

2.2 Method for formulation analysis

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

2.3 Methods for residue analysis

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These

methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

Methods for residue analysis in plant and animal matrices are not required as there are no food or feed uses associated with paclobutrazol with either the registered uses on nursery and greenhouse ornamentals, or with the proposed use on golf course turf.

3.0 Impact on human and animal health

3.1 Hazard assessment

3.1.1 Toxicology summary

The toxicology database for paclobutrazol is complete and contains all required guideline toxicity studies to satisfy the data requirements. For the purpose of this major new use application, the registrant provided acute toxicity studies performed with the proposed end-use product TRIMMIT. In addition, several new studies were provided including six acute toxicity studies, an acute rat neurotoxicity study, a short-term dog oral toxicity study, an in vivo Hershberger assay, in vitro steroidogenesis and aromatase assays, and several paclobutrazol metabolite studies including an acute oral study and genotoxicity studies. Certain aspects of the previous evaluations were revisited and relevant scientific studies published in the peer reviewed literature were also incorporated into the hazard assessment. Overall, the scientific quality of the toxicology database is acceptable, and the database is considered adequate to characterize the toxic effects that may result from exposure to paclobutrazol.

Paclobutrazol belongs to the triazole class of pesticides. It is a plant growth regulator that affects the isoprenoid pathway and alters the levels of plant hormones by inhibiting gibberellin synthesis and increasing cytokinin levels, consequently reducing stem elongation. Paclobutrazol also has fungicidal properties. Paclobutrazol has two stereogenic centers, but the production process yields only (2*S*,3*S*)- and (2*R*,3*R*)-enantiomers because of steric-hindrance effects (Wu et al., 2015). The studies submitted to Health Canada at the time of the initial registration were performed with the racemic mixture (2*RS*,3*RS*)-paclobutrazol at >92% purity. It contained the (2*RS*,3*SR*)-paclobutrazol form at ≤ 2.5%. The currently manufactured paclobutrazol is the racemic mixture (2*RS*,3*RS*)-paclobutrazol at ≥96% and it contains the 2*RS*,3*SR*-paclobutrazol form at ~1%. The 2*R*,3*R*-paclobutrazol enantiomer has more effective fungicidal activity than the 2*S*,3*S*-paclobutrazol enantiomer, which performs better as a plant growth regulator (Guo, 2021; Burden, 1987). Throughout this evaluation, the name paclobutrazol refers to the racemic mixture (2*RS*,3*RS*)-paclobutrazol.

Toxicokinetic studies were conducted in rats and dogs. Following a single oral low dose in rats of paclobutrazol radiolabelled on the triazole moiety, 75–87% of the administered dose (AD) was excreted within 48 hours. In male rats, 23–48% of the AD was excreted in urine and 44–64% of the AD in feces, while in female rats the urinary route was predominant, 48–64% of the AD, with 26–41% of the AD excreted in feces. Most (81–91%) of the urinary excretion occurred within 24 hours, indicating rapid absorption. The same pattern was observed in dogs following a

single oral low dose. The peak levels in the blood occurred 0.5 to 1.5 hours after dosing in dogs. The fecal excretion pattern in rats suggested, and was further confirmed in bile-cannulated animals, that most of the fecal excretion was of biliary origin and, thus, the full extent of absorption was greater than that suggested by urinary excretion. After a single oral high dose administration in rats, higher levels of radioactivity were found in urine than in feces in both sexes and excretion was slightly lower in males. Tissue levels at 48 to 96 hours following administration in rats were very low. The gastrointestinal contents accounted for most of the residual radioactivity in rats and dogs. In rats, paclobutrazol was extensively metabolized but biotransformation was limited to the tertiary butyl moiety, with no metabolism detected in the triazole or halogenated phenyl rings. The parent compound was detected in trace amounts in urine and bile at all doses, but at ~5% in feces at the high dose. The two main metabolites in urine, bile and feces were paclobutrazol diol and paclobutrazol acid, which were both excreted in conjugated and unconjugated forms. Males excreted more of the acid metabolite form while females excreted more of the diol metabolite form. A study from the published literature suggests that (2*S*,3*S*)-paclobutrazol enantiomer is preferably transformed and eliminated compared to the (2*R*,3*R*)-paclobutrazol enantiomer (Wu et al., 2015). A differential evaluation of paclobutrazol enantiomers was not performed, nor required. Considering the difference was slight, it was not considered to have a significant impact on the overall hazard assessment.

Based on the new acute toxicity studies submitted to PMRA, the technical grade active ingredient paclobutrazol was of low acute toxicity by the oral, dermal and inhalation routes of exposure in rats. It was mildly irritating to the eyes and minimally irritating to the skin of rabbits, and was negative for skin sensitization in mice according to the local lymph node assay (LLNA). The new acute oral study in rats provided an LD₅₀ of greater than 2000 mg/kg bw; however, the studies submitted previously for the original registration indicated an acute oral hazard classification of moderate toxicity for the technical grade active ingredient. There was no information to suggest that the results of the previous studies are less valid than the results of the new study. Therefore, technical paclobutrazol will continue to be reflected as moderately acutely toxic via the oral route.

Additional studies were submitted to characterize the oral acute toxicity and genotoxic potential of triazole lactic acid (CGA 205369), a metabolite of paclobutrazol. No triazole metabolites were identified from the metabolism studies in rats, but they were present in environmental fate studies. Triazole lactic acid was of low oral acute toxicity in rats. There was no evidence of genotoxicity with the metabolite triazole lactic acid in *in vitro* studies, including gene mutation assays in bacteria and mammalian cells and a clastogenicity assay in mammalian cells.

The acute toxicity of the end-use product TRIMMIT, containing paclobutrazol, was low via the oral, dermal and inhalation routes of exposure in rats. It was non-irritating to the eyes and skin of rabbits, and was negative for skin sensitization in mice according to the LLNA method.

In an acute oral neurotoxicity study in rats, no clinical signs of toxicity were observed at any dose level and there were no deaths during the study. A treatment-related decrease in mean body weight gain was noted for males from the high-dose group. Food consumption was decreased at the high-dose level in both sexes. There was no evidence of neuropathological alterations and no treatment-related selective neurotoxic effects observed in this study. In zebrafish (*Danio rerio*),

which is a surrogate model for vertebrate development, paclobutrazol produced perturbations of neurotransmitter synthesis and content through oxidative stress (Guo et al., 2022), and locomotion hyperactivity in larvae, and anxiolytic exploratory behaviour and an inhibition of innate aggressive behaviour in adults (Hussain et al., 2020; Guo et al., 2022). A published study in mice treated via gavage every two days over a 28-day period, reported variable effects on levels of different neurotransmitters in the brain (Xu and Yang, 2020). The acute neurotoxicity study in rats described above used comparable or even higher doses of paclobutrazol than those used in the mouse study and examined clinical signs as well as brain weight and brain histopathology. Other than fewer rearings observed in females, no behavioral changes, or gross/histopathological changes were observed in the brain. Additionally, the absence of any specific clinical signs of neurotoxicity and lack of effect on brain weight in short- or long-term studies in mice and rats indicated an absence of selective neurotoxicity of paclobutrazol in mammals.

In repeat-dose toxicity studies, paclobutrazol caused reductions in body weight gain and increases in liver lesions in dietary short-term and two-year studies. Increased duration of exposure did not exacerbate the effects on the liver. Paclobutrazol did not demonstrate any evidence of genotoxic potential or tumourigenicity.

The 28-day dietary range-finding toxicity studies in mice and rats submitted at the time of the initial registration of paclobutrazol were re-examined and it was confirmed that liver effects were the most sensitive endpoint for establishing NOAELs in these studies, consistent with other studies. Although the range-finding studies did not assess all the required parameters to meet the guideline, sufficient assessment of the livers were conducted to establish a NOAEL for liver effects. Liver effects are considered the most sensitive endpoints in the paclobutrazol database, in agreement with the effects observed in the database of other pesticides of this class.

In a 90-day oral (capsule) toxicity study in dogs, at the high-dose level there was an overall decrease in body weight in both sexes, as well as reduced body weight gain during the first week in males and over the entire study period in females. Liver weights were increased in high-dose males and females compared to concurrent controls. This finding in males was also associated with increased incidences of minimal hepatocyte vacuolation and minimal to slight hepatocyte fine fat deposition and slight centrilobular mononuclear cell infiltration. Plasma triglycerides and alkaline phosphatase (ALP) were increased, and albumin concentration was decreased at all time-points in both sexes. Total protein concentration was also decreased in females at week 8. At terminal sacrifice, hepatic enzymatic activity was increased, namely aminopyridine-N-demethylase (APDM) and ALP concentrations were increased in both sexes, and alanine transaminase (ALT) concentration was increased in males from the high-dose group at terminal sacrifice. Absolute and relative kidney weights were increased in both sexes. Also at the high dose, decreased testes and epididymides weights, testes and prostate size as well as absence of spermatozoa were observed. The onset of puberty in dogs is irregular and some individuals could have been at a prepubescent stage by terminal sacrifice. While a similar effect was not observed in the 1-year dog study, the difference compared to the control group in the 90-day study was potentially biologically relevant, as published studies suggest that paclobutrazol may impact endocrine sensitive tissues at high doses.

The 2-year dietary combined chronic toxicity/carcinogenicity study in rats was re-assessed for tumour incidence. It was noted that the incidence of uterine stromal polyps in females was increased in all treated groups compared to controls (10%, 10%, 14% compared to 0%). Uterine stromal polyps are benign tumours that are not uncommon in aging rats and it was also noted that there was an unusually low incidence of these polyps in the control group. From historical control data (HCD) submitted by the applicant from studies performed in the same strain of rats around the same time period, the calculated mean incidence for stromal polyps in female rats of this age is 6.7 ± 3.1 % ranging from 0 to 12%. Considering the unusually low incidence of these benign tumours in the controls, as supported by additional HCD, the absence of a treatment-related increase in uterine stromal polyps in the 18-month oncogenicity study in mice and the absence of genotoxicity in a battery of assays for paclitaxel, the benign uterine stromal polyps in the low- and mid-dose female rats were not considered treatment related and the increased incidence in high-dose females outside the historical control range was considered equivocal.

In a 2-generation dietary reproductive toxicity study in rats, there was no evidence of sensitivity of the young, reproductive toxicity, or adverse effects in endocrine tissues up to the highest dose tested. At the highest dose, adverse effects in parental animals included decreased body weight and body weight gains in both generations, increased incidences of chromodacryorrhea, thickened eyelids, and dental malocclusion in both sexes, decreased food consumption, increased liver weight with centrilobular fatty changes in the F₀ generation animals and increased cytoplasmic eosinophilia of centrilobular hepatocytes and inflammatory cell infiltration in F₀ female animals. At the same dose level, offspring toxicity consisted of marginally decreased body weights in the F₁ and F₂ generations, increased liver weights and increased incidences of chromodacryorrhea, thickened eyelids and dental malocclusion in both sexes. No treatment-related adverse effects were observed at the mid- or low-dose level.

Cleft palate was observed at the highest dose tested in one of two developmental toxicity studies in rats. Both studies showed an increased incidence of partially ossified transverse processes on the 7th cervical vertebra and an increased incidence of extra (14th) ribs in the absence of maternal toxicity. Several urogenital variations were also observed in one study. Since fetal effects were observed in both rat developmental toxicity studies in the absence of maternal toxicity, these studies provided evidence of sensitivity of the young. A published study conducted according to the same protocol used in the above studies confirmed these findings, although no sensitivity of the young was observed (Vergieva, 1998).

In one of two developmental toxicity studies in rabbits, multiple vertebral variations were observed in the fetuses at the highest dose tested, in the presence of maternal toxicity (decreased body weight and body weight gain, and two deaths). Encephalocele, a rare malformation, was also observed in one of these fetuses. In the second study, decreased body weight and increased incidence of scoliosis and flexed forepaws were observed in fetuses at the highest dose tested in the presence of maternal toxicity (decreased body weight and food consumption). At the mid-dose level, another fetus with encephalocele was observed. No HCD were available for this observation, but publicly available HCD confirmed that encephalocele is a rare observation in New Zealand white rabbit fetuses. While this effect was considered equivocal at the mid-dose and high dose levels, the toxicology reference doses provide a sufficient margin to this effect.

The same data were evaluated by foreign regulatory authorities, namely the USEPA and EFSA, and neither reported this observation as treatment-related.

Most of the information in the published literature regarding potential impacts of paclobutrazol on reproduction and development are experiments performed in an aquatic environment on zebrafish. Study protocols were designed to examine the potential to elicit gonadal effects on adult zebrafish and developmental effects on zebrafish embryos exposed to paclobutrazol. As a toxicology model, zebrafish have the potential to identify pathways of developmental toxicity due to their similarity with those of mammals (Caballero and Candiracci, 2018). However, care must be taken in extrapolating results from zebrafish to mammals, as aquatic organisms appear to be more sensitive to the effects of paclobutrazol than mammals.

In zebrafish embryos, paclobutrazol at ≥ 1 ppm in the water affected eye development by inhibiting the production of retinoic acid, damaging retinal cell division and the photoreceptors resulting in decreased eye size. This effect was attributed to the paclobutrazol-induced decreased expression of aldehyde dehydrogenase. The paclobutrazol-induced decreased eye size was partly reversed by retinoic acid (Wang et al., 2017). In the 2-generation reproductive toxicity study in rats discussed previously, no treatment-related macro- or microscopic changes were observed in the eyes of rat pups at up to 1250 ppm.

Embryonic developmental toxicity was observed in zebrafish when embryos were exposed to paclobutrazol during early stages of development. Zebrafish embryos exhibited pharyngeal arch development and skull formation defects when exposed to a high dose of paclobutrazol within 60 hours post fertilization. Furthermore, zebrafish embryos exposed to paclobutrazol at different stages exhibited different severities of effects in each tissue related to development of digestive organs (pancreas, intestine and liver) derived from embryonic endoderm (Wang et al., 2019). It was also suggested that paclobutrazol can impact the development of the heart and craniofacial cartilage in zebrafish embryos and decrease their survival and hatching rates (Yekti et al., 2014).

While in vitro studies in zebrafish embryos have identified developmental effects on various organs, the available guideline developmental toxicity studies in rats have identified non-serious skeletal variations in developing fetuses, further indicating a greater sensitivity of aquatic organisms such as the zebrafish model, to potential effects of paclobutrazol.

Given the reproduction and developmental toxicity studies were conducted according to older OECD test guidelines, additional mechanistic studies from both the registrant and published scientific literature were assessed for endocrine sensitivity. These results were considered in the overall weight of evidence (WoE) for the potential of paclobutrazol to have an impact on the mammalian endocrine system.

Mechanistic studies for endocrine activity

Paclobutrazol was negative for androgenicity and anti-androgenicity in all five androgen-dependent tissues taken at necropsy from castrated rats in the Hershberger assay, it was a positive inhibitor of both testosterone and estradiol production in H295R cells in the steroidogenesis assay, and was a positive inhibitor of aromatase in a human recombinant (CYP

19) assay. Although paclobutrazol was a positive inhibitor in both in vitro assays, the inhibition occurred at high concentrations ($\geq 1 \mu\text{M}$ and $\geq 31.6 \mu\text{M}$, for testosterone and estradiol inhibition, respectively – and at $\geq 100 \mu\text{M}$ for aromatase inhibition), indicating a low potency and non-specific effect. In the same assay, under the same conditions, the positive control substances were approximately four orders of magnitude more potent than paclobutrazol. Some published in vitro assays indicated paclobutrazol had androgen receptor antagonist activity in CHO cells (Andersen et al., 2002) and aryl hydrocarbon receptor (AhR) transactivator activity in human hepatoma cells (Long et al., 2003), again at high concentrations ($\geq 20 \mu\text{M}$ and $\geq 50 \mu\text{M}$, respectively). However, Andersen et al., (2002) also reported an absence of effect on aromatase activity in human placental microsomes (at $50 \mu\text{M}$).

Borgert et al., (2014) developed a classification system to identify substances with potential endocrine effects, and attributed a rank of 1–3 to the endpoints used in the verification of the hypothesis (1 being the most relevant to the hypothesis). In this system, the results from a Hershberger assay (rank 1) are critical to the characterization of a substance suspected of having anti-androgenic activities, as it is an in vivo test that is consistent and reproducible, and is representative of organism-level effects. Confidence that the chemical has anti-androgenic potential increases as the number of significantly affected organs increases, and decreases as fewer endpoints respond (Borgert et al., 2014). Based on the Borgert et al., (2014) ranking system, paclobutrazol was a weak androgen receptor antagonist (rank 2 for in vitro androgen receptor assay and rank 3 for in vitro steroidogenesis assay). More importantly, it was clearly negative for the rank 1 evidence (in other words, in vivo Hershberger assay).

The USEPA requires a statistically significant decrease in two or more endpoints in the Hershberger assay to suggest anti-androgenic activity (USEPA, 2011). As noted above, paclobutrazol was negative for all five endpoints in the Hershberger assay. While some effects observed in the available in vivo toxicity studies indicate potential anti-androgenic activity (decreased testes and epididymides weights, decreased testes and prostate size, and absence of spermatozoa in a short-term toxicity study in dogs, and small focus of atrophic tubules in one testis observed in a short-term toxicity study in rats), these effects were observed at the high dose level only in both studies and were not observed in longer term studies.

The USEPA screened (Tier 1 screening) paclobutrazol as a potential candidate for the USEPA Endocrine Disruptor Screening Program (EDSP). ToxCast assays were used to inform on estrogen and androgen bioactivity. The overall weight of evidence showed it did not have significant estrogen receptor bioactivity (based on $\text{EC}_{50} > 100 \mu\text{M}$ in in vitro assays), but was identified as having androgen receptor bioactivity. Paclobutrazol was included in List 2 of chemicals for screening, but no data has been requested or generated for List 2 chemicals to date.

Several published reviews, that include summaries from various regulatory authorities, suggest that several triazole pesticides have the potential to impact steroid hormone homeostasis (Sanderson, 2006; Goetz et al., 2007; Kjærstad et al., 2010a, Kjærstad et al., 2010b; Goetz and Dix, 2009; Draskau et al., 2021) and affect fetal development (Zhou et al., 2016). Although these published reports indicated no major endocrine flags in mammals treated with paclobutrazol, studies described above indicated that paclobutrazol has some anti-androgenic activity at high dose/concentrations. A comparison of paclobutrazol with several other triazoles/conazoles was

conducted based on the measurements of endocrine sensitive endpoints tested with in silico prediction/simulation tools and in vitro assays.

Endocrine Disruptome (Kolšek et al., 2014) is a computational tool that has been used to predict the possible effects of triazole fungicides on the human endocrine system. It considers the molecular docking approach based on the AutoDock Vina algorithm (Trott and Olson, 2010) implemented for twelve human nuclear receptors as follows: androgen receptor (AR), estrogen receptors alpha and beta (ER alpha and ER beta), glucocorticoid receptor (GR), liver X receptors alpha and beta (LXR alpha and LXR beta), peroxisome proliferator activated receptors alpha (PPAR alpha), beta/delta (PPAR beta), and gamma (PPAR gamma), retinoid X receptor alpha (RXR alpha), and thyroid receptors alpha (TR alpha) and beta (TR beta). The investigated triazole compounds were docked to the structures of these human nuclear receptors, and a docking score of the compound on every receptor structure was computed and further used to classify the binding of investigated ligand to the nuclear receptors (Kolšek et al., 2014).

Predictions obtained using the Endocrine Disruptome computational tool reflected that investigated triazole fungicides can influence the activity of some of the human nuclear receptors (Gridan et al., 2019). All investigated triazole fungicides (cyproconazole, flutriafol, triticonazole, epoxiconazole, tetraconazole, triadimenol, prothioconazole, metconazole and paclobutrazol) are predicted as having antagonistic effects on the androgen receptor. Based on the predictions, paclobutrazol is most likely to interact with the androgen receptor and less likely to interact with all the other endocrine receptors tested, including the estrogen receptor, consistent with the reported in vitro findings available from the scientific literature.

A potency ranking of several triazoles/conazoles including paclobutrazol based on their effects on endocrine sensitive endpoints as reported in the PMRA database and/or the publicly available peer-reviewed scientific literature is summarized below.

In a published study, in vitro endpoints for several conazoles were compared for their respective potency to impact endocrine sensitive endpoints. These endpoints were androgen receptor antagonism, estrogen receptor antagonism, AhR transactivation and four aspects of steroidogenesis (estradiol, testosterone and progesterone production, and aromatase inhibition) (Dreisig et al., 2013). Although paclobutrazol showed positive results for androgen receptor antagonism and/or disruption of steroidogenesis, it had a lower potential to impact endocrine sensitive endpoints than other triazoles/conazoles (ketoconazole, epoxiconazole, tebuconazole, propiconazole, prochloraz [imidazole], difenoconazole, triticonazole, hexaconazole, triadimefon, and triadimefol). This is reflected by the high concentrations (LOECs and IC₅₀s) required to obtain a positive response and places paclobutrazol among the least potent of the triazoles/conazoles presented.

While paclobutrazol shares a similar profile for embryotoxicity with that of propiconazole, another triazole pesticide, the latter was more potent than paclobutrazol for more endocrine sensitive endpoints (Dreisig et al., 2013; Unpublished studies). An increase in the measurement of anogenital distance (AGD) is a sensitive marker of anti-androgenic effects of a xenobiotic (Mylchreest et al., 2000; McIntyre et al., 2001; Wolf et al., 2004). While there were no AGD measurements available for paclobutrazol, the toxicology profiles for other conazoles (including

tebuconazole, propiconazole, uniconazole-P, ipconazole, metconazole, difenoconazole, epoxyconazole, mefentrifluconazole, prothioconazole, and tetraconazole) indicated that effects on AGD and/or developmental and reproductive effects occurred at higher doses than liver effects. As previously noted, the NOAEL for liver effects is used to set reference doses for health risk assessment, which is considered protective of endocrine findings. The overall concern for the lack of AGD measurements in studies with paclobutrazol is tempered by the fact that liver toxicity NOAELs are well established for paclobutrazol. *In silico*, *in vitro* and embryotoxicity information on paclobutrazol suggest that paclobutrazol is among the least potent of the triazoles/conazoles for endocrine activity and embryotoxicity.

Few published studies examine the effects of paclobutrazol on the thyroid, however, any effects that were identified are not consistent between studies or species, namely rats and zebrafish. In a subchronic (28-day) oral gavage toxicity study in rats (Liu et al., 2022), decreased L-thyroxine (T4) levels were observed in male animals and slight inflammation of the thyroid follicular cells was observed in female rats at ≥ 32.5 mg/kg bw/day, the lowest dose tested. Although the changes were slight, L-triiodothyronine (T3) levels were also decreased in both sexes at this dose. In comparison, in a supplemental 90-day dietary toxicity study in rats, no histopathological changes were observed in the thyroid gland at the highest dose tested (93/107 mg/kg bw/day in ♂/♀). Liu et al., (2022) reported that in both sexes at the high dose (260 mg/kg bw/day), there were modulations of lipid biomarkers indicative of effects on the thyroid (namely modulation of phosphatidyl glycerols, phosphatidylserine, phospholipid acid, phosphatidylethanolamines). Another study using high doses of paclobutrazol (200 mg/kg bw and 500 mg/kg bw) identified the insulin growth factor (IGF) pathway as one of the targets of paclobutrazol by using network pharmacology, which involves innovative methods combining biology, pharmacology and computational simulations (Yue et al., 2022). Conversely, the opposite effects, namely increased T4 and increased levels of T3, were observed in zebrafish embryos along with increased levels of oxidation and apoptosis biomarkers. Also in this study, thyroid stimulating hormone (TSH) mRNA levels were increased at the lowest dose tested only (Wang et al., 2020). The relevance of this finding to treatment is questionable when considering the broader weight of evidence across the paclobutrazol database and the inherent uncertainty introduced by an extrapolation from zebrafish to mammals.

For example, in the available mammalian studies, while hormone levels were not measured, no down-stream (apical) treatment-related effects were observed in the short-term dietary toxicity studies in mice and rats, 2-generation reproductive toxicity study in parental animals, or 2-year combined chronic toxicity/carcinogenicity study that could be attributed to thyroid toxicity.

Overall WoE and conclusions:

Considering the entirety of the evidence from the available data, including applicant-submitted study reports, data from the open scientific literature on paclobutrazol and other triazoles/conazoles, data from the Endocrine Disruptome tool to characterize triazole interaction with human nuclear receptors, and the information from ToxCast screening assays, there is evidence that paclobutrazol has mild anti-androgenic activity under certain conditions. In determining appropriate uncertainty factors for health risk assessments of paclobutrazol, the following lines of evidence were considered:

- 1) Where suspected endocrine sensitive effects were observed in the guideline and supplemental paclobutrazol toxicity studies or in vivo studies from the literature, these effects were observed at dose levels at least threefold higher than the NOAELs selected as a point of departure to set reference values for the human health risk assessment.
- 2) The guideline rat in vivo Hershberger assay, considered to be the most important test for androgenic/anti-androgenic activity, performed with paclobutrazol was negative.
- 3) No major endocrine flags were noted from the guideline and supplemental toxicity studies. The sex ratio was not affected in the DART studies. The 28-day dietary toxicity range-finding study in mice, the 90-day dietary toxicity study in rats, or the 2-year rat combined chronic toxicity/carcinogenicity study did not show effects on the thyroid gland or reproductive organs assessed. More importantly, the reproductive organs in the 2-generation reproductive toxicity study in rats were also not affected.
- 4) Positive results observed in an androgen receptor, a steroidogenesis inhibitor, or an aromatase inhibitor assay, occurred only at high concentrations of paclobutrazol, thus showing low potency.
- 5) The most sensitive endocrine effects were noted in a non-mammalian species (zebrafish), for which the extrapolation to mammals is uncertain and must be interpreted with caution.
- 6) Available in vitro assays and in silico predictions, including predictions from the Endocrine Disruptome tool, characterized paclobutrazol as a low potency androgen receptor ligand and inhibitor compared to structural analogues and other conazoles/triazoles having an impact on the endocrine system.
- 7) Compared to several conazoles, paclobutrazol is much less potent conazole pesticide with respect to effects on endocrine sensitive endpoints both in vitro and in vivo.
- 8) Liver toxicity represents the most sensitive endpoint in the database for paclobutrazol. The liver toxicity is well characterized for paclobutrazol and evidence from structural analogues with similar toxicity profiles suggest that endocrine sensitive endpoints are likely to be less sensitive than liver toxicity endpoints.
- 9) Sensitivity of the young was observed in the guideline and supplemental toxicity studies for paclobutrazol and consequently a threefold PCPA (*Pest Control Products Act*) factor will be retained when using a developmental toxicity endpoint as a point of departure for the human risk assessment (as further detailed below).

Based on the weight of evidence, the overall concern for database uncertainties is low and the application of an additional UF_{DB} is not required, as there is an adequate margin to the critical NOAELs selected as points of departure when setting reference values for the human health risk assessment.

The identification of the metabolite mentioned in the text is presented in Appendix I, Table 2. Results of the toxicology studies conducted on laboratory animals with paclobutrazol submitted by the applicant (including new studies as well as previously submitted studies that were revisited) as well as data reported from the open scientific literature were also summarized in Appendix I, Table 3. The toxicology studies of the paclobutrazol associated end-use product, TRIMMIT are summarized in Appendix I, Table 4. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 5.

3.1.2 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.⁵

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies including gavage developmental toxicity studies in rats and rabbits and a dietary 2-generation reproductive toxicity study in rats. There were some uncertainties related to the lack of dosing during a critical window of development in the developmental toxicity studies, limited evaluations of some endocrine sensitive parameters in both the reproductive and developmental toxicity studies, and the identified potential for endocrine-related impairments from the open peer reviewed scientific literature. However, as discussed in the preceding sections of the document, it was determined based on the WoE that the application of an additional database uncertainty factor is not required to provide an adequate margin of exposure to the critical NOAELs selected as points of departure for the human risk assessment.

With respect to concerns regarding potential prenatal and postnatal toxicity, evidence of sensitivity of the young was observed in the developmental toxicity study in rats. Skeletal variations (an increased incidence of rudimentary 14th ribs and increased incidences of partially unossified transverse processes on the 7th cervical vertebra) were observed in the absence of maternal toxicity. These variations are not considered serious in nature and the degree of concern is low. In the developmental toxicity studies in rabbits, fetuses showed body weight effects and musculo-skeletal variations at a maternally toxic dose level (body weight effects, decreased food consumption and deaths). Equivocal evidence of sensitivity of the young was observed in the form of two observations of a rare malformation (encephalocele) in rabbits. One occurred at the high dose in a supplemental study in the presence of maternal toxicity and the other at the mid-dose in a guideline developmental toxicity study in rabbits, in the absence of maternal toxicity. The PMRA considered the incidence of encephalocele to be equivocal, and the endpoints selected for human risk assessment will provide a margin of exposure that will protect the population of concern. There was no evidence of sensitivity of the young in the rat 2-generation reproductive toxicity study. It is noted that in the rat developmental toxicity study, a malformation (cleft palate), considered to be a serious endpoint, was observed at the highest dose tested. However, this effect was tempered by the presence of maternal toxicity at this dose.

Overall, effects in the young that were observed in the absence of maternal toxicity in the developmental toxicity studies in rats were not serious in nature and therefore, the retention of a threefold PCPA factor for sensitivity of the young is required when a developmental endpoint is selected as the point of departure for the human risk assessment. The toxicology reference values

⁵ SPN2008-01. The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides.

selected for risk assessment provide an intrinsic margin to other endpoints in the young, some of which were serious in nature. For exposure scenarios involving other subpopulations, including children, the risk was considered well-characterized and the PCPA factor is reduced to onefold.

3.2 Toxicology reference values

3.2.1 Route and duration of exposure

Exposure to paclobutrazol is characterized as short-to intermediate-term in duration predominantly by the dermal and inhalation routes for chemical handlers, and through the dermal route for postapplication workers. For golfers, contact with treated turf should primarily occur via the dermal route of exposure. The duration of exposure is expected to be of short- to intermediate-term in duration.

3.2.2 Occupational and residential toxicology reference values

Short- and intermediate-term dermal exposure

Adults and youth

For short- and intermediate-term dermal residential (golfing) and occupational exposures, the developmental NOAEL of 10 mg/kg bw/day from the developmental toxicity study in rats was selected for risk assessment, based on an increased incidence of skeletal variations at the LOAEL of 40 mg/kg bw/day. A repeat-dose dermal toxicity study was not available, thus necessitating the use of an oral study for risk assessment.

For residential scenarios, the target margin of exposure (MOE) for this endpoint is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a PCPA factor of threefold for the reasons outlined in section 3.1.2. The selection of this study and target MOE is protective of these populations, including the unborn children of exposed women.

For occupational scenarios, the target MOE for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of concerns regarding prenatal toxicity, as outlined in the *Pest Control Products Act* Hazard Characterization section, an additional threefold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females 13–49 years of age.

Children

For short- and intermediate-term dermal residential (golfing) exposures for children, the NOAEL for liver toxicity of 4.6 mg/kg bw/day from the 28-day dietary range-finding toxicity study in rats was selected for risk assessment. This NOAEL is based on an increased incidence of liver hypertrophy with midzonal macrovacuolation, increased liver weight and increased cholesterol at the LOAEL of 87 mg/kg bw/day. The liver weight and histopathology results from the interim sacrifice of the 2-year combined chronic toxicity/carcinogenicity study in rats confirmed the lack

of durational effects on the liver. Consequently, the use of a NOAEL from a short-term study as a point of departure for an intermediate-term exposure scenario was considered acceptable. A repeat-dose dermal toxicity study was not available, thus necessitating the use of an oral toxicity study for risk assessment.

For residential scenarios for children, the target MOE for this endpoint is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As the endpoint used for exposure scenarios concerning the general population (prenatal and developmental effects) was not relevant to children, the selection of this study and target MOE is considered to be protective of this population, and as outlined in section 3.1.2, the PCPA factor was reduced to onefold.

Short- and intermediate-term inhalation exposure (adults)

For short- and intermediate-term occupational exposures via the inhalation route, the developmental NOAEL of 10 mg/kg bw/day from the developmental toxicity study in rats was selected for risk assessment, based on an increased incidence of skeletal variations at the LOAEL of 40 mg/kg bw/day. A repeat-dose inhalation toxicity study was not available, thus necessitating the use of an oral toxicity study for risk assessment.

For occupational scenarios, the target MOE for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of concerns regarding prenatal toxicity, as outlined in the *Pest Control Products Act* hazard characterization section, an additional threefold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females 13-49 years of age.

3.2.3 Acute Reference Dose (ARfD)

3.2.3.1 Acute Reference Dose for general population (excluding females 13–49 years of age)

To estimate acute dietary risk for the general population (excluding females 13–49 years of age), the acute oral (gavage) neurotoxicity study in rats with a NOAEL of 30 mg/kg bw was selected for risk assessment. At the LOAEL of 150 mg/kg bw, decreased rearing counts was observed in females on Day 1 at the time of peak effect. This effect was the result of a single exposure and therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section 3.1.2, the PCPA factor was reduced to onefold. The composite assessment factor (CAF) is thus 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{30 \text{ mg/kg bw}}{100} = 0.3 \text{ mg/kg bw of paclobutrazol}$$

3.2.3.2 Acute Reference Dose (ARfD) for females 13–49 years of age

To estimate acute dietary risk in females of 13–49 years of age, the developmental toxicity studies in rats with a developmental NOAEL of 10 mg/kg bw/day, was selected for the risk assessment. At the LOAEL of 40 mg/kg bw/day, skeletal variations were observed in the absence of maternal toxicity. These effects may have been the result of a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* hazard characterization section, the PCPA factor was reduced to threefold. Thus, the CAF is 300.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{10 \text{ mg/kg bw}}{300} = 0.03 \text{ mg/kg bw of paclobutrazol}$$

This ARfD provides a sufficient margin of exposure for developmental toxicity in rats, 333 to the NOAEL for skeletal variations and 3333 to the NOAEL for cleft palate, and a margin of 2500 (skeletal variations) and 833 (equivocal encephalocele) to the NOAEL for developmental toxicity in the rabbit, and is thus considered protective of pregnant women and their fetuses.

3.2.4 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 2.1 mg/kg bw/day from the 2-year combined chronic/carcinogenicity study in rats was selected for risk assessment, based on the increased incidence of liver lesions (hypertrophy and steatosis) and decreased body weight gain at the LOAEL of 11 mg/kg bw/day. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* hazard characterization section, the PCPA factor was reduced to onefold. The CAF is thus 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2.1 \text{ mg/kg bw/day}}{100} = 0.02 \text{ mg/kg bw/day of paclobutrazol}$$

The ADI provides a margin of 500 to the NOAEL for the developmental toxicity study in rats (5000 to the NOAEL for cleft palate), and a margin of 3750 (skeletal variations) and 1250 (equivocal encephalocele) to the NOAELs for the effects that were observed in the developmental toxicity study in rabbits. It also provides a margin of 705 to the NOAEL for the equivocal tumourigenicity observed in female rats in the 24-month dietary chronic toxicity/oncogenicity study.

3.2.5 Cancer assessment

As previously discussed, a slight increase in the incidence of uterine stromal polyps in females in the rat 2-year chronic dietary toxicity/oncogenicity study with paclobutrazol was considered

equivocal based on the weight of evidence. Overall, the toxicology reference values selected for the non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of paclobutrazol.

3.2.6 Aggregate toxicology reference values

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (drinking water and diet), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). Short- to intermediate-term aggregate exposure to paclobutrazol may be comprised of drinking water and residential (golfing) exposure via the dermal route (children, youth and adults).

The toxicology endpoint selected as a point of departure for aggregation for all populations, except children, was the increased incidence of skeletal variations. For the oral and dermal routes, the developmental NOAEL of 10 mg/kg bw/day from the developmental toxicity study in rats was selected with a target MOE of 300. The PCPA factor for this point of departure was threefold as set out in the *Pest Control Products Act* hazard characterization section.

The toxicology endpoint selected as a point of departure for aggregation for children was liver toxicity. For the oral and dermal routes, the NOAEL for liver toxicity of 4.6 mg/kg bw/day from the 28-day dietary range-finding toxicity in rats was selected with a target MOE of 100. The PCPA factor for this point of departure was onefold as set out in the *Pest Control Products Act* hazard characterization section.

3.3 Dermal absorption

A rat in vivo dermal absorption study for paclobutrazol was reviewed previously (PRVD2013-04). Based on the data presented in the study, a dermal absorption value of 19.3% was selected for the risk assessment of paclobutrazol end-use products. This value is applicable for the occupational and residential risk assessments of TRIMMIT which contains the same source of active ingredient, Paclobutrazol Technical (Reg. No. 24198) and is the same formulation type (suspension concentrate) as the formulation used in the dermal absorption study.

3.4 Occupational and residential exposure assessment

3.4.1 Acute hazards of end-use product and mitigation measures

3.4.1.1 TRIMMIT

The acute hazard assessment indicated that TRIMMIT (Paclobutrazol SC (A8164F) (23.5% a.i.)) is of low acute toxicity by the oral, dermal, and inhalation routes in the rat. It is not irritating to the eyes and skin of rabbits. It is not a skin sensitizer in mice using the LLNA method.

Based on these low acute hazards, and no hazard signal words required on the label, no additional personal protective equipment (PPE) is triggered for workers during mixing, loading, application, clean-up and repair. The PPE on the label is as follows: wear a long-sleeved shirt,

long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair. Gloves are not required during application within a closed cab.

3.4.2 Occupational exposure and risk assessment

3.4.2.1 Mixer, loader and applicator exposure and risk assessment

Individuals have potential for exposure to paclobutrazol during mixing, loading, application, clean-up and repair. Dermal and inhalation exposure estimates were generated from the Agricultural Handlers Exposure Task Force (AHETF) database, the Outdoor Residential Task Force (ORETF) database and the Pesticide Handlers Exposure Database (PHED, v1.1) for mixers, loaders and applicators applying TRIMMIT to golf course turf using a groundboom sprayer, a turf gun sprayer or a backpack sprayer. The exposure estimates are based on handlers wearing a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair (Appendix I, Table 6).

Dermal exposure was estimated by coupling the unit exposure values for the appropriate exposure scenario with 19.3% dermal absorption value (PRVD2013-04) and the amount of product handled per day, which was derived from the maximum application rate, the standard area treated per day values for each equipment and spray volume specified on the label for handheld equipment. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day and 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Dermal and inhalation unit exposure values were combined, since the dermal and inhalation reference values are based on the same study and thus on the same adverse toxicological effects. Total daily exposure estimates were compared to the selected toxicological reference value to obtain the margin of exposure (MOE); the target MOE is 300. Calculated MOEs are greater than the target MOE of 300 for all chemical handler scenarios for golf course turf and are therefore not of health concern (Appendix I, Table 7).

Considering both the acute toxicity and the risk assessment, the label directions for TRIMMIT, which include the personal protective equipment, are adequate to protect workers.

3.4.2.2 Postapplication exposure and risk assessment

There is potential for exposure to workers entering areas treated with TRIMMIT to complete tasks such as transplanting, harvesting, mowing, watering, scouting and hand pruning. Given the nature of activities performed, exposure should be primarily via the dermal route based on dermal contact with treated turf. Inhalation exposure is not expected as paclobutrazol is considered non-volatile with a vapour pressure of 1.7×10^{-9} kPa at 20°C, which is less than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product for outdoor uses [1×10^{-4} kPa (7.5×10^{-4} mm Hg) at 20-30° C]. As such, a quantitative inhalation risk assessment is not required and the restricted-entry interval of until residues have dried is acceptable to allow suspended particles to settle and vapours to dissipate.

A postapplication dermal exposure risk assessment was conducted for each postapplication activity with the number of applications possible at the maximum rate. A turf transferable residue (TTR) study was not submitted for paclobutrazol. Therefore, exposure during each postapplication activity on treated turf was estimated with the day zero standard TTR of 1% of the maximum application rate dislodged from treated turf, the shortest re-treatment interval of 7 days for the maximum number of applications (three) and with the 10% standard dissipation rate per day, using ARTF transfer coefficients (TCs) values and the standard exposure duration of 8 hours workday. The MOEs were calculated using the toxicological reference value specified for paclobutrazol. Calculated MOEs for all postapplication activities on treated turf are greater than the target MOE of 300 on Day 0, after the maximum number of applications, and are therefore not of health concern (Appendix I, Table 8). Therefore, the proposed restricted-entry interval of until sprays have dried is acceptable for workers entering treated golf course turf.

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk assessment

TRIMMIT is not a domestic class product and is not permitted for use in residential settings; therefore, a residential handler exposure assessment is not required.

3.4.3.2 Postapplication exposure and risk assessment

TRIMMIT is proposed for use on golf course turf which includes residential/recreational areas. As such, a postapplication residential exposure and risk assessment is required.

3.4.3.2.1 Golf courses treated with TRIMMIT

Since TRIMMIT is for use on golf course turf, there is the potential for postapplication residential/ recreational exposure to paclobutrazol for golfers (adults, youth and children 6 to <11 years of age) entering treated turf areas of golf courses. The primary route of exposure for these individuals is through the dermal route for a short- to intermediate-term duration.

Dermal exposure to golfers is estimated by coupling the turf transferable residue (TTR) value with the activity specific transfer coefficient based on ARTF studies data from the 2012 United States Environmental Protection Agency Residential Standard Operating Procedures. TTR was calculated by using 1% of the maximum application rate with the shortest re-treatment interval of 7 days with the maximum number of applications (three), and the 10% dissipation rate per day. Exposure estimates after correcting for the dermal absorption of 19.3% were compared to the selected toxicological reference values for adults, youth and children 6 to <11 years of age to obtain the MOEs; the target MOE is 300 for adults and youth, and 100 for children 6 to <11 years of age. The calculated MOEs for dermal exposure are presented in Appendix I, Table 9. The estimated MOEs were all greater than the target MOE for each population. Therefore, health risks are not of concern for golfers playing on treated golf courses after the sprays have dried.

3.4.4 Bystander exposure and risk assessment

Bystander exposure is considered negligible as application is limited to golf courses only when there is low risk of drift to areas of human habitation and human activity (other than golf courses) such as parks, school grounds, and playing fields, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

Therefore, bystander exposure and risk are not of health concern since the potential for drift is expected to be minimal.

3.5 Dietary exposure and risk assessment

3.5.1 Exposure from residues in food of plant and animal origin

Residue data for paclobutrazol in plant and animal foodstuffs are not required as there are no food or feed uses associated with paclobutrazol with either the registered uses on nursery and greenhouse ornamentals, or with the proposed use on golf course turf.

3.5.2 Exposure from drinking water

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 estimated environmental concentrations (EECs) are intended to screen out pesticides that are not expected to pose any concern related to drinking water sources (groundwater and surface water). EECs for paclobutrazol in drinking water sources were calculated using the Pesticide in Water Calculator (PWC) version 2.0.

For surface water, PWC calculates the amount of pesticide entering a water body by runoff and spray drift, and the subsequent degradation of the pesticide in the water system. Groundwater EECs are calculated by simulating leaching through a layered soil profile and reporting the average concentration in the top 1-metre of a water table for several scenarios representing different regions of Canada. All scenarios are run for 50 years. Only the highest EECs from across the groundwater scenarios are reported.

The use pattern selected for the Level 1 drinking water modelling was intended to represent all proposed uses: 1 application of 172.5 g a.i./ha followed by 3 applications of 280 g a.i./ha, with a 7-day re-application interval. The EECs were modelled as a combined residue of paclobutrazol with the transformation products CGA 144907 and NOA 457654, the latter of which represented the tautomer pair hydroxyl-triazole and triazolone. The major fate inputs for the drinking water modelling and the Level 1 drinking water EECs are presented in Tables 10 and 11, respectively, of Appendix I.

Level 1 surface water EECs were not refined. The Level 1 groundwater EECs were refined at Level 2 using more specific, but still conservative, inputs with respect to application rate, application timing, and geographic scenario. The groundwater EECs cover all regions of Canada but are modified to represent turf only. A parent-daughter-granddaughter approach was used where the EECs for paclobutrazol and CGA 149907 were calculated separately from those for

NOA 457654. The refined use pattern and groundwater EECs are presented in Appendix I, Table 12. Given the refined modelling, the groundwater EECs do not allow for future use expansion into other crops and cover only single turf ground-spray applications of no more than 280 g a.i./ha with an interval of 7 days and cumulative yearly applications of no more than 1012.5 g a.i./ha.

3.5.3 Dietary risk assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 4.02, 05-10-c), which incorporates consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the years 2005–2010.

3.5.3.1 Acute dietary exposure results and characterization

The acute dietary exposure (drinking water alone, refined Level 1) is estimated to be 16% (0.005 mg/kg bw/day)] of the ARfD for females 13–49 years old (95th percentile, deterministic) and is considered acceptable (Appendix I, Table 13).

3.5.3.2 Chronic dietary exposure results and characterization

The chronic dietary exposure to paclobutrazol from drinking water alone (refined, Level 1) is estimated to be 7.9% (0.002 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants (< 1 year) at 29.4% (0.006 mg/kg bw/day) of the ADI, which is not of health concern (Appendix I, Table 13).

3.6 Aggregate exposure and risk assessment

There is potential for exposure to paclobutrazol for individuals via different routes of exposure concurrently. As such, for golfers, the chronic dietary exposure values from drinking water for specific subpopulations were aggregated with the residential/recreational dermal exposure values. Aggregate exposure estimates were compared to the aggregate toxicological reference values to obtain the MOEs; the target MOE is 300 for adults and youth, and 100 for children 6 to <11 years of age. The results of the aggregate risk assessment are presented in Appendix I, Table 14. The calculated MOEs were greater than the target MOE for each subpopulation, as such, there are no health risks of concern, and the golfers can enter the treated golf course once the sprays have dried.

3.7 Cumulative assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of mammalian toxicity. A Science Policy Note (SPN2018-02) entitled Cumulative Health Risk Assessment Framework describes the framework and methodology that Health Canada's PMRA uses for assessing the cumulative health effects of pesticides. Consistent with the approach outlined in SPN2018-02, Health Canada followed a weight-of-evidence approach to explore the potential for a common mechanism of mammalian toxicity for this active ingredient with other pesticides. Health Canada considered chemicals

within the same class of pesticides, which takes into consideration similarities with respect to structure and pesticidal mode of action.

In addition to identifying a common mechanism of toxicity, other important considerations must be explored as part of the process in determining the need to conduct a cumulative risk assessment (CRA). These considerations include defining and comparing the use patterns of the different chemicals belonging to a class of pesticides with a common mechanism of toxicity to determine if the same uses are registered, whether the uses are wide-ranging, if there are residential uses, the potential routes of exposure and the potential for co-occurrence of exposure to the different chemicals. There are no food uses associated with paclobutrazol. As no food uses are proposed for paclobutrazol, no dietary exposure from food commodities is anticipated. Accordingly, the potential contribution of paclobutrazol to the cumulative exposure of the conazole/triazole class would be through non-dietary exposure and drinking water exposure only.

Paclobutrazol is part of a group of plant growth regulators that acts as a gibberellin biosynthesis inhibitor. Other gibberellin biosynthesis inhibitors of the same class that are known to target the inhibition of gibberellic acid are registered in Canada (prohexadione-calcium, trinexapac-ethyl); however, the toxicological effects following exposure to this class of plant growth regulators are considered indicative of more generalized toxicity, and a common mechanism of mammalian toxicity has not been identified. Paclobutrazol is also part of the conazole class and shares fungicidal activities and structural similarities with other fungicides that contain a triazole moiety (for example, propiconazole, tebuconazole, difenoconazole, triticonazole, uniconazole-p, triadimefon, triadimenol, hexaconazole, metconazole). As a result of these structural similarities, conazole fungicides share common metabolites including 1,2,4-triazole and triazole conjugates.

Canadians may be exposed to these pesticides and pesticide metabolites through their diet, therefore, Health Canada examined the toxicology databases of these active ingredients and compared apical endpoints among the available toxicity studies. Variable toxicological responses are found for conazoles including: hepatotoxicity and hepatocarcinogenicity in mice, thyroid tumours in rats, as well as developmental, reproductive, and neurological effects in rodents. No clear common mechanism for toxicity has been confirmed on which to base a cumulative assessment for any of these effects for the conazole active ingredients. Furthermore, USEPA's most recent dietary (food and drinking water) assessment of the common triazole metabolites (USEPA, 2022) from direct exposure to the metabolites, as well as indirect exposure resulting from consumption of parent conazole fungicides followed by *in vivo* conversion to the metabolites, showed no health risks of concern. Combined non-dietary (including dermal, hand-to-mouth, object-to-mouth and soil ingestion) and dietary exposures also showed no health risks of concern.

3.8 Maximum residue limits

Not applicable as there are no food uses associated with paclobutrazol with either the registered uses on nursery and greenhouse ornamentals, or with the proposed use on golf course turf.

3.8.1 Health incident reports

As of 8 June 2023, the PMRA has received one human incident involving the active ingredient paclobutrazol. The incident was considered to be unlikely related to the reported exposure to paclobutrazol. The symptom as experienced by the individual (difficulty breathing) is not typical for the reported product when taking into consideration the reported route of product exposure (pesticide spill on hands). Additionally, the details surrounding the timing of symptom onset relative to paclobutrazol exposure were not clear.

The paclobutrazol product, Trimmit Plant Growth Regulator, contains precautionary statements to minimize inhalation exposure in mixers, loaders, and applicators.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

The environmental fate parameters for paclobutrazol and its major transformation products (TPs) are provided in Appendix I, Table 15. A summary of the major transformation products for paclobutrazol is provided in Appendix I, Table 16.

Abiotic processes are not expected to be important routes of dissipation for paclobutrazol in the environment. Paclobutrazol does not undergo significant hydrolysis or phototransformation. Volatilization is not expected to be an important route of dissipation for paclobutrazol based on its vapour pressure and Henry's law constant values.

Paclobutrazol is classified as slightly persistent to persistent in aerobic soils and persistent in anaerobic soils. Biotransformation in aerobic soils is the main route of dissipation in the environment, forming two major transformation products: CGA 149907 and NOA 457654. In soil laboratory studies conducted with paclobutrazol, CGA 149907 and NOA 457654 were observed to be more persistent than paclobutrazol. In contrast, these transformation products were observed to be non-persistent to moderately persistent in studies in which they were used as starting materials. The reason for this difference in persistence is uncertain. Depending on soil type, aerobic biotransformation of paclobutrazol may also result in large amounts of residues that are strongly bound to soil, and mineralization to CO₂.

In the field, paclobutrazol is slightly to moderately persistent. Carryover between growing seasons is not a concern. Considering the results of laboratory studies (K_{oc} values, soil column leaching), multi-criteria assessments (the criteria of Cohen et al. (1984) and Groundwater Ubiquity Scores (Appendix I, Table 17)), groundwater modelling, and field studies, paclobutrazol and its transformation products have the potential to be mobile in soil and are likely to leach to groundwater. A precautionary label statement is required that instructs users to avoid using TRIMMIT in areas more conducive to leaching (in other words, where the soils are permeable and particularly where the water table is shallow).

Paclobutrazol is persistent in aerobic and anaerobic aquatic systems, where it is expected to partition rapidly from water to sediment. Large amounts of strongly bound residues may form in

some sediments. Based on its bioconcentration factor, it is not likely to accumulate in aquatic organisms.

4.2 Environmental risk characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. The EECs used in the risk assessment and their calculation details are presented in Appendix I, Tables 18 (all organisms except birds and mammals) and 21 (birds and mammals). Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Acute and chronic ecotoxicological data for non-target terrestrial, freshwater and marine organisms are summarized in Appendix I, Table 19. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level). Toxicity endpoints used in the risk assessment and their associated uncertainty factors are in Appendix I, Tables 20 and 21.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that pose negligible risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value ($RQ = \text{exposure}/\text{toxicity}$), and the risk quotient is then compared to the level of concern (LOC = 0.4 for acute risk to pollinators, 2 for glass plate studies using the standard beneficial arthropod test species *Typhlodromus pyri* and *Aphidius rhopalosiphi*, and 1 in all other cases). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary.

If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to terrestrial organisms

TRIMMIT is applied as a foliar spray to golf course turf and grassy weeds. Terrestrial organisms, such as earthworms, bees, birds, mammals and terrestrial vascular plants may be exposed to paclobutrazol through direct contact with spray or spray drift, contact with sprayed surfaces, or from ingestion of contaminated food. A risk assessment for paclobutrazol and its major transformation products was performed based on available toxicity data for earthworms, bees, birds, mammals, and terrestrial plants. Toxicity data for the major transformation products CGA 149907 and NOA 457654 was available only for earthworms.

Earthworms and bees

Earthworms may be exposed to paclobutrazol in soil when it is applied to turf. Foraging bees may be exposed to spray droplets during application (contact exposure) or through the ingestion of pollen and nectar contaminated with paclobutrazol (oral exposure). Additionally, bee brood may be exposed to paclobutrazol if foraging bees bring contaminated pollen and nectar back to the hive. The screening level risk quotients (≤ 0.28) for earthworms and bees were below the relevant levels of concern (Appendix I, Table 20). Also, turf is not a bee-attractive plant; therefore, the use of paclobutrazol on turf is not expected to result in exposure of bees as there is low potential for turf to be visited by pollinators. The risks to earthworms and bees from the use of TRIMMIT are negligible.

Birds and wild mammals

Birds and small wild mammals may be exposed to paclobutrazol through ingestion of contaminated food items sprayed with paclobutrazol. The screening level risk assessment assumed:

- The maximum paclobutrazol residue concentrations in food items;
- A diet composed entirely (100%) of a particular food (for example, insects or short grass); and,
- The feeding guild assumed to have the highest exposure for each animal weight category.

The results of the screening level risk assessment are in Appendix I, Table 21. The risk quotients indicated negligible risk to: all size classes of birds on an acute basis, large birds on a chronic basis, and small and large mammals on an acute basis (RQs: ≤ 0.70). The level of concern (in other words, 1) was slightly exceeded for the remaining risk quotients corresponding to: chronic risk to small and medium birds (RQs: 1.39 and 1.09), acute risk to medium mammals (RQ: 1.11), and chronic risk to all size classes of mammals (RQs: 1.22 to 2.36).

The screening level assumptions are conservative. With respect to both acute and chronic risk, it is not likely that bird and mammal diets consist entirely of one food item that is highly contaminated. In addition, considering chronic risk, it is unlikely that animals will remain in only one area (in particular, golf courses) for a prolonged period to forage for food.

The highest level of concern exceedances were linked to chronic risk to birds and mammals (RQs: 1.09 to 2.36). Chronic risk quotients were calculated based on no observed effect levels (NOELs). For birds, the NOEL of 35 mg a.i./kg bw/d was established based on a LOEL of 69 mg a.i./kg bw/d that resulted in a 26% reduction in female body weight. There were no significant effects on reproductive parameters at any test dose, the maximum of which was 138 mg a.i./kg bw/d. When considering the LOEL instead of the NOEL in risk quotient calculations, the maximum chronic risk quotient for birds is 0.71 (below the LOC; Appendix I, Table 22).

For mammals, the NOEL of 23 mg a.i./kg bw was established based on a LOEL of 117 mg a.i./kg bw/d for males and 124 mg a.i./kg bw/d for females that resulted in relatively minor 5 to 13% reductions in body weight gain. There were no significant effects on reproductive parameters at any test dose, the maximum of which was 117 mg a.i./kg bw/d for males and 124 mg a.i./kg bw/d for females. When considering the LOEL instead of the NOEL to calculate risk quotients, the maximum chronic risk quotients for mammals is 0.46 (below the LOC; Appendix I, Table 22).

In general, chronic effects on birds and mammals observed at the LOEL are expected to be even lower with more realistic feeding habits that include a diet consisting of diverse food sources obtained from different foraging areas that do not typically include golf courses. Overall, considering the relatively low level of concern exceedances and conservatism in the risk assessment, the acute and chronic risks to birds and mammals do not require risk mitigation.

Non-target terrestrial plants

Non-target terrestrial plants may be exposed to paclobutrazol through direct spray or spray drift. At the screening level, which assumed direct spray exposure, the risk quotients exceeded the level of concern of 1 (Appendix I, Table 20). Thus, the risk assessment was refined to consider off-field exposure to 6% spray drift one-metre downwind from the point of application. The refined risk quotients ranged from 0.63 to 8.5 (Appendix I, Table 23). Since some of the refined risk quotients still exceeded the level of concern, spray buffer zones are required to protect sensitive terrestrial habitats.

4.2.2 Risks to aquatic organisms

Aquatic organisms could be exposed to paclobutrazol through spray drift or runoff that enter aquatic habitat. A risk assessment for paclobutrazol and its major transformation products was performed based on available toxicity data for invertebrates, fish, amphibians, algae, and vascular plants. Toxicity data for the major transformation products CGA 149907 and NOA 457654 was available only for vascular plants. The screening level risk assessment assumed exposure from direct overspray to a small water body. The risk quotients for marine organisms ranged from <0.025 to <0.052 (<LOC), which indicate acceptable risk to marine organisms (Appendix I, Table 24). For freshwater organisms, risk quotients exceeded the level of concern for fish, amphibians and vascular plants (RQs: 2.57 to 54.7). Risks to these organisms were further characterized by considering exposure via spray drift one metre downwind from the point of application, and runoff.

Spray drift to aquatic habitats

The refined risk assessment for paclobutrazol exposure considered a reduction in spray drift from 100% to 6% and resulted in risk quotients below the level of concern for freshwater fish. However, the risk quotients for amphibians (1.44) and freshwater vascular plants (3.28) still exceeded the level of concern (Appendix I, Table 25). Spray buffer zones are required to protect sensitive freshwater habitats.

Runoff to aquatic habitats

The refined risk assessment for paclobutrazol exposure due to runoff considered runoff from a treated field into an adjacent water body, and the subsequent degradation of paclobutrazol in the water and sediments. Further details on the runoff risk assessment are in Appendix I, Table 18. The risk quotients still exceeded the level of concern for freshwater fish, amphibians, and vascular plants (Appendix I, Table 25). Since paclobutrazol is a plant growth regulator, the significant growth inhibition observed in the laboratory aquatic vascular plant study and associated high risk quotient of 33.0 are not unexpected. However, it is unlikely that aquatic plants along with freshwater fish (RQ: 1.55) and amphibians (RQ: 4.64) will be chronically exposed to the modelled conservative paclobutrazol levels in the water column, given the rapid partitioning of paclobutrazol from water to sediment that is expected in aquatic systems. In the two test systems assessed in the aquatic biotransformation study, approximately 30 to 85% of the initially applied radioactivity was observed in the sediment seven days after application. The amount of applied radioactivity in sediments increased until test termination at 120 days after application. Nevertheless, since there may be risk to aquatic organisms from runoff containing paclobutrazol residues, standard label statements are required to mitigate runoff.

4.2.3 Environment incident reports

As of 8 June 2023, no environment incidents related to paclobutrazol have been submitted to the PMRA.

5.0 Value

Value information in the form of use history information from the United States and a Canadian precedent registration was submitted for review. TRIMMIT was first registered in the United States on golf courses in 1987. Since then, TRIMMIT has become a commercial standard turf growth regulator. The use history information demonstrated that TRIMMIT reduces turf growth and improves turf health, colour, density, and vigour. The frequency of mowing can be reduced by 50% for up to two months after each application. TRIMMIT also suppresses *Poa annua* growth and seed head production. All uses and claims requested for the Canadian registration are found on the United States TRIMMIT (renamed as Power-Guard 2SC PGR in 2013) label. Products containing paclobutrazol are currently registered in Canada for reduction of internode elongation, resulting in more desirable compact plants, on container grown ornamental bedding plants and plugs in greenhouses.

Trinexapac-ethyl is the only active ingredient currently registered for reduction of the frequency of mowing and the amount of grass clippings on well-maintained turf on golf courses and commercial sod farms. The registration of TRIMMIT provides users with another option to regulate turfgrass growth as well as suppress *Poa annua* growth on golf courses, which has been available in the United States for many years.

The application of TRIMMIT is compatible with current management practices including IPM on turfgrass. The label recommends using with high nitrogen fertility to maintain turfgrass appearance and reduce discolouration. The target plants are very unlikely to develop resistance to TRIMMIT.

6.0 Pest control product policy considerations

6.1 Assessment of the active ingredient under the Toxic Substances Management Policy

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, in other words, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, paclobutrazol and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03⁶ and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that paclobutrazol and its transformation products do not meet all of the TSMP Track 1 criteria.

Please refer to Appendix I, Table 27 for further information on the TSMP assessment.

6.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.⁷

The list is used as described in the PMRA Science Policy Note SPN2020-01⁸ and is based on existing policies and regulations, including the *Toxic Substance Management Policy* and

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

⁷ SI/2005-114, last amended on June 24, 2020. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

⁸ PMRA's Science Policy Note SPN2020-01, *Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under paragraph 43(5)(b) of the Pest Control Products Act*

Formulants Policy,⁹ and taking into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act, 1999*, (substances designated under the *Montreal Protocol*).

The PMRA has reached the conclusion that Paclobutrazol Technical does not contain any substances identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*. The end-use product TRIMMIT contains the preservative 1,2-benzisothiazolin-3-one, which contains low levels of polychlorinated dibenzodioxins and furans (TSMP Track 1 substances). As the use of this preservative in pest control products at a maximum of 0.1% was reassessed by the PMRA in 2012 and was found to be acceptable because dioxin and furan levels are low/being managed as outlined in the PMRA Regulatory Directive DIR99-03 for the implementation of TSMP, the Agency position at this time is that no further action is required.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Proposed regulatory decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Paclobutrazol Technical and TRIMMIT, containing the technical grade active ingredient paclobutrazol, for use on turfgrass on golf courses to slow the growth of turfgrass and suppress *Poa annua*.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

Additional information being requested

Good Laboratory Practice (GLP)-compliant five-batch data representing commercial-scale production at the approved manufacturing site must be provided as post-market information.

⁹ DIR2006-02, *Formulants Policy and Implementation Guidance Document*

List of abbreviations

↑	increased
↓	decreased
°C	degrees centigrade
µg	microgram(s)
µM	micromolar(s)
♀	female
♂	male
1/n	exponent for the Freundlich isotherm
3-MA	3-methyladenine
4-OH ASDN	4-hydroxyandrostenedione
5-HIAA	5-Hydroxyindole-3-acetic acid
5-HT	serotonin
a.i.	active ingredient
abs	absolute
ACh	acetylcholine
AChE	acetylcholinesterase
AD	administered dose
ADD	absorbed daily dose
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and elimination
AGD	anogenital distance
AHETF	Agricultural Handler Exposure Task Force
AhR	Aryl hydrocarbon receptor
AICAR	5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside
AKT	murine viral thymoma viral oncogene
ALB	albumin
aldh	aldehyde dehydrogenase
ALOX	arachidonate 5-lipoxygenase gene
ALP	alkaline phosphatase
ALS	acetolactate synthase
ALT	alanine aminotransferase
AMPK	adenosine monophosphate-activated protein kinase
AOPWIN	Atmospheric Oxidation Program for Microsoft Windows
APDM	aminopyrine n-demethylase
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate transaminase
ATG5	autophagy related 5 gene

atm	atmosphere
ATPD	Area Treated Per Day
BAF	bioaccumulation factor
Bax	Bcl-2 associated X, apoptosis regulator
BCF	bioconcentration factor
Bcl-2	B cell leukemia/lymphoma apoptosis regulator 2
BECN1	beclin 1 gene
BRAF	murine sarcoma viral oncogene homolog B1
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
C	Celsius
CAF	composite assessment factor
CALUX	chemically activated luciferase expression
CaN	calcineurin
CAS	Chemical Abstracts Service
CAT	catalase
CEPA	Canadian Environmental Protection Act
CHO	Chinese hamster ovary cell line
cm	centimetre(s)
cm ³	cubic centimetre(s)
CO ₂	carbon dioxide
CR	Chemical-Resistant
CREA	creatinine
Cu/Zn-SOD	copper/zinc superoxide dismutase
CXCL-cle	chemokine (C-X-C motif) ligand gene
CYP	cytochrome P450 family enzyme
d	day(s)
DA	dopamine
DACO	data code
DART	developmental and reproductive toxicity
DEEM	Dietary Exposure Evaluation Model
DER	data evaluation report
DF	dry flowable
DFOP	double first-order in parallel
Dio1	iodothyronine deiodinase
DIR	Directive
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOC	dissolved organic carbon
DT ₅₀	dissipation time 50% (the time required to observe a 50% decline in

	concentration)
DT ₉₀	dissipation time 90% (the dose required to observe a 90% decline in concentration)
dw	dry weight
EC ₂₅	effective concentration on 25% of the population
EC ₅₀	effective concentration on 50% of the population
EDD ₅₀	effective dietary dose on 50% of the population
EDE	estimated daily exposure
EDSP	Endocrine Disruptor Screening Program
EEC	estimated environmental concentration
EFH	Exposure Factors Handbook
EFSA	European Food Safety Agency
EGFR	epidermal growth factor receptor
EIIS	USEPA Ecological Incident Information System
ELS	early life-stage
EPI	Estimation Program Interface
ER	estrogen receptor
ER ₂₅	effective rate for 25% of the population
F0	parental generation
F1	first filial generation
F2	second filial generation
fc	food consumption
g	gram(s)
GABA	gamma-aminobutyric acid
GAP	Good Agricultural Practice
GD	gestational day
GIT	gastrointestinal tract
GLP	Good Laboratory Practice
Glu	glutamate
gnat	G protein subunit alpha transducin
GR	glucocorticoid receptor
GST	glutathione-S-transferase
GUS	groundwater ubiquity score
h	hour(s)
H4IIE	rat hepatocellular carcinoma-derived cell line
ha	hectare(s)
HCD	historical control data
HDT	highest dose tested
Hg	mercury
hpf	hours post fertilization

HPLC	high performance liquid chromatography
hr	hour
hr(s)	hour(s)
IBR	integrated biomarker response
IC _{25/50}	concentration estimated to inhibit 25/50% of the enzyme activity
IGF	insulin growth factor
IORE	indeterminate order rate equation
IPM	Integrated Pest Management
ISO	International Standardization Organisation
IUPAC	International Union of Pure and Applied Chemistry
K _d	soil-water partition coefficient
K _F	Freundlich adsorption coefficient
kg	kilogram(s)
km	kilometre
K _{oc}	organic-carbon partition coefficient
K _{ow}	n-octanol-water partition coefficient
KOWWIN	K _{ow} Estimation Program for Microsoft Windows
kPa	kilopascal
L	litre(s)
LADD	lifetime average daily dose
LC3	microtubule-associated protein light chain 3
LC ₅₀	lethal concentration on 50% of the population
LD ₅₀	lethal dose on 50% of the population
LDD ₅₀	lethal dietary dose on 50% of the population
LLNA	local lymph node assay
LOAED	lowest observed adverse effect dose
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	level of detection
LOEC	lowest-observed effect concentration
LOEL	lowest-observed effect level
LOQ	limit of quantitation
LR ₅₀	lethal rate 50%
LXR	liver X receptors
m	metre
M/L	Mixer/Loader
M/L/A	Mixer/Loader/Applicator
m ³	cubic metre(s)
MAOA	monoamine oxidase A

MAPK	mitogen-activated protein kinase
MAS	maximum average score
MCF	Michigan Cancer Foundation-7 cell line
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
mm	millimetre(s)
MNE	normetanephrine
MOA	mode of action
MOE	margin of exposure
MOEC	median observable effect concentration
mol	mole(s)
mPa	milliPascal(s)
MRID	US Master Record Identification Number
MRL	maximum residue limit
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MS/MS	tandem mass spectrometry
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
N	North
N/A	not applicable
N/R	not required
NIOSH	National Institute for Occupational Safety and Health
nm	nanometres
NOAEC	no observed adverse effect concentration
NOAED	no observed adverse effect dose
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEDD	no observed effect dietary dose
NOEL	no observed effect level
NOER	no observed effect rate
NZW	New Zealand white
OC	organic carbon content
OECD	Organisation for Economic Co-operation and Development
OM	organic matter content
OPPTS	Office of Prevention, Pesticides and Toxic Substances
ORETF	Outdoor Residential Task Force
p53	tumour protein 53
p62	sequestosome 1
Pa	Pascal

PBI	plantback interval
PC	protein carbonyl
PCPA	<i>Pest Control Products Act</i>
PE	phosphatidylethanolamine
PG	phosphatidyl glycerol
PGR	plant growth regulator
PHED	Pesticide Handler Exposure Database
PHI	preharvest interval
pKa	dissociation constant
PLA2G	phospholipase A2 group
PMRA	Pest Management Regulatory Agency
PPAR	peroxisome proliferator activated receptors
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
PRVD	proposed re-evaluation decision
PS	phosphatidylserine
PTGS	prostaglandin-endoperoxide synthase
PWC	Pesticide in Water Calculator
RA	risk assessment
RAC	raw agricultural commodity
RBC	red blood cells
RD	residue definition
RED	Reregistration Eligibility Decision
REI	restricted entry interval
rel	relative
ROS	reactive oxidative species
RQ	risk quotient
RSD	relative standard deviation
RTI	Retreatment Interval
RXR	retinoid X receptor
s.s.	statistically significant
S9	mammalian metabolic activation system
SC	suspension concentrate
SD	standard deviation
SFO	single first-order
SI	stimulation index
SOD	superoxide dismutase
SPN	Science Policy Note
STMdR	supervised trial median residue
STMdR	supervised trial mean residue

$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TC	Transfer Coefficient
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TG	triglyceride
TH	thyroid hormone(s)
TNOS	total nitric oxide synthase
TP	transformation product
TR	thyroid receptor
t_R	representative half-life
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
T-SOD	total superoxide dismutase
TTR	Turf Transferable Residue
TV101	human hepatoblastoma-derived cell line
UAN	urea ammonium nitrate
UF _{DB}	uncertainty factor (database)
UGT	UDP glucuronosyltransferase gene family
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
vtg1	vitellogenin 1
w/w	weight per weight
WBC	white blood cells
wk	week(s)
WoE	weight of evidence
WP	wettable powder
wt/wts	weight/weights
XDH	xanthine dehydrogenase
λ	wavelength
μM	micromolar
μPa	microPascal

Appendix I Tables and figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method type	LOQ	Reference
Clay	-	Paclobutrazol	HPLC-MS-MS	1 ppb	PMRA No. 3116813
		R79105			
Sandy loam	-	Paclobutrazol	HPLC-MS-MS	1 ppb	PMRA No. 3116813
		R79105			
Drinking water	-	Paclobutrazol	HPLC-MS-MS	0.05 ppb	PMRA No. 3116814, 3116815
		R79105			
Surface water	-	Paclobutrazol	HPLC-MS-MS	0.05 ppb	PMRA No. 3116814, 3116815
		R79105			
Ground water	-	Paclobutrazol	HPLC-MS-MS	0.05 ppb	PMRA No. 3116814
		R79105			

Table 2 Identification of select metabolite of paclobutrazol

Code	Chemical name	Source
CGA 205369	2-Hydroxy-3-(1H-1,2,4-triazol-1-yl)propanoic acid	environmental degradate, residue in plants

Table 3 Toxicity Profile of Technical Paclobutrazol

Effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study type/Animal/PMRA No.	Study results
Toxicokinetics studies	
<p>Excretion and tissue retention of a single oral dose (10 mg/kg)</p> <p>Wistar (Alpk) rats</p> <p>PMRA No. 1232560</p>	<p>Three male and three female rats were dosed by gavage with ¹⁴C-labelled paclobutrazol at 10 mg paclobutrazol/kg bw. One male and one female rat were given the material with higher specific activity placed in metabolism cages. From these animals, urine and feces were collected over solid carbon dioxide and expired air (from the 2 rats) was drawn through a series of traps to remove water vapour and other expired gases. Using triazole-labelled paclobutrazol following a single dose of 10 mg ¹⁴C-paclobutrazol/kg bw, 75–87% of the dose was excreted within 48 hours. In males, 23–48% was excreted in urine and 44–64% in feces while in females the urinary route was predominant, 48–64% of the dose, with 26–41% excreted in feces. No significant excretion occurred in expired air. Most (81–91%) of the urinary excretion occurred within 24 hours indicating rapid absorption. Fecal excretion was somewhat slower than urinary excretion suggesting that some of the fecal ¹⁴C was of biliary origin and, thus, the full extent of absorption may have been greater than that suggested by urinary excretion. Tissue levels at 96 hours were very low. Whole body radiography after 72 hours indicated the GI contents accounted for most of the residual radioactivity.</p>
<p>Whole body autoradiography study in the rat following a single oral dose (250 mg/kg)</p> <p>Wistar (Alpk) rats</p> <p>PMRA No. 1232562</p>	<p>One male and one female rat were given single oral (gavage) doses of 250 mg test material/kg bw and were placed in glass metabolism cages. Urine and feces were collected over solid carbon dioxide and removed at 24 and 48 hours. Expired air was drawn through traps which were analyzed at 24 and 48 hours for radioactivity. Forty-eight hours after dosing the rats were sacrificed. Following a single oral dose of 250 mg ¹⁴C-paclobutrazol/kg bw, a whole body autoradiogram prepared 48 hours after dosing indicated that most of the radiolabelling was in the GI contents. In the male the amount in large intestine was larger than in the female which was consistent with the excretion pattern</p>

Study type/Animal/PMRA No.	Study results
	observed. Low levels of radioactivity were noted in liver, kidney and perirenal fat.
<p>Excretion and tissue retention of a single oral dose (5 mg/kg)</p> <p>Sprague-Dawley rats</p> <p>PMRA No. 1232564</p>	<p>Four male and four female rats were given a single dose, 5 mg of ¹⁴C-test material/kg bw, by gavage and then placed in individual glass metabolism cages for collection of urine and feces. Urine and feces were frozen immediately by being collected over solid carbon dioxide and were removed at 24-hour intervals for 7 days post-dosing. The cages were rinsed after each collection. After 7 days the rats were sacrificed. Blood samples and brain, liver, kidney, heart, fat, GI contents, muscle, spleen, bone, gonads, lung and carcass were saved. Liver, kidney, fat, blood, plasma, GIT contents and carcass were analyzed for residual radioactivity. All fecal and urinary samples were analyzed for radioactivity. After a single oral dose of paclobutrazol at 5 mg/kg bw the test material was excreted in urine and feces mainly within 48 hours after dosing. Seven days after dosing tissue levels were low or not detectable. Radioactivity was found in GIT contents and in liver in most rats and in kidney in one female. None was detected in fat. There were no differences between males and females.</p>
<p>Excretion and tissue retention of a single oral dose (250 mg/kg)</p> <p>Sprague-Dawley rats</p> <p>PMRA No. 1232565</p>	<p>Four males and four females were given a single oral (gavage) dose of test material at 250 mg/kg bw. The animals were then placed in individual all glass metabolism cages. Urine and feces were collected over solid carbon dioxide and were removed at 24-hour intervals. The cages were rinsed after each collection. Seven days after dosing the animals were sacrificed. Blood, brain, liver, heart, fat, GIT contents, muscle, spleen, femur, gonads, lung and residual carcass were sampled. Radioactivity in liver, fat, kidneys, blood, plasma, GI contents and carcass were determined. Radioactivity of each collected sample of urine and feces was determined. Following a single oral dose of 250 mg ¹⁴C-paclobutrazol/kg bw, most of the radioactivity was recovered in urine and feces in 72 hours with somewhat higher amounts in urine than in feces. There were no large differences between sexes although fecal excretion was slightly slower in males. Compared to excretion of a single dose of 5 mg/kg bw the rate of excretion was slower especially in the first 24 hours.</p>

Study type/Animal/PMRA No.	Study results
	Tissue residues were largely confined to GI tract and liver and were low. There was no indication of accumulation in the tissues.
<p>Bioaccumulation of repeated oral doses (5 mg/kg/day)</p> <p>Sprague-Dawley rats</p> <p>PMRA No. 1232566</p>	<p>Groups of 3 male rats received 5 mg ¹⁴C-paclobutrazol/kg bw/day for 3, 7, 14, 21, 28, 35, 42 or 49 (7 groups) days. The animals were sacrificed one day after the final dose except for the six extra groups dosed for 49 days which were sacrificed at 3, 7, 14, 21, 28 or 35 days after the final dose. Tissue levels increased with duration of dosing mainly in the organs of biotransformation and excretion. Fat levels were low, near the level of detection throughout dosing. Following cessation of dosing the tissue levels fell rapidly indicating that there was little bioaccumulation of paclobutrazol or its metabolites.</p>
<p>Absorption, excretion and tissue retention of a single oral dose (5 mg/kg)</p> <p>Beagle dogs</p> <p>PMRA No. 1232567</p>	<p>Three male and three female dogs received a single oral (gavage) dose of 5 mg ¹⁴C-paclobutrazol/kg bw. Each dog was placed in an individual metabolism cage and urine and feces were collected over solid carbon dioxide and removed at 24-hour intervals, Blood samples from the jugular vein were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 168 hours. The metabolism cages were rinsed daily and the washings were analyzed. Seven days after dosing the dogs were sacrificed. Blood, plasma, brain, liver, kidney, heart, spleen, bone, GIT contents, fat, gonads and lungs were retained. Liver, kidney, fat, blood, plasma and GI contents were analyzed for radioactivity. The collected samples of urine, feces, blood (and plasma) were analyzed for radioactivity. Following administration of 5 mg test material/kg bw to dogs, the material was rapidly absorbed with peak levels in blood at 0.5 to 1.5 hours after dosing. Most of the radioactivity was in the plasma. Excretion was rapid with most of radioactivity found in urine and feces being excreted within 24 hours of dosing, urinary excretion was slightly higher than fecal excretion. There were no sex differences noted. The only tissue residue observed was in the liver of one male dog. There was no evidence of bioaccumulation of the test material in the tissues.</p>
<p>Biotransformation in the rat</p> <p>Wistar (Alpk:AP) rats</p> <p>PMRA No. 1232568</p>	<p>Ten female rats were each given a single oral dose of 250 mg ¹⁴C-paclobutrazol/kg bw metabolism cages. Urine and feces were collected over solid carbon dioxide and removed at daily intervals for 3 days. Additionally, two male and two female rats were anesthetized while bile cannulas were installed. Following recovery, each</p>

Study type/Animal/PMRA No.	Study results
	<p>rat received a single oral dose of 250 mg ¹⁴C-paclobutrazol/kg bw and were placed in individual restraining cages. Bile, urine and feces were collected at 24-hour intervals for four days. At the end of the dosing periods all rats were sacrificed. Paclobutrazol, given as a single dose, was readily absorbed with no parent compound detected in feces after 5 mg/kg bw and only 5% of the dose excreted as the parent compound in feces at 250 mg/kg bw. The compound was extensively metabolized but biotransformation was limited to the tertiary butyl moiety with no metabolism detected in the triazole or halogenated phenyl rings. The two main metabolites in urine, bile and feces were paclobutrazol diol and paclobutrazol acid which were both excreted in conjugated and unconjugated forms. A mechanism of biotransformation involving a two-stage oxidation process by way of the hepatic mixed function oxidase system is proposed. Following oxidation to the diol, the fate of the compound (excretion or further oxidation to the carboxylic acid) was sex and dose-dependent. At 250 mg/kg males excreted about 20% of the dose in urine mainly as the acid while females excreted about 30% of the dose by this route but mainly as free and conjugated diol (2/3 diol 1/3 acid). At 5 mg/kg bw the same pattern was observed in males but females excreted more acid than at 250 mg/kg. In both sexes most of the dose was excreted in bile as diol conjugates which were eliminated in feces.</p>
Acute Toxicity Studies	
<p>Acute oral toxicity Mouse (Alderley Park SPF) PMRA No. 1231127</p>	<p>LD₅₀ (♂) = 490 (394-642) mg/kg bw LD₅₀ (♀) = 1219 mg/kg bw</p> <p>Moderate acute oral toxicity</p> <p>Deaths occurred in ♂ ≥ 800 mg/kg bw and in ♀ at ≥ 400 mg/kg bw, all within 48 hours after dosing. Unsteady gait was common in both sexes. Coma, hypothermia, piloerection and urinary incontinence were also common. Most survivors showed weight gains by Day 14.</p>
<p>Acute oral toxicity Rat (Alderley Park SPF) PMRA No. 1231127</p>	<p>LD₅₀ (♂) = 1954 (1147-4985) mg/kg bw LD₅₀ (♀) = 1336 (837-1969) mg/kg bw</p> <p>Slight acute oral toxicity</p>

Study type/Animal/PMRA No.	Study results
	Deaths occurred at ≥ 640 mg/kg. All deaths occurred within 3 days for ♀ or 4 days for ♂.
Acute oral (up-and-down) Rat (Sprague-Dawley) PMRA No. 3277879	LD ₅₀ (♀) > 2000 mg/kg bw Low acute oral toxicity. 2000 mg/kg bw: 1/5 animal hypoactivity on day 1, 3/5 animals reduced fecal output days 1-2
Acute oral toxicity Guinea pigs (Dunkin Hartley) PMRA No. 1231127	LD ₅₀ (♂) = 542 (432-717) mg/kg bw LD ₅₀ (♀) = between 400 and 640 mg/kg bw Moderate acute oral toxicity Deaths occurred within 48 hours after dosing at ≥ 800 mg/kg bw in ♂ and at ≥ 640 mg/kg bw ♀. Unsteady gait was also observed in most animals dosed at ≥ 400 mg/kg bw. Comatose animals were only observed at the highest dose (800 mg/kg bw for ♂, 640 mg/kg bw for ♀). The survivors appeared normal by Day 2. Weight loss was observed following treatment but weight gains were observed in all survivors by Day 14.
Acute oral toxicity Rabbit (New Zealand White) PMRA No. 1231127	LD ₅₀ (♂) = 835 (200–2300) mg/kg bw LD ₅₀ (♀) = 937 (555–2026) mg/kg bw Moderate acute oral toxicity All animals died at ≥ 1000 mg/kg bw. Most deaths occurred within 3 days after dosing. Unsteady gait was common. At the highest dose level there was excessive salivation (males), respiratory difficulties, increased tone of limbs, hypothermia and in two ♀, coma. Most signs of toxicity were no longer present by Day 10. Weight loss was observed in all animals following dosing and not all animals had recovered their initial body weight by Day 14.
Acute dermal Rat (Sprague-Dawley) PMRA No. 3277880	LD ₅₀ > 2000 mg/kg bw Low acute dermal toxicity. No clinical signs of toxicity
Acute inhalation Rat (Wistar) PMRA No. 3280224	LC ₅₀ > 2.02 mg/L Low acute inhalation toxicity 2.02 mg/L: wet fur on the day of exposure and the

Study type/Animal/PMRA No.	Study results
	majority of animals also exhibited staining around the nose. One female exhibited increases sensitivity to touch from days 1–3
Eye irritation Rabbit (New Zealand White) PMRA No. 3277881	MAS = 8.1/110 MIS = 13.7/110 at 24 hours Persistence past 72 hours Mildly irritating to the eye
Skin irritation Rabbit (New Zealand White) PMRA No. 3277882	MAS = 0.33/8 MIS = 1/8 at 1 hour Minimally irritating
Skin sensitization LLNA Mouse (CBA) PMRA No. 3277883	Negative Not a dermal sensitizer.
Short-Term Toxicity Studies	
28-day range-finding oral toxicity (diet) Mouse (CrI:CD-1(ICR)BR) PMRA No. 3396823	Supplemental (range-finding) NOAEL for liver effects: 8.6/10 mg/kg bw/day ♂/♀ LOAEL for liver effects: 182/212 mg/kg bw/day ♂/♀ Effects at the LOAEL: hepatocyte centrilobular hypertrophy with cytoplasmic basophilic granules and micro- and macro-vacuolation, ↑ rel liver wt, ↑ ALT, ↓ cholesterol, ↓ TG (♂♀); ↑ abs liver wt (♂) Limitations relative to current guideline include: low number of required organs weighed. However, endocrine sensitive tissues were examined; the brain, gonads, kidneys, lungs, liver, thymus, spleen and heart were weighed; and histological examination was performed for thyroid including parathyroids glands, uterus, ovaries, seminal vesicles, both testes with epididymides and the liver. The methodology and findings pertaining to the liver were judged to be of sufficient quality and robustness to determine a NOAEL for liver effects.

Study type/Animal/PMRA No.	Study results
<p>28-day range-finding oral toxicity (diet)</p> <p>Rat (Sprague-Dawley)</p> <p>PMRA No. 3396822</p>	<p>Supplemental (range-finding)</p> <p>NOAEL for liver effects: 88/4.6 mg/kg bw/day ♂/♀ LOAEL for liver effects: 130/87 mg/kg bw/day ♂/♀</p> <p>Effects at the LOAEL: ↑ incidence hepatocellular hypertrophy, ↑ liver wt (♂/♀); ↓ fc, ↑ incidence of liver midzonal macrovacuolation, ↑ cholesterol (♀)</p> <p>Limitations according to current guideline include: eyes were not examined, only PT and APTT were measured as part of hematology examinations, only GPT and cholesterol were measured as part of clinical chemistry examinations, only the liver was weighed and examined for histopathology.</p> <p>The methodology and findings pertaining to the liver were judged to be of sufficient quality and robustness to determine a NOAEL for liver effects.</p>
<p>90-day oral toxicity (diet)</p> <p>Rat (Wistar (Alpk:AP))</p> <p>PMRA No. 1231115</p>	<p>Supplemental</p> <p>Urinary concentration of a metabolite of paclobutrazol (the butyl acid) was measured at week 9–11. The metabolite was detected in significant quantities in the urine of the female controls, but the source of this metabolite was unknown, resulting in questions concerning the acceptability of the procedures followed in the study. For this reason, the study was considered to be supplemental.</p> <p>93/107 mg/kg bw/day ♂/♀: ↓ bwg, ↓ fc, ↑ liver wt, ↑ APDM activity, ↓ PT, ↓ kaolin-cephalin time (♂/♀); small focus of atrophic tubules in one testis (0, 0, 0, 2) (♂); ↑ cholesterol, ↑ ALT (♀)</p> <p>No effects on brain, testes and/or ovary weights. No abnormalities (macro- and microscopic) at necropsy on adrenals, pituitary, thyroid, seminal vesicles.</p>
<p>90-day oral (capsule)</p> <p>Dog (Beagle)</p> <p>PMRA No. 3277884</p>	<p>NOAEL= 15 mg/kg bw/day LOAEL= 450 mg/kg bw/day</p> <p>Effects at the LOAEL: ↓ bw, ↓ bwg, ↑ liver wt, ↑ ALP, ↑ APDM activity, ↓ ALB, ↑ TG, ↑ kidney wt (♂/♀); ↑ incidence of minimal hepatocyte vacuolation, ↑ incidence of minimal to slight hepatocyte fine fat deposition, ↑ incidence of slight mononuclear cell</p>

Study type/Animal/PMRA No.	Study results
	infiltration, ↑ incidence of slight mononuclear cell infiltration, ↓ testes and epididymides wt, ↓ testes and prostate size, absence of spermatozoa, ↑ ALT (♂); ↓ total protein (♀)
Chronic toxicity/Oncogenicity studies	
18-month oncogenicity (diet) Crl:CD(SD)BR mice PMRA No. 1231138	NOEL: 15 mg/kg bw/day ♂/♀ LOEL: 85 mg/kg bw/day ♂/♀ Effects at the LOEL: ↓ fc (first few weeks only), ↑ liver wt (♂/♀); ↓ TG, ↑ severity of liver steatosis (interim and terminal) (♂) No evidence of tumourigenicity
24-month chronic toxicity/oncogenicity (diet) Rat (Crl:CD(SD)) PMRA No. 1231122, 1231138	NOAEL: 2.1/2.8 mg/kg bw/day ♂/♀ LOAEL: 11/14 mg/kg bw/day ♂/♀ Effects at the LOAEL: ↑ incidence of liver hypertrophy/steatosis (♂); ↓ bwg (♀) At the next dose (72 mg/kg bw/day): equivocal ↑ incidence of uterine stromal polyps (0%, 10%, 10%, 14%) Historical control data: 6.7% ± 3.1% range: 0-12% Equivocal evidence of tumourigenicity in ♀
Developmental/Reproductive toxicity studies	
2-generation dietary reproductive toxicity Rat (Wistar (Alpk:AP)) PMRA No. 1231142	Parental toxicity NOAEL: 23/25 mg/kg bw/day ♂/♀ LOAEL: 117/124 mg/kg bw/day ♂/♀ Effects at the LOAEL: ↓ bw, ↓ bwg (F ₀ and F ₁), ↑ incidence of chromodacryorrhea, thickened eyelids, dental malocclusion (F ₀ and F ₁) (♂♀); ↓ fc (1–2 wks F ₀) (♂); ↓ fc (F ₀ and F ₁), ↑ liver wt (F ₀ and F ₁) with centrilobular fatty changes (F ₀), ↑ cytoplasmic eosinophilia of centrilobular hepatocytes and inflammatory cell infiltration (F ₀) (♀) Reproductive toxicity NOAEL: 117/124 mg/kg bw/day ♂/♀ LOAEL: not determined Offspring toxicity NOAEL: 25 mg/kg bw/day ♀

Study type/Animal/PMRA No.	Study results
	<p>LOAEL: 124 mg/kg bw/day ♀</p> <p>Effects at the LOAEL: ↓ wt, ↑ liver wt (F₁ and F₂), ↑ incidence of chromodacryorrhea, thickened eyelids, dental malocclusion (♂♀)</p> <p>No evidence of sensitivity of the young</p> <p>Limitations relative to current guideline include: endocrine sensitive endpoints not measured: oestrus cycle measurements including qualitative or quantitative examination of the ovarian primordial or growing follicle population, sperm parameter measurements, timing of sexual maturation, anogenital distance, pituitary, testis, epididymis, prostate, seminal vesicles, coagulating gland, and uterus weights, examination of pup thyroid gland at necropsy.</p>
<p>Developmental toxicity (gavage)</p> <p>Rat (Wistar (Alpk:AP))</p> <p>PMRA No. 1231134</p>	<p>Maternal NOAEL: 40 mg/kg bw/day</p> <p>Maternal LOAEL: 100 mg/kg bw/day</p> <p>Effects at the maternal LOAEL: ↓ bwg</p> <p>Developmental NOAEL: not determined</p> <p>Developmental LOAEL: 40 mg/kg bw/day</p> <p>Effects at the developmental LOAEL: ↑ transverse processes on 7th cervical vertebra partially ossified (bilateral and unilateral + bilateral), ↑ extra 14th ribs (bilateral)</p> <p>Effects at the high dose: ↑ cleft palate (3 fetuses in 2 litters)</p> <p>Evidence of sensitivity of the young</p> <p>Evidence of treatment-related malformations at maternally toxic dose</p> <p>Limitations relative to current guideline include: maternal animals were not dosed during most of the period of fetal phenotypic sex differentiation which is known to be hormone dependent; thyroid gland weight and histology as well as thyroidal hormones measurements were not performed in dams and no particular attention was given to the reproductive tracts; anogenital distance not measured.</p>

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<p>Developmental toxicity (gavage)</p> <p>Rat (Wistar (Alpk:AP))</p> <p>PMRA No. 1231136</p>	<p>Maternal NOAEL: 100 mg/kg bw/day Maternal LOAEL: not determined</p> <p>Maternal No adverse effects</p> <p>Developmental NOAEL: 10 mg/kg bw/day Developmental LOAEL: 40 mg/kg bw/day</p> <p>Effects at the developmental LOAEL: ↑ transverse processes on 7th cervical vertebra partially ossified (unilateral), ↑ extra (14th) short ribs (bilateral), ↑ incidence of bilateral slight to moderate pelvic dilatation, ↑ incidence of unilateral slight to extreme pelvic dilatation, ↑ bilateral slight to moderate ureteral dilation, ↑ incidence of unilateral slight to extreme ureteral dilation, ↑ incidence of unilateral kinked ureter</p> <p>Evidence of sensitivity of the young</p> <p>No evidence of treatment-related malformations</p> <p>Limitations relative to current guideline include: maternal animals were not dosed during most of the period of fetal phenotypic sex differentiation which is known to be hormone dependent; thyroid gland weight and histology as well as thyroidal hormones measurements were not performed in dams and no particular attention was given to the reproductive tracts; anogenital distance</p>
<p>Developmental toxicity (gavage)</p> <p>Rabbit (New Zealand white)</p> <p>PMRA No. 1232576</p>	<p>Supplemental</p> <p>Maternal 75 mg/kg bw/day: abortions</p> <p>125 mg/kg bw/day: ↓ bw (GD 6-9), ↓ bwg, deaths, ↓ fc GD 6-9</p> <p>Developmental 125 mg/kg bw/day: multiple vertebral variations, one case of encephalocele (equivocal), ↑ incidence of partially ossified skull (interparietal)</p> <p>Limitations relative to current guideline include: inadequate number of pregnant ♀ including control</p>

Study type/Animal/PMRA No.	Study results
	group; maternal animals were not dosed during most of the period of fetal phenotypic sex differentiation which is known to be hormone dependent.
Developmental toxicity (gavage) Rabbit (New Zealand white) PMRA No. 1232601	Maternal NOAEL: 75 mg/kg bw/day Maternal LOAEL: 125 mg/kg bw/day Effects at the maternal LOAEL: ↓ bw, ↓ fc (GD 7-10) Developmental NOAEL: 25 mg/kg bw/day Developmental LOAEL: 75 mg/kg bw/day Effect at the developmental LOAEL: one case of encephalocele (equivocal) Equivocal evidence of sensitivity of the young Equivocal evidence of treatment-related malformations in the absence of maternal toxicity Limitations relative to current guideline include: maternal animals were not dosed during most of the period of phenotypic sex differentiation which is known to be hormone dependent.
Genotoxicity studies	
In vitro bacterial assay <i>S. typhimurium</i> PMRA No. 1232637	Negative Tested up to limit concentration ± metabolic activation
In vivo chromosome aberration assay (gavage) Wistar (Alpk:SPF) rats PMRA No. 1227766	Negative for clastogenicity Tested up to MTD for 5 days
Dominant lethal assay CD-1 ♂ mice PMRA No. 1232554	Negative Tested up to 300 mg/kg bw/day for 5 days 300 mg/kg bw/day: piloerection, urinary incontinence, and tremors at dosing, 1 death on day 4 of the dosing period
In vitro Mouse lymphoma mutation assay	Negative Tested up to 140 µg/mL ± metabolic activation

Study type/Animal/PMRA No.	Study results
Mouse L5178Y TK +/- cells PMRA No. 1232551	Evidence of cytotoxicity at $\geq 102.5 \mu\text{g/mL}$
In vivo Mouse micronucleus assay C57BL/6JBL10/Alpk mice PMRA No. 1148783	Negative Tested up to 373 mg/kg bw $\geq 233 \text{ mg/kg bw}$: subdued nature, urinary incontinence, hunched posture, tiptoe gait, eye discharge, piloerection, reduced stability, splayed and abnormal gaits (♂/♀) 373 mg/kg bw: laboured breathing, coldness (♂/♀)
In vivo unscheduled DNA synthesis in rat hepatocytes Wistar (Alpk:AP-SPF) ♂ rats PMRA No. 1232557	Negative Tested up to 400 mg/kg bw 400 mg/kg bw: evidence of cytotoxicity
Neurotoxicity Studies	
Acute neurotoxicity (gavage) Rat (Wistar) PMRA No. 3277887	NOAEL= 150/30 mg/kg bw/day ♂/♀ LOAEL= 500/150 mg/kg bw/day ♂/♀ Effects at the LOAEL: \downarrow body temperature on Day 1 (3–4 hours post-dose), \downarrow bwg on Days 1–2, \downarrow fc Days 1–2 (♂); \downarrow motor activity (number of rearings, \downarrow total distance travelled (equivocal)) (♀)
Additional studies	
Hershberger bioassay Castrated ♂ CrI:CD(SD) Sprague-Dawley rats; weight of five androgen-dependent tissues taken at necropsy PMRA No. 3266383	Negative for androgenicity and anti-androgenicity No paclobutrazol treatment-related effects were noted in any of the 5 androgen-dependent tissues. Dosing was considered adequate based on the dose-response \uparrow in liver wt ($\geq 30\%$ at the high dose).
Steroidogenesis assay In vitro H295R cell cultures (derived from human adrenal carcinoma, possess all the key enzymes necessary for testosterone and estradiol biosynthesis) PMRA No. 3260413	Steroidogenesis inhibitor Decreases (statistically significant at $p < 0.05$) in testosterone concentrations were observed at $1 \times 10^{-6} \text{ M}$ and above ($\downarrow 19\text{--}88\%$) Decreases (statistically significant at $p < 0.05$) in estradiol concentrations was decreased at $3.16 \times 10^{-5} \text{ M}$ and above ($\downarrow 36\text{--}67\%$)

Study type/Animal/PMRA No.	Study results
	Reference compounds known to interfere with steroidogenesis functioned as expected. Hormone levels were measured with enzyme immunoassay kits.
<p>Aromatase assay</p> <p>In vitro recombinant microsomes containing human aromatase and cytochrome P450 reductase</p> <p>PMRA No. 3260442</p>	<p>Aromatase enzyme inhibitor</p> <p>Paclbutrazol</p> <p>Aromatase activity averaged 0.7287 ± 0.0091 nmol/mg protein/min at 1.0×10^{-10} M and 0.0835 ± 0.0008 nmol/mg protein/min at 1.0×10^{-3} M.</p> <p>IC₅₀ range for three runs: 2.0×10^{-4} M to 1.58×10^{-4} M</p> <p><u>4-OH ASDN (positive control)</u></p> <p>Aromatase activity averaged 0.6006 ± 0.0866 nmol/mg protein/min at 10^{-10} M and 0.0026 ± 0.0006 nmol/mg protein/min at 10^{-5} M.</p> <p>IC₅₀ for the three runs was 3.16×10^{-8} M</p>
Metabolite studies (Triazole lactic acid)	
<p>Acute oral (up-and-down)</p> <p>Rat (Sprague-Dawley)</p> <p>PMRA No. 3277890</p>	<p>LD₅₀ (♀) > 2000 mg/kg bw</p> <p>No clinical signs of toxicity</p> <p>Low acute oral toxicity</p>
<p>Bacterial reverse mutation assay</p> <p>S. typhimurium strains TA1535, TA1537, TA98 and TA100 and E. coli strains WP2 and WP2 uvrA</p> <p>PMRA No. 3277891</p>	<p>Negative</p> <p>Tested up to limit concentration ± metabolic activation.</p>
<p>In vitro mammalian cell gene mutation assay (HGPRT locus)</p> <p>CHO cells</p> <p>PMRA No. 3277889</p>	<p>Negative</p> <p>Tested up to 1600 µg/mL ± metabolic activation.</p> <p>Cytotoxicity +S9 at ≥ 400 µg/mL</p>
<p>In vitro Chromosomal aberration assay in rat lymphocytes</p> <p>PMRA No. 327788</p>	<p>Negative</p> <p>Tested up to 1600 µg/mL ± metabolic activation.</p> <p>Cytotoxicity +S9 at 1600 µg/mL</p>

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Additional data from the open scientific literature	
<p>Study on endocrine disruption effect of paclobutrazol and uniconazole on the thyroid of male and female rats based on lipidomics (Liu et al., 2022).</p> <p>SD rats dosed orally (gavage) with paclobutrazol at 32.5 or 260 mg/kg bw/day in distilled water for 28 days</p> <p>Lipidomics in combination with network pharmacology were used to investigate the thyroid endocrine disturbance on blood lipid levels caused by paclobutrazol, and to screen potential lipid biomarkers.</p> <p>PMRA No. 3428888 p. 693</p>	<p>Non-guideline</p> <p>≥ 32.5 mg/kg bw/day: ↓ T3 (not s.s.) (♂/♀); ↓ T4 (♂); inflamed thyroid follicular cells (♀)</p> <p>260 mg/kg bw/day: ↓ T4, shrunk and split thyroid follicular structure forming split tendency and distortion, ↑ thyroid interstitial follicular edema gap (♀)</p> <p>Male thyroid histology reported as: “male rats also experienced different degrees of thyroid damage after administration of paclobutrazol”</p> <p>Upregulated and downregulated lipid biomarkers of thyroid endocrine disruption in both sexes of rats:</p> <p>260 mg/kg bw/day: 3 PGs, 1 PS, 1 PA, 2 PEs (♂<♀)</p> <p>Identified common targets by Cytoscape: AKT1 and AKT2, EGFR, BRAF, MAPK1, MAPK8, MAPK10, MAPK14, IGF-1, IGF-IR</p>
<p>Network pharmacology combined with metabolomics approach to investigate the toxicity mechanism of paclobutrazol (Yue et al., 2022).</p> <p>Sprague-Dawley (SD) rats dosed orally (gavage) at 0, 200, 500 or 1000 mg/kg bw/day in distilled water for 30 days</p> <p>PMRA No. 3428888 p. 1529</p>	<p>Non-guideline</p> <p>≥200 mg/kg bw/day: ↑ incidence of mild to moderate hepatocyte cytoplasm puffing and spotty necrosis, ↑ incidence and severity of renal tubular degeneration and abnormal dilations or renal corpuscles, ↓ urine CREA</p> <p>≥500 mg/kg bw/day: ↑ incidence of loose cytoplasm in renal corpuscles, Bowman’s capsule shrinks and minor exudation, ↑ AST, ↑ serum CREA</p> <p>1000 mg/kg bw/day: ↑ ALT, ↑ BUN</p> <p>Metabolomics profiling: In the serum sample, 27, 14, and 10 potential biomarkers were significantly differentially expressed between the control group and paclobutrazol-exposed groups of high dose, middle dose, and low dose, respectively. In the urine sample, 30, 19, and 13 potential biomarkers were significantly differentially expressed between the control group and paclobutrazol-exposed groups of high dose, middle dose, and low dose, respectively. Further analysis with MetaboAnalyst 4.0</p>

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	<p>identified 4 impacted metabolic pathways in the serum, including phenylalanine metabolism (L-phenylalanine; phenylpyruvate; hippurate), phenylalanine, tyrosine, and tryptophan biosynthesis (phenylpyruvate; L-phenylalanine), arachidonic acid metabolism (arachidonate), and tryptophan metabolism (L-tryptophan). There were 2 major metabolic pathways in the urine sample, including pentose and glucuronate interconversions (β-D-glucuronoside) and riboflavin metabolism (riboflavin).</p> <p>Network pharmacology: 1497 hepatotoxicity-related and 1181 nephrotoxicity-related targets were obtained. Ultimately, 133 hepatotoxicity- and 94 nephrotoxicity-related targets were tentatively identified using Venn analysis. In total, there were 10 related targets acquired after integrating metabolomics with the network pharmacology analysis result, of which 9 genes were hepatotoxicity-related (ALOX5, CYP1A2, CYP2A6, CYP2E1, MAOA, PLA2G2A, PTGS1, UGT2B7, XDH) and 4 were nephrotoxicity-related (CYP1A2, PLA2G2A, PLA2G4A, XDH). Of these, with the molecular docking approach, it was determined that CYP1A2, CYP2A6, XDH, CYP2E1, MAOA, PLA2G2A and PTGS1 had good binding affinity to the targets with a binding energy < -5.0 kcal/mol (after 100 times of docking analysis for each target)</p>
<p>Synergistic effect of fenpropathrin and paclobutrazol on early life stages of zebrafish (<i>Danio rerio</i>) (Wang et al., 2020)</p> <p>~350 zebrafish embryos (2 hours post-fertilization (hpf))/dish (in triplicate) were exposed to control vehicle or 1/320 (0.07 mg/L), 1/80 (0.29 mg/L) or 1/20 (1.2 mg/L) LC₅₀ at 96h of paclobutrazol for 96 hours</p> <p>PMRA No. 3428888 p. 1478</p>	<p>Non-guideline</p> <p>Paclobutrazol toxicity (LC₅₀ at 96h [mg a.i./L]): Embryos (23.43), juvenile (15.46) fish \leq adult (13.69), larval (13.16) fish</p> <p>0.07 mg/L: \uparrow GST, \downarrow p53 mRNA, \downarrow cas3 mRNA, \downarrow dio1 mRNA, \uparrow tsh mRNA, \uparrow ER beta1 mRNA, \downarrow crh mRNA</p> <p>0.07 and 1.2 mg/L: \uparrow ER alpha mRNA, \uparrow cyp17 mRNA</p> <p>\geq 0.07 mg/L: \uparrow T-SOD, \uparrow Cu/Zn-SOD, \uparrow ROS, \downarrow CYP450, \uparrow T4 levels</p> <p>0.29 mg/L: \uparrow MDA, \uparrow T3 levels, \downarrow vtg1 mRNA</p> <p>1.2 mg/L: \uparrow cas9 mRNA, \uparrow CXCL-clc mRNA, \uparrow IL-8 mRNA</p>

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<p>Single day treatment-a feasible tool in revealing not dependent on maternal toxicity teratogenic potential (Vergieva, 1998).</p> <p>13 Wistar rat dams/group dosed at 50 or 200 mg/kg bw/day from GD 6 to 15 by gavage in 0.5% water solution of gumma arabicum.</p> <p>or</p> <p>7-11 Wistar rat dams/group dosed with a single dose of 200 or 500 mg/kg bw on GD 7, 9, 11 or 13 by gavage in 0.5% water solution of gumma arabicum</p> <p>PMRA No. 3428888 p. 1368</p>	<p>Non-guideline</p> <p>Maternal toxicity</p> <p>≥50 mg/kg bw/day: ↓ bwg (GD 6-15 dosing)</p> <p>200 mg/kg bw/day: ↓ bw (GD 6-15 dosing)</p> <p>Developmental toxicity</p> <p>200 mg/kg bw/day (GD 6-15 dosing): combined open eyes and micrognathia (2/116 fetuses in 2/11 litters), cleft palate (2/39 fetuses), short mandibula (6.4%)</p> <p>200 mg/kg bw (GD 11 dosing): combined open eyes and micrognathia (14/76 fetuses in 3/6 litters), cleft palate (12/25, 48%)</p> <p>500 mg/kg bw (GD 9 dosing): shortened mandibular (7/60 fetuses)</p> <p>500 mg/kg bw (GD 11 dosing): external anomalies (21/58 fetuses in 5/6 litters), cleft palate (100% of fetuses examined), shortened mandibular (25/32 fetuses)</p>
<p>Integrated gender-related effects of profenofos and paclobutrazol on neurotransmitters in mouse.</p> <p>6 mice/sex/group dosed every two days at 0, 9.8, 24.5 or 49 mg/kg bw paclobutrazol in 0.5% CMC by gavage for 28 days</p> <p>(Xu and Yang, 2020).</p> <p>PMRA No. 3428888 p. 1502</p>	<p>Non-guideline</p> <p>≥ 9.8 mg/kg bw: ↓ 5-HIAA wks 3–4 (♂/♀); ↓ MNE at wks 3–4 (♂); ↓ 5-HT at wks 3–4 (♀)</p> <p>≥ 24.5 mg/kg bw: ↑ ACh at wk 2 (♂/♀); ↓ 5-HT at 2 wks, ↑ dopamine wk 1 (♂); ↓ ACh at wk 4 (♀)</p> <p>49 mg/kg bw: ↑ dopamine wks 3 (♂/♀); ↑ dopamine wk 2, ↑ ACh at wk 3 (♂), ↑ dopamine (wks 1 and 4), ↓ MNE at wks 3–4 (♀)</p> <p>Integrated biomarker response (IBR): In the female groups, the comprehensive responses for the six biomarkers increased at the first week of exposure as IBR of the mice were greater than zero. In the male groups, the neurotransmitter profiles in the mice increased at the first two weeks of exposure and then decreased in the following two weeks.</p>
<p>Paclobutrazol exposure induces apoptosis and impairs autophagy in hepatocytes via the AMPK/mTOR signaling pathway (Luo, 2021).</p>	<p>Non-guideline</p> <p>IC₅₀ at 72h: 360 μM, paclobutrazol + rapamycin slightly increased viability, paclobutrazol + 3-MA slightly decreased viability compared to paclobutrazol alone</p>

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<p>HepaRG human hepatocytes (8×10^4 cells/well) dosed at 0, 90, 180 or 360 μM paclobutrazol for 24 hours ($n = 6$, triplicate)</p> <p>HepaRG human hepatocytes (1×10^5 cells/well) dosed at 0, 90, 180 or 360 μM paclobutrazol for 72 hours ($n = 6$, triplicate) with or without rapamycin or 3-MA.</p> <p>PMRA No. 3428888 p. 720</p>	<p>$\geq 90 \mu\text{M}$: \uparrow ROS levels, \uparrow SOD levels, \downarrow ATG5 and BECN1 mRNA levels, \downarrow BECN1 protein levels, \uparrow p62 protein levels, \downarrow transformation LC3I to LC3II (decreased autophagy), \downarrow AMPK phosphorylation levels, \uparrow mTOR phosphorylation levels</p> <p>$\geq 180 \mu\text{M}$: \uparrow CAT levels, \uparrow MDA levels, \downarrow ATG5 protein levels</p> <p>360 μM: \uparrow annexinV-positive cells, \downarrow Bcl-2 levels, \uparrow Bax levels, \uparrow cleaved caspase-3 levels</p> <p>Resveratrol (20 μM) and AICAR (2 mM) prevented paclobutrazol induced effects on measured pro- and anti-apoptosis protein expression promoting autophagy and inhibiting apoptosis</p>
<p>Retinoic acid protects and rescues the development of zebrafish embryonic retinal photoreceptor cells from exposure to paclobutrazol (Wang, 2017).</p> <p>15 zebrafish embryos/group were exposed to 0, 0.1, 1, 5 or 10 ppm paclobutrazol with or without retinoic acid (RA) from 2 to 72 h post-fertilization (hpf), and paclobutrazol-treated embryos (2–72 hpf) were exposed to RA for additional hours until 120 hpf.</p> <p>PMRA No. 3428888 p. 1463</p>	<p>Non-guideline</p> <p>$\geq 0.1 \text{ ppm}$: \downarrow aldh1a2 (at 48 hpf)</p> <p>$\geq 1 \text{ ppm}$: \downarrow eye size, \downarrow photoreceptor layer, \downarrow aldh1a3 (at 48 hpf)</p> <p>5 ppm: \downarrow gnat1, \downarrow gnat2</p> <p>The paclobutrazol-induced decreased expression of aldh was reversed by retinoic acid. The paclobutrazol-induced decreased eye size was partly reversed by retinoic acid</p>
<p>Enantioselective neurotoxicity and oxidative stress effects of paclobutrazol in zebrafish (<i>Danio rerio</i>) (Guo et al., 2022).</p> <p>60 zebrafish/aquarium exposed to 10 mg/L (2SR, 3SR)-paclobutrazol [racemate], (2S, 3S)-paclobutrazol, (2R, 3R)-paclobutrazol or dimethyl sulfoxide sacrificed after 4, 7 or 14 days.</p> <p>PMRA No. 3396215 p. 160</p>	<p>Non-guideline</p> <p>LC₅₀ at 96 h of racemate: 20.89 mg/L LC₅₀ at 96 h of (2S, 3S)-paclobutrazol: 21.62 mg/L LC₅₀ at 96 h of (2R, 3R)-paclobutrazol: 18.41 mg/L</p> <p>\uparrow SOD and CAT activities (2% to 58%); (2R, 3R)-paclobutrazol exposed group at day 4 and 7 were 1.09–1.35-fold larger than those in (2S, 3S)-paclobutrazol-treated group</p> <p>\uparrow MDA (14% to 103%), \uparrow PC (5% to 82%); (2R, 3R)-paclobutrazol > (2S, 3S)-paclobutrazol-treated group</p>

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	<p>↓AChE, ↑ACh; AChE activity and ACh content in (2<i>R</i>, 3<i>R</i>)-paclobutrazol-treated group were 0.61–0.88 and 1.24–1.57 times than those in (2<i>S</i>, 3<i>S</i>)-paclobutrazol-treated group</p> <p>↑ CaN activities (36% to 86%); (2<i>R</i>, 3<i>R</i>)-paclobutrazol > (2<i>S</i>, 3<i>S</i>)-paclobutrazol (1.24-1.53 fold), ↑ TNOS (7% to 70%); (2<i>R</i>, 3<i>R</i>)-paclobutrazol > (2<i>S</i>, 3<i>S</i>)-paclobutrazol (1.21-1.53 fold)</p> <p>↑ DA (1.51-1.73 fold), ↓ Glu (1.16-1.70 fold), ↓ GABA (1.1-1.57 fold); (2<i>R</i>, 3<i>R</i>)-paclobutrazol > (2<i>S</i>, 3<i>S</i>)-paclobutrazol</p> <p>(2<i>R</i>, 3<i>R</i>)-paclobutrazol had stronger binding with the receptors than (2<i>S</i>, 3<i>S</i>)-enantiomer through molecular docking.</p> <p>The integrated biomarker response values further demonstrated that (2<i>R</i>, 3<i>R</i>)-paclobutrazol showed stronger toxicity to zebrafish than (2<i>S</i>, 3<i>S</i>)-enantiomer. All paclobutrazol treatments peaked after 7 days.</p>
<p>Toxic effects of paclobutrazol on developing organs at different exposure times in zebrafish (Wang et al., 2019).</p> <p>Zebrafish embryos (80/plate in triplicate) were exposed to 0, 0.34, 3.4 or 17 μM paclobutrazol beginning at 24, 36, 48, 60, 72 or 96 hours post-fertilization (hpf), and survival rate at 120 hpf was evaluated.</p> <p>PMRA No. 3428888 p. 1429</p>	<p>Non-guideline</p> <p>Survival rate</p> <p>≥ 3.4 μM: ↓ survival rate at 120 hpf (exposure starting from 48 hpf)</p> <p>17 μM: ↓ survival rate at 120 hpf (all exposures) an early paclobutrazol exposure had an impact on the survival rate of embryos: Exposure starting at 24 and 36 hpf led to lower survival rates compared to exposure starting at 48, 60, 72 or 96 hpf.</p> <p>Pericardial edema</p> <p>≥ 3.4 μM: ↑ incidence of pericardial edema at 120 hpf (exposure starting ≤ 48 hpf)</p> <p>17 μM: ↑ incidence of pericardial edema at 120 hpf (exposure starting at 60 or 72 hpf)</p> <p>Head skeleton, early embryonic stages and precursor cell differentiation</p> <p>≥ 3.4 μM: ↑ incidence of mild to severe malformation of pharyngeal arch development (embryos exposure</p>

Study type/Animal/PMRA No.	Study results
	<p>starting at 24 and 36 hpf). The severity of this observation decreased in embryos exposure starting at ≥ 60 hpf (no effects of paclobutrazol at 72 or 96 hpf).</p> <p>Developing digestive organs $\geq 0.34 \mu\text{M}$: \uparrow incidence and severity of liver-development adverse effects (exposure starting at 24 hpf). Adverse developmental effects in liver were less severe and frequent when exposure started after 48 hpf, even at the high dose, \uparrow incidence and severity of pancreas hypoplasia (exposure starting at 24 hpf). Adverse developmental effects in pancreas were less severe and frequent when exposure started from 36 hpf,</p> <p>0.34 and 3.4 μM: \uparrow incidence of mild to severe intestine hypoplasia (70% of embryos with exposure starting at 24 or 36 hpf)</p> <p>17 μM: \uparrow incidence of mild to severe intestine hypoplasia (100% of embryos with exposure starting at 24 or 36 hpf)</p> <p>Observation less frequent with exposure starting at 60 hpf and only 4% of embryos at the high dose with exposure starting at 96 hpf</p>
<p>The effect of paclobutrazol on the development of zebrafish (<i>Danio rerio</i>) embryos (Yekti et al., 2014).</p> <p>Zebrafish embryos exposed to 0, 5, 10, 20, 50, 100 or 150 ppm (equivalent to 0, 17, 34, 68, 170 or 340 μM) in 0.01% DMSO (in triplicate)</p> <p>PMRA No. 3428888 p. 1519</p>	<p>Non-guideline</p> <p>≥ 5 ppm: \uparrow pericardial edema at 3 dpf, \uparrow heart looping defect at 3 dpf, \downarrow heart beat rate at 3 dpf, \downarrow head length at 5 dpf, \downarrow eye size at 5 dpf, \downarrow ceratohyal cartilage length and width at 5 dpf, \downarrow lower jaw length at 5 dpf, \downarrow trabecula length at 5 dpf, \downarrow col2a1 expression at 5 dpf (chondrocytes maturation)</p> <p>≥ 10 ppm: \uparrow apoptosis in the pericardial heart chamber at 3 dpf, \downarrow sox9a expression in the pharynx at 2 dpf (craniofacial chondrocyte differentiation and maturation), \downarrow dlx2 expression at 1.5 dpf (migratory neural crest cells)</p> <p>≥ 20 ppm: \downarrow survival at 5 dpf, \downarrow hatching rate at 5 dpf, \downarrow head width at 5 dpf</p>
<p>Waterborne exposure of paclobutrazol at environmentally relevant concentration induces locomotion hyperactivity in larvae and anxiolytic</p>	<p>Non-guideline</p> <p>1. $\geq 10 \mu\text{g/L}$: \uparrow burst movement per minute</p>

Study type/Animal/PMRA No.	Study results
<p>exploratory behavior in adult zebrafish (Hussain, 2020).</p> <p>1. Acute neurotoxicity in 96 hours post-fertilization (hpf) zebrafish larvae (48/group) exposed to 10 or 100 µg/L paclobutrazol for 24 hours. Or 2. Subchronic neurotoxicity in 6-month old adult zebrafish (30 fish/group) exposed to 100 or 1000 µg/L paclobutrazol for 14 days.</p> <p>PMRA No. 3428888 p. 340</p>	<p>light and dark periods (3- to 1.5-folds), ↑ rotation movement in the dark period</p> <p>10 µg/L: ↓ total distance traveled in both dark and light periods, ↓ distance covered light+dark period</p> <p>100 µg/L: ↑ distance covered in the dark period, ↓ distance covered in the light period</p> <p>2. ≥100 µg/L: ↑ time spent in the top and total distance travelled at the top</p> <p>≥100 µg/L: ↓ average speed, ↑ freezing time movement, ↓ rapid movement time ratio</p> <p>1000 µg/L: ↓ mirror biting, ↓ longest duration in the mirror side, ↑ Ach, ↓ AChE, ↓ GABA, ↑ DA, ↓ SOD, ↓ ROS, ↓ cortisol, ↓ 5-HT</p>
<p>Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro (Andersen et al., 2002).</p> <p>MCF-7 cells dosed at 10^{-8} to 5×10^{-5} M paclobutrazol in ethanol in presence of absence of 10 pM 17β-estradiol (triplicate or quadruplicate)</p> <p>ER transactivation: 2×10^5 MCF-7 cells per well dosed at 10^{-8} to 5×10^{-5} M paclobutrazol in ethanol in triplicate or quadruplicate</p> <p>AR transactivation: 5×10^3 CHO cells per well in DMEM/F12 containing 10% charcoal-treated FBS dosed at 10^{-8} to 5×10^{-5} M paclobutrazol in ethanol in presence or absence of synthetic androgen R1881 (triplicate or quadruplicate). Hydroxyflutamide 0.1–1000 nM used as positive control</p> <p>Aromatase assay: Human placental microsomes tested at 50 µM paclobutrazol.</p>	<p>Non-guideline</p> <p>Cytotoxicity of paclobutrazol: MCF-7 cells: > 100 µM CHO cells: > 100 µM</p> <p>Estrogenicity of paclobutrazol: Results not reported for paclobutrazol</p> <p>Androgenicity of paclobutrazol: Paclobutrazol did not act as agonist. Paclobutrazol caused an inhibition of AR transactivation at ≥ 20 µM in presence or absence of androgen R1881</p> <p>Aromatase activity of paclobutrazol: No agonistic or antagonistic activity</p>

Study type/Animal/PMRA No.	Study results
4-OH ASDN at 1 µM used as positive control. PMRA No. 3428888 p. 1	
Effects of currently used pesticides in the AhR-CALUX assay: Comparison between the human TV101L and the rat H4IIE cell line (Long et al., 2003). In vitro AhR-chemically activated luciferase expression (CALUX) assay Human TV101L hepatoma cells (7 × 10 ⁴ cells per plate) Rat H4IIE hepatoma cells (2.21 × 10 ⁵ cells/mL) Both assays performed at 1, 2, 10, 25 or 50 µM paclobutrazol in ethanol (in quadruplicate) in presence (antagonistic effects) or absence (agonistic effects) of positive control TCDD at 10 nM (TV101L) or 10 pM (H4IIE) PMRA No. 3428888 p. 703	Non-guideline Paclobutrazol elicited differential responses in the two cell lines: Weak agonistic response in human cell line, no response in rat cell line Human TV101L cell line LOEC: 50 µM, effect observed was 182% (agonistic response) of control solvent in absence of TCDD MOEC: 50 µM No antagonistic response was observed Rat H4IIE cell line No agonistic or antagonistic effect response

Table 4 Toxicity profile of end-use product TRIMMIT containing paclobutrazol

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons.

Study type/Animal/PMRA #	Study results
Acute toxicity studies	
Acute Oral (up-and-down) Rat (Wistar) PMRA No. 3116762	LD ₅₀ ♀ = 2958 mg/kg bw 5000 mg/kg bw: all animals died within 2 days, dark red discoloration of the lungs 1750 mg/kg bw: decreased activity, hunched posture and incoordination, recovery by Day 1 Low acute oral toxicity

Study type/Animal/PMRA #	Study results
Acute Dermal Rat (Wistar) PMRA No. 3116763	LD ₅₀ ♂♀ > 5000 mg/kg bw Low acute dermal toxicity
Acute Inhalation Rat (Wistar) PMRA No. 3116764	LC ₅₀ ♂♀ > 3.99 mg/L 2.67 mg/L: one female died on Day 1 ≥ 2.67 mg/L: laboured respiration, increased respiratory rate, hunched posture, ataxia, decreased activity, prostration, weak and wasted condition. Animals recovered and all clinical signs ceased on Day 3 or 7. Decedent had dark red discoloration of the lungs Low acute inhalation toxicity
Primary Eye Irritation Rabbit (New Zealand white) PMRA No. 3116765	MAS ^a = 0/110 MIS ^b = 2/110 at 1 hour Non-irritating
Primary Skin Irritation Rabbit (New Zealand white) PMRA No. 3116766	MAS ^a = 0/8 MIS ^b = 0/8 Non-irritating
Skin Sensitization LLNA Mouse (CBA/J) PMRA No. 3116767	Negative Not a dermal sensitizer

Table 5 Toxicology reference values for use in health risk assessment for paclobutrazol

Exposure scenario	Study	Point of departure and endpoint	CAF ¹ or target MOE
Acute dietary (general population)	Acute oral neurotoxicity study in rats	NOAEL = 30 mg/kg bw Decreased number of rearings at 150 mg/kg bw.	100
ARfD = 0.3 mg/kg bw			

Exposure scenario	Study	Point of departure and endpoint	CAF ¹ or target MOE
Acute dietary (females 13-49 years of age)	Oral developmental toxicity study in rats	Developmental NOAEL = 10 mg/kg bw Increased incidence of skeletal variations at 40 mg/kg bw/day in the absence of maternal toxicity	300
ARfD = 0.03 mg/kg bw			
Repeated dietary	2-year dietary combined carcinogenicity/chronic toxicity study in rats	NOAEL = 2.1 mg/kg bw/day Increased incidence of liver lesions (hypertrophy/steatosis) and decreased body weight gain at 11 mg/kg bw/day	100
ADI = 0.02 mg/kg bw/day			
Short- and intermediate-term dermal (adults and youth) ²	Oral developmental toxicity study in rats	Developmental NOAEL = 10 mg/kg bw/day Increased incidence of skeletal variations at 40 mg/kg bw/day in the absence of maternal toxicity.	300
Short- and intermediate-term inhalation (adults) ³	Oral developmental toxicity study in rats	Developmental NOAEL = 10 mg/kg bw/day Increased incidence of skeletal variations at 40 mg/kg bw/day in the absence of maternal toxicity	300
Short- and intermediate term dermal (children)	28-day dietary range-finding toxicity study in rats	NOAEL for liver effects = 4.6 mg/kg bw/day Increased incidence of liver midzonal macrovacuolation, increased liver weight, increased cholesterol, increased incidence of hepatocellular hypertrophy at 87 mg/kg bw/day	100
Short- and intermediate term aggregate (adults and youth) Oral and dermal	Oral and dermal: Oral developmental toxicity study in rats	Common endpoint: Increased incidence of skeletal variations Oral and Dermal: Developmental NOAEL = 10 mg/kg bw/day	Oral and dermal: 300
Short- and intermediate term aggregate (children) Oral and dermal	Oral and dermal: 28-day dietary range-finding toxicity study in rats	Common endpoint: Liver toxicity Oral and dermal: NOAEL for liver effects = 4.6 mg/kg bw/day	Oral and dermal: 100
Cancer	Equivocal evidence of tumourigenicity in the rat at the highest dose tested. Toxicology reference values selected for non-cancer risk assessment are protective of any residual concerns regarding carcinogenic potential.		

¹ CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary

assessments; MOE (margin of exposure) refers to a target MOE for occupational and residential assessments.

² Since an oral NOAEL was selected, a dermal absorption factor (19.3%) was used in a route-to-route extrapolation.

³ Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 6 AHETF/PHED/ORETF unit exposures for chemical handler risk assessment

Scenario	Unit exposure (µg/kg a.i. handled)					
	Worker task	Personal protective equipment	Dermal	Dermal adjusted with 19.3% dermal absorption	Inhalation	Dermal + Inhalation
AHETF exposure for Mixing/Loading + Application (ML + A)						
A	Open mixing & loading Liquid, (AHETF)	Single layer (SL) + Chemical-resistant (CR) gloves	58.5	11.29	0.63	11.92
B	Applicator, open-cab groundboom (AHETF)	SL + CR gloves	25.4	4.90	1.68	6.58
AHETF exposures for Mixing + Loading + Application (M/L/A)						
A + B	Open mixing & loading + groundboom application	SL + CR gloves	83.9	16.19	2.31	18.50
ORETF (M/L/A)						
Turf handgun sprayer (M/L/A)		SL + CR gloves	785 (median)	151.51	4	155.51
PHED (M/L/A)						
Backpack sprayer (M/L/A)		SL+ CR gloves	5445.85	1051.05	62.1 (moderate)	1113.15

AHETF = Agriculture Handler Exposure Task Force

ORETF= Outdoor Residential Exposure Task Force

PHED = Pesticide Handler Exposure Database

Table 7 Mixer/Loader/Applicator (M/L/A) and risk for TRIMMIT

Equipment	Task	PPE	M/L/A unit exposure (µg/kg a.i. handled) ¹ (Dermal, adjusted for 19.3% dermal absorption +Inhalation)	Maximum rate (kg a.i./ha)	ATPD (ha/day) ²	Total daily exposure (mg/kg bw/day) ³	MOE ⁴ target MOE = 300
						Dermal + Inhalation	Dermal + Inhalation
Groundboom	MLA	SL + CR gloves	18.5 (AHETF)	0.277	16	0.00103	9756
Turf handgun sprayer	MLA	SL + CR gloves	155.51 (ORETF)	0.277	16	0.00861	1161
Backpack sprayer	MLA	SL + CR gloves	1113.15 (PHED)	0.277	0.375	0.00145	6919

SL = Single layer of clothing, a long sleeved-shirt and long pants

CR = Chemical-resistant gloves

MLA = Mixer, loader and applicator

AHETF = Agriculture Handler Exposure Task Force

ORETF = Outdoor Residential Exposure Task Force

PHED = Pesticide Handler Exposure Database

¹ AHETF/ORETF/PHED total (adjusted dermal + inhalation) unit exposures from Table 6.

² Default Area Treated per day (ATPD table, 20-9-2017). For backpack sprayer, 150 L can be applied per day with a minimum of 400 litres/ha spray dilution = 0.375 ha/day

³ Total daily exposure = (Combined unit exposure (dermal adjusted with 19.3% dermal absorption + inhalation)) × ATPD × rate / (80 kg bw × 1000 µg/mg).

⁴ For paclobutrazol, NOAEL of 10 mg/kg bw/day from a rat development study, target MOE = 300.

Table 8 Postapplication occupational exposure and risk for TRIMMIT on day 0 after last application

Crop	# of total applications ¹ ; RTI (days)	Rate (g a.i./ha)	TTR ($\mu\text{g}/\text{cm}^2$) ²	Postapplication activity	TC (cm^2/hr) ³	Exposure (mg/kg bw/day) ⁴	MOE ⁵
Golf course turf	3; 7	277	0.0473	Transplanting, Planting, harvesting	6700	0.0061	1635
				Mowing, watering, irrigation repair, cup changing, misc. grooming	3500	0.0032	3130
				Scouting, hand pruning, aerating, mechanical weeding, seeding	1000	0.0009	10954

¹RTI = Retreatment Interval, the shortest re-treatment interval of 7 days supported by VRD was used to calculate TTR.

²Day zero TTR after third application on golf course turf, calculated as the standard 1% TTR after first application, 10% dissipation per day.

³ARTF Transfer coefficients from PMRA TC Table (July 11, 2018)

⁴Dermal Exposure = (Peak TTR \times TC \times 8 hr/day \times 19.3% dermal absorption) / (80 kg BW \times 1000 $\mu\text{g}/\text{mg}$)

⁵Based on short-to intermediate-term NOAEL of 10 mg/kg bw/day, target MOE = 300

Table 9 Postapplication residential/recreational exposure and risk for golfers

Postapplication activity	Dermal absorption (DA)	TTR ¹ ($\mu\text{g}/\text{cm}^2$)	Age (yrs.)	TC ² (cm^2/hr)	ED ³ (hr/day)	BW ⁴ (kg)	Exposure ⁵ (mg/kg bw/day)	MOE ⁶
Golfing	19.3% (PRVD 2013-04)	0.0473	16+	5300	4	80	0.0024	4134
			11 – <16	4400	4	57	0.0028	3548
			6 – <11	2900	4	32	0.0033	1390

¹ Day zero TTR after third application, calculated in the default DFR calculator using the standard 1% TTR after first application and 10% dissipation per day.

² TC = Transfer coefficients from Residential SOPs

³ ED = Exposure duration

⁴ BW = Body weight

⁵ Exposure = (dermal absorption value of 19.3% \times Peak TTR \times TC \times ED) / (BW \times 1000 $\mu\text{g}/\text{mg}$)

⁶ Based on the NOAEL of 10 mg/kg bw/day for adults and youth and 4.6 mg/kg bw/day for children 6-<11, target MOE = 300 for adults and youth and 100 for children.

Table 10 Major fate inputs for the modelling of the combined residues of paclobutrazol, CGA 149907 and NOA 457654

Fate Parameter	Value	Details
K_{oc}	7.04 L/kg	20 th percentile of 4 K_{oc} values
Water half-life*	Stable	Single study
Sediment half-life**	3600 days	Longer of 2 values (1 study on 2 systems)
Photolysis half-life	300 days	Single value
Hydrolysis	Stable	Single study
Soil half-life	3268 days	90% upper confidence bound on the mean from 4 soils

*Aquatic whole system

** Anaerobic aquatic whole system

Table 11 Level 1 EECs of combined residues of paclobutrazol, CGA 149907, and NOA 457654 in potential sources of drinking water as the parent equivalent for the combined residue

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)		
	Peak ¹	Average ²	Daily ³	Yearly ⁴	Overall ⁵
1 application of 172.5 g a.i./ha plus 3 applications of 280 g a.i./ha at 7-day interval	1500	1400	54	9.5	6.6

¹ peak of daily concentrations² average of post-breakthrough concentrations³ 90th percentile of the highest 1-day average concentration from each year⁴ 90th percentile of yearly average concentrations⁵ Average of all yearly average concentrations**Table 12 Refined EECs of combined residue of paclobutrazol, CGA 149907, and NOA 457654 in potential sources of drinking water as the parent equivalent**

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)		
	Peak ¹	Average ²	Daily ³	Yearly ⁴	Overall ⁵
1 application of 172.5 g a.i./ha plus 3 applications of 280 g a.i./ha at 7-day interval applied to turf	91	78	54	9.5	6.6

¹ peak of daily concentrations² average of post-breakthrough concentrations³ 90th percentile of the highest 1-day average concentration from each year⁴ 90th percentile of yearly average concentrations⁵ Average of all yearly average concentrations

Table 13 Dietary exposure risk assessment

Dietary risk from food and drinking water		
Acute dietary exposure assessment, 95th percentile	Population	Estimated risk % of acute reference dose (ARfD)
		Drinking Water
-ARfD = 0.3 mg/kg bw, except for females₁₃₊ -ARfD = 0.03 mg/kg bw for females₁₃₊ Estimated acute drinking water concentration (Refined, Level 1 ground water, peak of daily concentrations) = 0.091 ppm	All infants <1 year	5.5
	Children 1–2 years	2.3
	Children 3–5 years	1.8
	Children 6–12 years	1.4
	Males 13–19 years	1.5
	Males 20–49 years	1.5
	Adults 50+ years	1.4
	Females 13–49 years	16
Chronic dietary exposure assessment	Population	Estimated risk % of acceptable daily intake (ADI)
		Drinking Water
ADI = 0.02 mg/kg bw/day Estimated chronic drinking water concentration (Refined, Level 1 ground water, average of post-breakthrough concentrations) = 0.078 ppm	All infants <1 year	29.4
	Children 1–2 years	10.8
	Children 3–5 years	8.8
	Children 6–12 years	6.6
	Youth 13–19 years	5.6
	Adults 20–49 years	7.8
	Adults 50+ years	7.6
	Females 13–49 years	7.7
	Total population	7.9

Table 14 Aggregate exposure and risk for golfers

Custom population subgroup ¹	Exposure (mg/kg bw/day)			Aggregate MOE ³ (Target = 300)
	Postapplication (golfing) dermal ¹	Drinking water dietary exposure (mg/kg bw/day) ²	Aggregate exposure (dermal + dietary)	
Adults (16 <80 years old)	0.0024	0.001528	0.003928	2546
Youth (11 – <16 years old)	0.0028	0.001049	0.003849	2598
Children (6 – <11 years old)	0.0033	0.001369	0.00467	985

¹Postapplication dermal exposure from Table 9

²Values are the mean per capita.

³Aggregate MOE = short- to intermediate-term Aggregate NOAEL of 10 mg/kg bw/day for adults and youth or 4.6 mg/kg bw/day for children 6–<11 years of age/aggregate exposure. Target MOE is 300 for adults and youth and 100 for children 6 to <11 years of age.

Table 15 Fate and behaviour of paclobutrazol in the environment

Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
Abiotic transformation							
Hydrolysis	Paclobutrazol	Sterile aqueous buffered solutions (pH 4, 7 and 9) at 25°C	Stable	N/A	None	Paclobutrazol is stable to hydrolysis.	1232571
Photo-transformation on soil	Paclobutrazol	18 Acres soil (sandy loam; pH 6.6, 4.3% OM)	t_R/DT_{50} (summer sunlight equivalent at 25–30°N) = 172 days	SFO	None	Paclobutrazol does not undergo significant phototransformation on soil.	1232573
Aqueous photo-transformation	Paclobutrazol	Sterile pH 7 buffer water	t_R/DT_{50} (summer sunlight equivalent at 30–50°N) = 134 days	SFO	None	Paclobutrazol does not undergo significant aqueous phototransformation.	3116818
Photo-transformation in air	Paclobutrazol is not expected to be volatile under field conditions based on its vapour pressure (0.0019 mPa at 25°C) and Henry's law constant ($1/H \geq 10^8$ at 20°C). The AEROWIN (version 1.0) program in EPI Suite (version 4.11) predicts that 82% to 91% of paclobutrazol in the atmosphere is expected to be sorbed to atmospheric particles. The sorbed fraction may be resistant to atmospheric oxidation. Given the large fraction of paclobutrazol predicted to be sorbed to atmospheric particles, the AOPWIN program (version 1.92) in EPI Suite is not suitable for predicting the atmospheric half-life of paclobutrazol. A phototransformation study in air is not required.						N/A
Biotransformation							
Biotransformation in aerobic soil ²	Paclobutrazol	Sarpy soil (loam; pH 6.7, 2.2% OC)	$t_R = 1573$ days $DT_{50} = 313$ days	DFOP	CGA 149907 CO ₂ Unextracted residues	Paclobutrazol is classified as persistent in this soil.	3116820

Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
	Paclobutrazol	18 Acres soil (loam; pH 6.6, 2.7% OC)	$t_R = 748$ days $DT_{50} = 547$ days	DFOP	CGA 149907 CO ₂	Paclobutrazol is classified as persistent in this soil.	1232582
	Paclobutrazol	18 Acres soil (sandy clay loam; pH 5.7, 2.6% OC)	$t_R/DT_{50} = 283$ days	SFO	Unextracted residues	Paclobutrazol is classified as persistent in this soil.	1450165
		Gartenacker soil (sandy loam; pH 7.7, 2.2% OC)	Paclobutrazol $t_R/DT_{50} = 30.5$ days CGA 149907 $t_R/DT_{50} = 101$ days NOA 457654 $t_R/DT_{50} = 253$ days	SFO SFO SFO	CGA 149907 NOA 457654 (as tautomer pair with ketone) Unextracted residues	Paclobutrazol is classified as slightly persistent in this soil. CGA 149907 is classified as moderately persistent in this soil. NOA 457654 is classified as persistent in this soil.	
		Pappelacker soil (sandy loam; pH 7.7, 1.3% OC)	$t_R/DT_{50} = 27.1$ days CGA 149907 $t_R/DT_{50} = 55.2$ days NOA 457654 $t_R/DT_{50} = 407$ days	SFO SFO SFO	CGA149907 NOA 457654 (as tautomer pair with ketone) Unextracted residues CO ₂	Paclobutrazol is classified as slightly persistent in this soil. CGA 149907 is classified as moderately persistent in this soil. NOA 457654 is classified as persistent in this soil.	
	CGA149907	Frensham	$t_R = 357$ days	DFOP	The study did	CGA 149907 is	3116821

Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
	(synonym: R079105)	(sandy loam; pH 5.7, 1.3% OC)	DT ₅₀ = 39.2 days		not attempt to identify TPs.	classified as slightly persistent in this soil.	
		18 Acres (sandy clay loam; pH 6.1, 2.3% OC)	t _R = 206 days DT ₅₀ = 71.5 days	DFOP		CGA 149907 is classified as moderately persistent in this soil.	
		Gartenacker (loam; pH 7.5, 1.8% OC)	t _R /DT ₅₀ = 23.4 days	SFO		CGA 149907 is classified as slightly persistent in this soil.	
	NOA457654 (synonym: hydroxyl-triazole)	18 Acres (sandy clay loam; pH 5.2, 2.4% OC)	t _R /DT ₅₀ = 5.8 days	SFO	Unextracted residues CO ₂	NOA 457654 is classified as non-persistent in these soils.	3116830
		Gartenacker (silt loam; pH 7.0, 2.6% OC)	t _R /DT ₅₀ = 3.1 days	SFO	Unextracted residues CO ₂		
		Borstel (loamy sand; pH 6.0, 0.85% OC)	t _R /DT ₅₀ = 8.6 days	SFO	Unextracted residues CO ₂		
		Pappelacker (sandy loam; pH 7.1, 1.7% OC)	t _R /DT ₅₀ = 2.9 days	SFO	Unextracted residues CO ₂		
Biotransformation in anaerobic soil	Paclobutrazol	Sarpy (loam; pH 6.7, 2.2% OC)	Stable	N/A	None	Paclobutrazol is classified as persistent in anaerobic soil.	3116826
Biotransformation in aerobic water-	Paclobutrazol	Winchester Lake (water: pH 7.7,	t _R /DT ₅₀ = 647 days (whole	SFO	None	Paclobutrazol is classified as persistent in these aerobic	3116827

Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
sediment systems		3.1 mg/L DOC; sediment: sand, 0.6% OC)	system)		Unextracted residues	aquatic test systems. It partitioned rapidly from water to sediment.	
			$t_R = 135$ days; DT ₅₀ = 23.6 days (water)	DFOP			
			Stable (sediment)	N/A			
		Lake Okeechobee (water: pH 7.9, 36.7 mg/L DOC; sediment: sandy loam, 24.2% OC)	Stable (whole system)	N/A			
			$t_R = 7.1$ days; DT ₅₀ = 1.9 days (water)	IORE			
			Stable (sediment)	N/A			
Biotransformation in anaerobic water systems	Paclobutrazol	Winchester Lake (water: pH 8, 2.4 mg/L DOC; sediment: sand, 0.4% OC)	t_R /DT ₅₀ = 511 days (whole system)	SFO	CGA 149907 Unextracted residues	Paclobutrazol is classified as persistent in these anaerobic aquatic test systems. It partitioned rapidly from water to sediment.	3116829
			$t_R = 274$ days; DT ₅₀ = 22 days (water)	DFOP			
			t_R /DT ₅₀ = 357 days (sediment)	SFO			
		Lake Okeechobee (water: pH 8, 15.5 mg/L DOC; sediment: sandy loam,	$t_R = 846$ days; DT ₅₀ = 723 days (whole system)	DFOP			
			$t_R = 5.2$ days; DT ₅₀ = 2.4 days (water)	IORE			

Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
		14.1% OC)	Stable (sediment)	N/A			
Mobility							
Adsorption / desorption in soil	Paclobutrazol	Kagoshima (sandy loam, pH 5.8, 1.7% OC)	$K_{OC} = 88.6$ mL/g	N/A	N/A	Paclobutrazol is classified as having high mobility in this soil.	3195716
		ERTC (sandy loam, pH 4.8, 0.3% OC)	$K_{OC} = 237$ mL/g	N/A	n/a	Paclobutrazol is classified as having medium mobility in this soil.	
		Wisborough Green (silty clay loam, pH 4.8, 2.5% OC)	$K_{OC} = 99.7$ mL/g	N/A	N/A	Paclobutrazol is classified as having high mobility in this soil.	
		Aberford (clay loam, pH 7.2, 5.1% OC)	$K_{OC} = 33.4$ mL/g	N/A	N/A	Paclobutrazol is classified as having very high mobility in this soil.	
	CGA 149907	NRTC (sandy loam, pH 5.1, 2.0% OC)	$K_{OC} = 458$ mL/g	N/A	N/A	CGA 149907 is classified as having medium mobility in this soil.	3116833
		Kenny Hill (sandy loam, pH 7.4, 3.6% OC)	$K_{OC} = 208$ mL/g	N/A	N/A	CGA 149907 is classified as having medium mobility in this soil.	
		18 Acres (silty clay, pH	$K_{OC} = 265$ mL/g	N/A	N/A	CGA 149907 is classified as having	

Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
		5.9, 2.9% OC)				medium mobility in this soil.	
		ERTC (sandy clay loam, pH 4.8, 0.3% OC)	$K_{OC} = 577$ mL/g	N/A	N/A	CGA 149907 is classified as having low mobility in this soil.	
		Frensham (sandy loam, pH 5.9, 1.2% OC)	$K_{OC} = 406$ mL/g	N/A	N/A	CGA 149907 is classified as having medium mobility in this soil.	
		Gartenacker (loam, pH 7.1, 2.3% OC)	$K_{OC} = 213$ mL/g	N/A	N/A	CGA 149907 is classified as having medium mobility in this soil.	
	NOA 457654	Borstel (loamy sand, pH 6.4, 1.4% OC)	$K_{OC} = 6.95$ mL/g	N/A	N/A	NOA 457654 is classified as having very high mobility in this soil.	3116831
		Gartenacker (loam, pH 7.3, 2.3% OC)	$K_{OC} = 8.00$ mL/g	N/A	N/A	NOA 457654 is classified as having very high mobility in this soil.	
		Pappelacker (sandy loam, pH 6.9, 2.1% OC)	$K_{OC} = 7.10$ mL/g	N/A	N/A	NOA 457654 is classified as having very high mobility in this soil.	
		18 Acres (loam, pH not reported, 2.7% OC)	$K_{OC} = 11.5$ mL/g	N/A	N/A	NOA 457654 is classified as having very high mobility in this soil.	

Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
Soil leaching	Paclobutrazol	18 Acres (sandy loam, pH 6.3, 4.7% OM)	Soils were aged for nine weeks and were then leached for nine weeks.		None in the leachate	Triazole-labelled paclobutrazol was shown to have low mobility in this soil while methine-labelled paclobutrazol was immobile.	1232580
		Frenshem (loamy sand, pH 5.8, 2.0% OM)	During the aging period, unextracted residue (triazole-label only) and CGA 149907 were major transformation products, only in Gore Hill soil.		None in the leachate	Triazole-labelled paclobutrazol was shown to be mobile in this soil while methine-labelled paclobutrazol was immobile.	
		Gore Hill (clay loam, pH 7.5, 14% OM)	More than 85% of the total recovered radioactivity during the leaching period remained in the soil, while up to 13% was in leachate. Most of the recovered radioactivity in soil was in the top 10–15 cm.		None in the leachate	Triazole-labelled paclobutrazol was shown to be mobile in this soil while methine-labelled paclobutrazol was immobile.	
		Lilyfield (coarse sand, pH 5.7, 0.98% OM)	Neither paclobutrazol nor CGA 149907 were detected in leachate.		None in the leachate	Triazole-labelled paclobutrazol was shown to have low mobility in this soil while methine-labelled paclobutrazol was immobile.	

Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
Volatilization	A volatilization study is not required. Paclobutrazol is not expected to be volatile under field conditions based on its vapour pressure (0.0019 mPa at 25°C) and Henry's law constant ($1/H \geq 10^8$ at 20°C).						
Field studies							
Terrestrial field dissipation	Paclobutrazol formulated as 250 g a.i./L SC	Simcoe, Ontario (bare sandy loam soil, pH 7.5 and 1.99% OM in the 0–30 cm depth range)	$t_R = 277$ days $DT_{50} = 68$ days	DFOP	None	<p>Paclobutrazol declined to 26% of the initially applied mass in the 0 to 10 cm soil layer 364 days after treatment. Paclobutrazol is classified as moderately persistent in this soil, and is not likely to carry over from year to year.</p> <p>CGA 149907 was found in low amounts throughout the study, and reached a maximum concentration 281 days after treatment.</p> <p>Neither paclobutrazol nor CGA 149907 were detected in the 10 to 30 cm layer at any time up to 833 days after treatment. Since precipitation and irrigation data were</p>	3116770

Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
						not provided in the study report, it is uncertain if paclobutrazol and CGA 149907 may leach in this soil.	
		St. Davids, Ontario (bare silty clay soil, pH 7.7 and 4.28% OM in the 0–30 cm depth range)	$t_R = 181$ days $DT_{50} = 49$ days	DFOP	None	<p>Paclobutrazol declined to 9% of the initially applied mass in the 0 to 10 cm soil layer 366 days after treatment. Paclobutrazol is classified as moderately persistent in this soil, and is not likely to carry over from year to year.</p> <p>CGA 149907 was found in low amounts until 366 days after treatment, and reached a maximum concentration 295 days after treatment.</p> <p>Neither paclobutrazol nor CGA 149907 were detected in the 10 to 30 cm layer at any time up to 850 days</p>	

Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
						after treatment. Since precipitation and irrigation data were not provided in the study report, it is uncertain if paclobutrazol and CGA 149907 may leach in this soil.	
	Paclobutrazol formulated as 25% SC	New York, USA (bare soil site; 0-45 cm: loam, 45-120 cm: sandy loam; pH 7.1-8.4, 0.1-2.0% OC)	$t_R = 154.6$ days $DT_{50} = 63.8$ days	IORE	None	<p>Paclobutrazol decreased to 11–12% AR in the 0 to 10 cm layer at 359 days. Paclobutrazol is classified as moderately persistent in the New York soil, and is not likely to carry over from year to year.</p> <p>Paclobutrazol was not specifically analyzed in soil samples collected below 10 cm of depth, because less than 1% AR was found in core sections from 10 to 40 cm depth. Thus, paclobutrazol leaching was negligible in the</p>	3116769

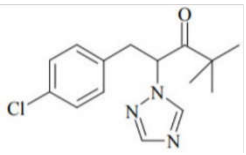
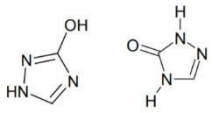
Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
						New York soil. Soil solution samples collected from 30 and 40.6 cm depth below a triazole-label test plot across 11 months of a terrestrial field dissipation study in California support the conclusion of negligible leaching of triazole-label paclobutrazol.	
Bioconcentration							
Bioconcentration in fish	Paclobutrazol	Bluegill sunfish (<i>Lepomis macrochirus</i>) were exposed to paclobutrazol under flow-through conditions at a nominal concentration of 0.5 mg a.i./L for an uptake period of 14 days, followed by a depuration	Whole-fish maximum BCF = 44 L/kg Elimination of paclobutrazol after three days of depuration was >95%. Residues returned to background levels after seven days of depuration.	N/A	Transformation products were not measured.	Paclobutrazol does not readily bioconcentrate in fish tissue under the conditions of the study. However, paclobutrazol concentrations were highly variable during the uptake period. Steady-state concentrations during uptake could not be confirmed. Measured and modelled whole-fish BCF data for several	3116847 3346669

Study type	Test item	Test medium	Value	Kinetic model	Identified major TPs ¹	Comments	PMRA No.
		period of 14 days.				<p>triazole compounds with structural similarity and a similar mode of action to paclobutrazol support a low BCF (in other words, < 100 L/kg) for paclobutrazol.</p> <p>Thus, paclobutrazol is unlikely to bioconcentrate or bioaccumulate in aquatic organisms.</p>	

¹ Unextracted residues are presented as a major transformation product as they were formed at >10% AR; however, the composition is unknown and may represent a mixture of the parent and TPs.

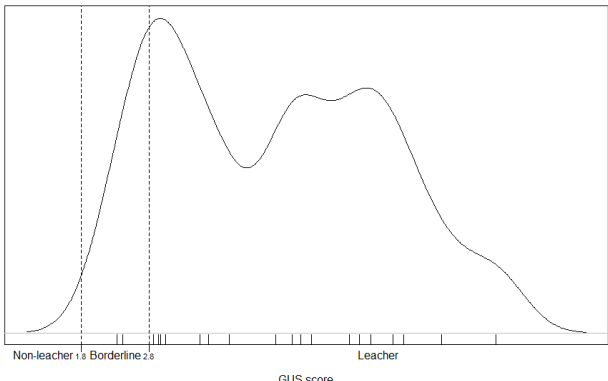
² Biotransformation in aerobic soil: the 90% upper confidence level on the mean of the t_R values from the four available soils (with the 18 Acres soils averaged) is 1130 days.

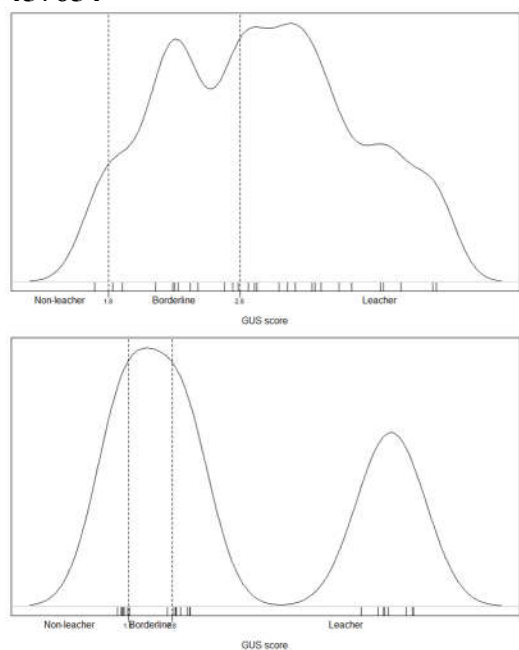
Table 16 Major transformation products of paclobutrazol

Major transformation product	Maximum mean concentration	Comments
<p>CGA 149907</p>  <p>Synonyms: CGA 132263, R 079105, ketone</p> <p>IUPAC: (2RS)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)pentan-3-one</p> <p>Molecular weight: 291.8 g/mole</p>	<p>Hydrolysis: not identified</p> <p>Phototransformation on dry soil: 4.15% AR (Day 33, irradiated; N/A for dark controls)</p> <p>Aqueous phototransformation: 8.7% AR (Day 30, irradiated; N/A for the dark controls)</p> <p>Aerobic biotransformation in soil: 26.3% AR (Day 35)</p> <p>Anaerobic biotransformation in soil: 10.7% AR (Day 31)</p> <p>Aerobic aquatic biotransformation: <3% AR (reported as total with other minor transformation products)</p> <p>Anaerobic aquatic biotransformation: 25.0% AR (Day 365)</p> <p>K_{oc}: mean of 355 (range of 208 to 577) mL/g</p>	<p>Major transformation product of the biotransformation of paclobutrazol in aerobic soil and anaerobic aquatic systems.</p> <p>Not considered a major transformation product in anaerobic soil as test system was still aerobic at the time >10% AR was observed.</p>
<p>NOA 457654</p>  <p>Synonyms: NOA457654, triazolone, R118624</p> <p>IUPAC: 1H-1,2,4-triazol-3-ol; 2,4-dihydro-1,2,4-triazol-3-one</p> <p>Molecular weight: 85.03 g/mole</p>	<p>Hydrolysis: not identified</p> <p>Phototransformation on dry soil: not identified</p> <p>Aqueous phototransformation: not identified</p> <p>Aerobic biotransformation in soil: 25.1% AR (Day 70) as tautomer pair</p> <p>Anaerobic biotransformation in soil: not identified</p> <p>Aerobic aquatic biotransformation: not identified</p> <p>Anaerobic aquatic biotransformation: not identified</p> <p>K_{oc}: mean of 8.38 (range of 6.95 to 11.5) mL/g</p>	<p>Major transformation product of the biotransformation of paclobutrazol in aerobic soil.</p>
<p>Carbon dioxide</p> <p>O=C=O</p> <p>Molecular weight: 44.01 g/mole</p>	<p>Hydrolysis: not identified</p> <p>Phototransformation on dry soil: not identified</p> <p>Aqueous phototransformation: 3.4% AR (Day 30)</p> <p>Aerobic biotransformation in soil: 56.9% AR (Day 28)</p> <p>Anaerobic biotransformation in soil:</p>	<p>Major transformation product of the biotransformation of paclobutrazol in aerobic soil.</p> <p>Not considered a</p>

Major transformation product	Maximum mean concentration	Comments
	10.6% AR (Day 90) Aerobic aquatic biotransformation: 1.6% AR (Day 120) Anaerobic aquatic biotransformation: 0.25% AR (Day 365)	major transformation product in anaerobic soil as net formation under anaerobic conditions was <10% AR.

Table 17 Leaching assessment of paclobutrazol residues

Leaching criteria of Cohen et al. (1984) ¹		
Criteria	Test item ²	Leaching criteria met?
	Paclobutrazol	
Solubility in water: >30 mg/L	23 mg/L in purified water	No
K _d (mL/g): <5 and usually <1 or 2	0.71–2.49 (4 soils)	Yes
K _{oc} : <300	33.43–236.8 (4 soils)	Yes
Henry's law constant (atm m ³ /mol): <10 ⁻²	2.41 × 10 ⁻¹⁰ atm m ³ /mol	Yes
pK _a : Negatively charged (either fully or partially) at ambient pH	Paclobutrazol is not expected to dissociate under environmental conditions.	No
Hydrolysis half-life: >20 weeks (>140 days)	Stable to hydrolysis	Yes
Soil phototransformation half-life: >1 week (>7 days)	Half-life = 171 days (SFO) Half-life equivalent under natural sunlight = 293–317 days	Yes
Half-life in soil: >2 to 3 weeks (>14 to 21 days)	27–547 days	Yes
Groundwater ubiquity score (GUS) assessment for paclobutrazol ³		
GUS distribution plot		Notes
<p style="text-align: center;">Paclobutrazol</p>  <p style="text-align: center;">GUS score</p>		The GUS distributions indicate that paclobutrazol and its transformation products are likely to be borderline leachers to leachers depending on the soil type.

Transformation product: CGA 149907 Transformation product: NOA 457654

- ¹ Cohen et al. (1984). Potential pesticide contamination of groundwater from agricultural uses. In: R.F. Kruger and J.D., Seibor, eds. Treatment and disposal of pesticide wastes. American Chemistry Society Symposium Series No. 259, American Chemical Society: Washington, DC.
- ² Sufficient information on the properties of the major transformation products were not available to assess their leaching potential using the criteria of Cohen et al. 1984.
- ³ Gustafson, D.I. 1989. Groundwater ubiquity score: A simple method for assessing pesticide leachability. Environmental Toxicology and Chemistry 8:339-357. GUS classifications are as follows: <1.8 = non-leacher; 1.8–2.8 = borderline leacher; >2.8 = leacher

Table 18 EECs for paclobutrazol in the environment

Substance	EEC		Calculation details	Notes
Soil: Screening level risk assessment				
Paclobutrazol	1007 g a.i./ha		Concentrations of paclobutrazol in soil were calculated based on: <ul style="list-style-type: none"> • direct spray of the application pattern resulting in the maximum EEC: $1 \times 172.5 \text{ g a.i./ha} + 3 \times 280 \text{ g a.i./ha}$ with a 7-day re-application interval • a soil half-life of 1133 days (the 90% upper confidence level on the mean of the t_R values from the soil aerobic biotransformation studies) • a soil bulk density of 1.5 g/cm^3 and a soil depth of 15 cm 	EECs in g a.i./ha were used to evaluate risks to non-target terrestrial plants (seedling emergence).
Paclobutrazol	0.447 mg/kg dw soil			
CGA 149907	0.444 mg/kg dw soil			
NOA 457654	0.129 mg/kg dw soil		EECs for the major TPs were calculated considering 100% transformation of the parent on a molar basis. The conversion factor was calculated as the molecular weight of the TP divided by the molecular weight of the parent. ¹	EECs in mg/kg dw soil were used to evaluate risks to earthworms.
Soil: Refined risk assessment – Spray drift				
Paclobutrazol	60.4 g a.i./ha		The paclobutrazol soil EEC in g a.i./ha (above) was adjusted to account for 6% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (field sprayer).	Used in the refined risk assessment for non-target terrestrial plants (seedling emergence).
Water: Screening level risk assessment (EEC in mg/L)				
Water depth:	15 cm	80 cm		
Paclobutrazol	0.671	0.126	Concentrations of paclobutrazol in water were calculated based on: <ul style="list-style-type: none"> • direct overspray of paclobutrazol to a one-hectare wetland with depths of 15 and 80 cm • the same application pattern used for soil EECs • a 1000 d water half-life (approximation for lack of whole-system decline of paclobutrazol in one of the two aerobic aquatic test systems) 	The EECs in surface water at 15-cm depth were used to evaluate risk to amphibians while the 80-cm depth EECs were used to evaluate risks to all other aquatic organisms.
CGA 149907	0.666	0.125		
NOA 457654	0.194	0.036		
Water: Refined risk assessment – Spray drift (EEC in mg/L)				
Water depth:	15 cm	80 cm		

Substance	EEC		Calculation details		Notes																					
Paclobutrazol	0.0403	0.0076	The paclobutrazol surface water EECs (above) were adjusted to account for 6% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (field sprayer).		Used in the refined risk assessment for aquatic organisms.																					
Water: Refined risk assessment – Spray drift to estuarine/marine environments																										
Not required. Risks to estuarine/marine organisms were negligible in the screening level risk assessment.																										
Water: Refined risk assessment – Runoff (EEC in mg/L)																										
Water depth:	15 cm	80 cm																								
Paclobutrazol	0.130	0.076	96-h concentration	<p>The PWC (version 2.0) model calculates the amount of pesticide entering a 1 ha water body of 15 or 80 cm depth via runoff from an adjacent 10 ha field, and the subsequent degradation of the pesticide in the water and sediment. The major paclobutrazol fate inputs used in the model were as follows:</p> <table border="1"> <thead> <tr> <th>Fate parameter</th> <th>Value</th> <th>Details</th> </tr> </thead> <tbody> <tr> <td>K_{oc}</td> <td>66.5 L/kg</td> <td>20th percentile of 4 K_{oc} values</td> </tr> <tr> <td>Water t_R^*</td> <td>Stable</td> <td>Single study</td> </tr> <tr> <td>Sediment t_R^{**}</td> <td>846 d</td> <td>Longer of 2 values (1 study on 2 systems)</td> </tr> <tr> <td>Photolysis t_R</td> <td>132 d</td> <td>Single value</td> </tr> <tr> <td>Hydrolysis</td> <td>Stable</td> <td>Single study</td> </tr> <tr> <td>Soil t_R</td> <td>1130 d</td> <td>90% upper confidence bound on the mean from 4 soils</td> </tr> </tbody> </table> <p>*aerobic aquatic whole system **anaerobic aquatic whole system</p> <p>Four application patterns were modelled. The application pattern resulting in the maximum EECs was selected for use in risk assessment, in other words, the same application pattern used for screening level water EECs. The model was</p>	Fate parameter	Value	Details	K_{oc}	66.5 L/kg	20 th percentile of 4 K_{oc} values	Water t_R^*	Stable	Single study	Sediment t_R^{**}	846 d	Longer of 2 values (1 study on 2 systems)	Photolysis t_R	132 d	Single value	Hydrolysis	Stable	Single study	Soil t_R	1130 d	90% upper confidence bound on the mean from 4 soils	<p>Used in the refined risk assessment for aquatic organisms.</p> <p>The 96-h and 21-d EECs were considered most relevant to the endpoints used in the paclobutrazol refined risk assessment. The paclobutrazol EECs for these time windows were identical for each water body depth.</p>
	Fate parameter	Value	Details																							
K_{oc}	66.5 L/kg	20 th percentile of 4 K_{oc} values																								
Water t_R^*	Stable	Single study																								
Sediment t_R^{**}	846 d	Longer of 2 values (1 study on 2 systems)																								
Photolysis t_R	132 d	Single value																								
Hydrolysis	Stable	Single study																								
Soil t_R	1130 d	90% upper confidence bound on the mean from 4 soils																								
	0.130	0.076	21-d concentration																							

Substance	EEC	Calculation details	Notes
		run for 50 years and the output was used to calculate representative peak concentrations for different time windows ranging from instantaneous to 90 days.	
Plant surfaces: Screening level and refined risk assessments (EEC in g a.i./ha)			
Paclobutrazol	599	In-field paclobutrazol EECs were calculated based on: <ul style="list-style-type: none"> • direct spray of paclobutrazol to foliage • the same application pattern used for soil EECs • an assumed half-life of 10 days on plant surfaces 	Used to evaluate in-field and off-field risks to non-target terrestrial plants (vegetative vigor).
	35.9	Off-field EECs were calculated by adjusting the in-field EECs by assuming 6% spray drift deposition of medium sized droplets 1-metre downwind of the point of application (field sprayer application).	
Pollinators (bees): Oral exposure to pollen and/or nectar, and direct contact exposure (EEC in µg a.i./bee)			
Paclobutrazol	8.01 (adult, oral)	Estimated oral exposure for bees = application rate (0.28 kg a.i./ha) × adjustment factor <ul style="list-style-type: none"> • Adult adjustment factor of 28.62 µg a.i./bee per kg a.i./ha was calculated as the food consumption of 0.292 g/bee per day × 98 µg a.i./g per kg a.i./ha (default tall grass residues). • Larvae adjustment factor of 12.15 µg a.i./bee per kg a.i./ha was calculated as the food consumption of 0.124 g/bee per day × 98 µg a.i./g per kg a.i./ha (default tall grass residues). 	Used to evaluate risks to pollinators (bees).
	3.40 (larvae, oral)		
	0.672 (adult, contact)		
Birds and mammals: Screening level and refined risk assessments			
See Table 21 for the EECs for food items for birds and mammals.			
¹ The molecular weights for paclobutrazol, CGA 149907 and NOA 457654 are 293.8, 291.8 and 85.03 g/mol, respectively.			

Table 19 Toxicity of paclobutrazol to non-target species

Organism	Exposure	Test substance	Endpoint	Comments/ Degree of toxicity ¹	PMRA #
Terrestrial organisms					
Invertebrates					
Earthworm (<i>Eisenia andrei</i>)	56-d Chronic	Paclobutrazol SC (4 g a.i./L)	NOEC \geq 3.92 mg a.i./kg dw soil	No effects on survival and reproduction at highest tested concentration.	3116837
		CGA 149907	NOEC = 171 mg/kg dw soil	Based on inhibition of reproduction.	3116862
		NOA 457654	NOEC = 165 mg/kg dw soil	Based on inhibition of reproduction.	3116863
Bee (<i>Apis mellifera</i> L.)	48-h Oral	Paclobutrazol SC	LD ₅₀ = 237 μ g a.i./bee	Practically non-toxic	3116838
	48-h Contact		LD ₅₀ > 235 μ g a.i./bee	Practically non-toxic	
	4-d Larval (repeated exposure)		EDD ₅₀ (adult emergence on Day 22) = 12 μ g a.i./bee/day	N/A	3116840
	10-d Chronic Oral		LDD ₅₀ > 161 μ g a.i./bee/day NOEDD = 161 μ g a.i./bee/day	N/A	3116841
Predatory arthropod, <i>Typhlodromus pyri</i>	Not required for use-site category #30 (Turf)				
Parasitic arthropod, <i>Aphidius rhopalopsiphi</i>					
Birds					
Bobwhite quail (<i>Colinus virginianus</i>)	5-d Dietary	Paclobutrazol	LD ₅₀ > 923 mg a.i./kg bw	Practically non-toxic.	1232590

Organism	Exposure	Test substance	Endpoint	Comments/ Degree of toxicity ¹	PMRA #
	One-generation (24-week) reproductive toxicity	Paclobutrazol	NOAED = 35 mg a.i./kg bw/d LOAED = 69 mg a.i./kg bw/d	The LOAED corresponded to a 26% reduction in female body weight. No significant effects on reproductive parameters at any test dose (max. dose: 138 mg a.i./kg bw/d)	2065738
Mallard duck (<i>Anas platyrhynchos</i>)	Oral gavage	Paclobutrazol	LD ₅₀ > 7913 mg a.i./kg bw	Practically non-toxic. No treatment-related mortalities were observed.	1232586
	5-d Dietary	Paclobutrazol	LD ₅₀ > 3339 mg a.i./kg bw/d	Practically non-toxic. No treatment-related mortalities were observed.	1232589
	One-generation (20-week) reproductive toxicity	Paclobutrazol	NOAED = 124 mg a.i./kg bw/d LOAED = 458 mg a.i./kg bw/d	The LOAED corresponded to: 23% reduction in hatchlings among live 3-week embryos and 20% reduction in hatchlings among eggs set and hatchling survivors among eggs	2065737

Organism	Exposure	Test substance	Endpoint	Comments/ Degree of toxicity ¹	PMRA #
				set.	
Japanese quail (<i>Coturnix japonica</i>)	Oral gavage	Paclobutrazol	LD ₅₀ > 2100 mg a.i./kg bw	Practically non-toxic. 20% mortality occurred at the highest dose tested.	1232587
Mammals					
Mouse (Alderley Park SPF)	Acute oral toxicity	Paclobutrazol	LD ₅₀ ♂ = 490 mg a.i./kg bw LD ₅₀ ♀ = 1219 mg a.i./kg bw	Moderately toxic (♂) Slightly toxic (♀)	1231127
Rat (Wistar (Alpk:AP))	2-generation dietary reproductive toxicity	Paclobutrazol	♂/♀ NOEL = 23/25 mg a.i./kg bw/d LOEL = 117/124 mg a.i./kg bw/d	The LOEL was based on ↓ in bw gain in parent F ₀ and F ₁ generations: over the entire test duration (F ₀ ♂ only: 5%, F ₁ ♀ only: 9%); during pregnancy (F ₀ and F ₁ : 8%); and during lactation (F ₁ only: 13%). No significant effect on reproductive parameters at any test dose (max. dose ♂/♀: 117/124 mg a.i./kg bw/d).	1231142

Organism	Exposure	Test substance	Endpoint	Comments/ Degree of toxicity ¹	PMRA #
Vascular plants					
Non-target terrestrial plants	Seedling emergence	Paclobutrazol	ER ₂₅ = 13 g a.i./ha	Based on soybean shoot length. There is uncertainty with this endpoint because the soybean negative control did not meet the validity criteria for seedling emergence. However, this was not the most sensitive seedling emergence endpoint and does not affect the risk assessment.	2065739
		Paclobutrazol SC 250 (24.5% purity)	ER ₂₅ = 7.07 g a.i./ha	Based on soybean shoot length.	3195745
	Vegetative vigour	Paclobutrazol	ER ₂₅ = 57 g a.i./ha	Based on tomato shoot length.	2066312
		Paclobutrazol SC 250 (24.5% purity)	ER ₂₅ = 36.3 g a.i./ha	Based on tomato shoot length.	3195746
	Freshwater organisms				
<i>Daphnia magna</i>	48-h Acute	Paclobutrazol	EC ₅₀ = 33.2 mg a.i./L	Slightly toxic	1232593
	22-d Chronic	Paclobutrazol	NOEC = 0.32 mg a.i./L	Based on inhibition of length and reproduction.	3116843

Organism	Exposure	Test substance	Endpoint	Comments/ Degree of toxicity ¹	PMRA #
Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-h Acute	Paclobutrazol	LC ₅₀ = 27.8 mg a.i./L	Slightly toxic	1232591
Bluegill sunfish (<i>Lepomis macrochirus</i>)	96-h Acute	Paclobutrazol	LC ₅₀ = 23.6 mg a.i./L	Slightly toxic	1232592
Fathead minnow (<i>Pimephales promelas</i>)	32-d Early life stage	Paclobutrazol	NOEC = 0.049 mg a.i./L	The LOEC was based on 25% inhibition of length and 41% inhibition of dry weight.	2065735
Amphibian	96-h Acute (bluegill as surrogate)	Paclobutrazol	LC ₅₀ = 23.6 mg a.i./L	Slightly toxic	N/A
	21-d Amphibian metamorphosis (<i>Xenopus laevis</i>)	Paclobutrazol	NOEC = 0.028 mg a.i./L	The LOEC was based on 4 to 7% inhibition of hind limb length and snout-vent length	3316065
Freshwater algae (<i>Rhaphidocelis subcapitata</i>)	96-h Acute	Paclobutrazol	EC ₅₀ (yield) = 6.42 mg a.i./L	Moderately toxic	1232595
Freshwater algae (<i>Anabaena flos-aquae</i>)	96-h Acute	Paclobutrazol	EC ₅₀ > 25 mg a.i./L	Indeterminate toxicity classification (slightly toxic, at most)	3116854
Vascular plants (<i>Lemna gibba</i>)	7-d	Paclobutrazol	EC ₅₀ (yield) = 0.00461 mg a.i./L	Very highly toxic	3116861
		CGA 144907	EC ₅₀ (yield) = 0.53 mg/L	Highly toxic	3116859
		NOA 457654	EC ₅₀ (yield) = 32 mg/L	Slightly toxic	3116860

Organism	Exposure	Test substance	Endpoint	Comments/ Degree of toxicity ¹	PMRA #
Milfoil (<i>Myriophyllum spicatum</i> L.)	4-week	Paclobutrazol	NOEC < 0.00075 mg a.i./L LOEC = 0.00075 mg a.i./L	Based on inhibition of stem length, fresh weight. Remained suppressed after six-week recovery period after 1 day of exposure to 75 and 150 µg a.i./L.	3195748
Hydrilla (<i>Hydrilla verticillata</i>)	4-week	Paclobutrazol	NOEC < 0.075 mg a.i./L LOEC = 0.075 mg a.i./L	Based on inhibition of stem length. Recovered to untreated control stem length after six weeks, regardless of duration of exposure to 750 µg a.i./L.	
Marine organisms					
Saltwater mysid (<i>Americamysis bahia</i>)	96-h Acute	Paclobutrazol	LC ₅₀ > 9.0 mg a.i./L	Indeterminate toxicity classification (moderately toxic, at most). <10% mortality at the highest concentration tested	3195725
Pacific oyster (<i>Crassostrea gigas</i>)	48-h Acute	Paclobutrazol	EC ₅₀ > 9.9 mg a.i./L	Indeterminate toxicity classification (slightly toxic, at most). No mortality	3195726

Organism	Exposure	Test substance	Endpoint	Comments/ Degree of toxicity ¹	PMRA #
				observed up to the highest concentration tested	
Sheepshead minnow (<i>Cyprinodon variegatus</i>)	96-h Acute	Paclobutrazol	LC ₅₀ > 24.3 mg a.i./L	Indeterminate toxicity classification (slightly toxic, at most). 10 and 100% mortality observed at 21.6 and 29.7 mg a.i./L, respectively	3195729

¹ USEPA classification, where applicable

Table 20 Screening level risk assessment for non-target terrestrial organisms (Except birds and mammals)

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ	LOC	LOC exceeded?
Terrestrial organisms									
Invertebrates									
Earthworm (<i>Eisenia andrei</i>)	56-d Chronic	Paclobutrazol SC (4 g a.i./L)	0.447 mg a.i./kg dw soil	NOEC \geq 3.92 mg a.i./kg dw soil	1	3.92 mg a.i./kg dw soil	\leq 0.11	1	No
		CGA 149907	0.444 mg/kg dw soil	NOEC = 171 mg/kg dw soil	1	171 mg/kg dw soil	0.0026	1	No
		NOA 457654	0.129 mg/kg dw soil	NOEC = 165 mg/kg dw soil	1	165 mg/kg dw soil	< 0.001	1	No
Bee (<i>Apis mellifera</i> L.)	48-h Oral	Paclobutrazol SC (approx. 24% purity)	8.01 μ g a.i./bee	LD ₅₀ = 237 μ g a.i./bee	1	237 μ g a.i./bee	0.034	0.4	No
	48-h Contact		0.672 μ g a.i./bee	LD ₅₀ > 235 μ g ai/bee	1	> 235 μ g a.i./bee	< 0.0029	0.4	No
	4-d Larval (repeated exposure)		3.40 μ g a.i./bee/d	EDD ₅₀ = 12 μ g ai/bee/d	1	12 μ g a.i./bee/d	0.28	0.4	No
	10-d Chronic Oral		8.01 μ g a.i./bee/d	NOEDD = 161 μ g a.i./bee/d	1	161 μ g a.i./bee/d	0.050	1	No
Vascular plants									
Non-target terrestrial plants	Seedling emergence (soybean, shoot length)	Paclobutrazol	1007 g a.i./ha	ER ₂₅ = 13 g a.i./ha	1	13	77.5	1	Yes
		Paclobutrazol SC 250 (24.5% purity)	1007 g a.i./ha	ER ₂₅ = 7.07 g a.i./ha	1	7.07	142	1	Yes
	Vegetative vigour	Paclobutrazol	599 g a.i./ha	ER ₂₅ = 57 g a.i./ha	1	57	10.5	1	Yes

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ	LOC	LOC exceeded?
	(tomato, shoot length)	Paclobutrazol SC 250 (24.5% purity)	599 g a.i./ha	ER ₂₅ = 36.3 g a.i./ha	1	36.3	16.5	1	Yes

Table 21 Screening level risk assessment for birds and mammals

	Effects metric (mg a.i./kg bw/d) ¹	Feeding guild (food item)	EDE (mg a.i./kg bw) ⁽²⁾	RQ	LOC	LOC exceeded?
Small bird (0.02 kg)						
Acute	> 210.0	Insectivore	48.7	< 0.23	1	No
Reproduction	35.0	Insectivore	48.7	1.39	1	Yes
Medium bird (0.1 kg)						
Acute	> 210.0	Insectivore	38.0	< 0.18	1	No
Reproduction	35.0	Insectivore	38.0	1.09	1	Yes
Large bird (1 kg)						
Acute	> 210.0	Herbivore (short grass)	24.6	< 0.12	1	No
Reproduction	35.0	Herbivore (short grass)	24.6	0.70	1	No
Small mammal (0.015 kg)						
Acute	200.0	Insectivore	28.0	0.14	1	No
Reproduction	23.0	Insectivore	28.0	1.22	1	Yes
Medium mammal (0.035 kg)						
Acute	49.0	Herbivore (short grass)	54.4	1.11	1	Yes
Reproduction	23.0	Herbivore (short grass)	54.4	2.36	1	Yes
Large mammal (1 kg)						
Acute	49.0	Herbivore (short grass)	29.1	0.59	1	No
Reproduction	23.0	Herbivore (short grass)	29.1	1.26	1	Yes

¹ The acute effect metric is the LD50 divided by an uncertainty factor of 10.

² EDE = Estimated dietary exposure; calculated using the following formula: (FIR/BW) × EEC, where
FIR: Food Ingestion Rate (Nagy, 1987)

For generic birds with body weight less than or equal to 200 g, the “passerine” equation was used:

Passerine Equation (body weight < or = 200 g): $FIR (g \text{ dry weight/day}) = 0.398(BW \text{ in g})^{0.850}$

For generic birds with body weight greater than 200 g, the “all birds” equation was used:

All birds Equation (body weight > 200 g): $FIR (g \text{ dry weight/day}) = 0.648(BW \text{ in g})^{0.651}$

For mammals, the “all mammals” equation was used: $FIR (g \text{ dry weight/day}) = 0.235(BW \text{ in g})^{0.822}$

BW: Generic body weight

EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994), using the TRIMMIT application scenario resulting in the highest EECs ($1 \times 172.5 \text{ g a.i./ha} + 3 \times 280 \text{ g a.i./ha}$ at 7-day intervals) and assuming a 10-day default half-life on food items such as vegetation. At the screening level, relevant food items representing the highest EEC for each feeding guild are used.

Table 22 Refined risk assessment for birds and mammals

	Effects metric (mg a.i./kg bw/d) ¹	Feeding guild (food item)	EDE (mg a.i./kg bw) ²	RQ	LOC	LOC exceeded?
Small bird (0.02 kg)						
Reproduction	69.0	Insectivore	48.7	0.71	1	No
Medium bird (0.1 kg)						
Reproduction	69.0	Insectivore	38.0	0.55	1	No
Small mammal (0.015 kg)						
Reproduction	117	Insectivore	28.0	0.24	1	No
Medium mammal (0.035 kg)						
Reproduction	117	Herbivore (short grass)	54.4	0.46	1	No
Large mammal (1 kg)						
Reproduction	117	Herbivore (short grass)	29.1	0.25	1	No

¹ In the refined assessment, the reproduction effect metric is the LOEL determined for bobwhite quail in PMRA No. 2065738 for birds, and the LOEL determined for the Wistar rat in PMRA No. 1231142 for mammals.

² EDE = Estimated dietary exposure; calculated using the following formula: $(FIR/BW) \times EEC$, where

FIR: Food Ingestion Rate (Nagy, 1987).

For generic birds with body weight less than or equal to 200 g, the “passerine” equation was used:

Passerine Equation (body weight < or = 200 g): $FIR (g \text{ dry weight/day}) = 0.398(BW \text{ in g})^{0.850}$

For generic birds with body weight greater than 200 g, the “all birds” equation was used:

All birds Equation (body weight > 200 g): $FIR (g \text{ dry weight/day}) = 0.648(BW \text{ in g})^{0.651}$

For mammals, the “all mammals” equation was used: $FIR (g \text{ dry weight/day}) = 0.235(BW \text{ in g})^{0.822}$

BW: Generic body weight

EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994), using the TRIMMIT application scenario resulting in the highest EECs ($1 \times 172.5 \text{ g a.i./ha} + 3 \times 280 \text{ g a.i./ha}$ at 7-day intervals) and assuming a 10-day default half-life on food items such as vegetation. The relevant food items representing the highest EEC for each feeding guild are used.

Table 23 Refined risk assessment for non-target terrestrial plants

Organism	Exposure	Test substance	Endpoint	EEC (g a.i./ha)	UF	Effects metric (g a.i./ha)	RQ	LOC	LOC exceeded?
Non-target terrestrial plants	Seedling emergence (soybean, shoot length)	Paclobutrazol	ER ₂₅ = 13 g a.i./ha	60.4	1	13	4.65	1	Yes
		Paclobutrazol SC 250 (24.5% purity)	ER ₂₅ = 7.07 g a.i./ha	60.4	1	7.07	8.5	1	Yes
	Vegetative vigour (tomato, shoot length)	Paclobutrazol	ER ₂₅ = 57 g a.i./ha	35.9	1	57	0.63	1	No
		Paclobutrazol SC 250 (24.5% purity)	ER ₂₅ = 36.32 g a.i./ha	35.9	1	36.3	0.99	1	No

Table 24 Screening level risk assessment for non-target aquatic organisms

Organism	Exposure	Test substance	EEC (mg/L)	Endpoint value (mg/L)	UF	Effects metric (mg/L)	RQ	LOC of 1 exceeded?
Freshwater organisms								
<i>Daphnia magna</i>	48-h Acute	Paclobutrazol	0.126	EC ₅₀ = 33.2	2	16.6	0.008	No
	22-d Chronic	Paclobutrazol	0.126	NOEC = 0.32	1	0.320	0.39	No
Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-h Acute	Paclobutrazol	0.126	LC ₅₀ = 27.8	10	2.78	0.045	No
Bluegill sunfish (<i>Lepomis macrochirus</i>)	96-h Acute	Paclobutrazol	0.126	LC ₅₀ = 23.6	10	2.36	0.053	No
Fathead minnow (<i>Pimephales promelas</i>)	32-d Early life stage	Paclobutrazol	0.126	NOEC = 0.049	1	0.049	2.57	Yes
Amphibian	96-h Acute (bluegill surrogate)	Paclobutrazol	0.671	LC ₅₀ = 23.6	10	2.36	0.28	No
	21-d Amphibian metamorphosis (<i>Xenopus laevis</i>)	Paclobutrazol	0.671	NOEC = 0.028	1	0.028	24.0	Yes
Freshwater algae (<i>Rhaphidocelis subcapitata</i>)	96-h Acute	Paclobutrazol	0.126	EC ₅₀ = 6.42	2	3.21	0.039	No
Freshwater algae (<i>Anabaena flos-aquae</i>)	96-h Acute	Paclobutrazol	0.126	EC ₅₀ > 25	2	> 12.5	< 0.010	No
Vascular plants (<i>Lemna gibba</i>)	7-d	Paclobutrazol	0.126	EC ₅₀ = 0.00461	2	0.002	54.7	Yes
		CGA 144907	0.125	EC ₅₀ = 0.53	2	0.265	0.47	No
		NOA 457654	0.036	EC ₅₀ = 32	2	16.0	0.002	No
Marine organisms								
Saltwater mysid (<i>Americamysis bahia</i>)	96-h Acute	Paclobutrazol	0.126	LC ₅₀ > 9.0	2	> 4.5	< 0.028	No

Organism	Exposure	Test substance	EEC (mg/L)	Endpoint value (mg/L)	UF	Effects metric (mg/L)	RQ	LOC of 1 exceeded?
Pacific oyster (<i>Crassostrea gigas</i>)	48-h Acute	Paclobutrazol	0.126	EC ₅₀ > 9.9	2	> 4.95	< 0.025	No
Sheepshead minnow (<i>Cyprinodon variegatus</i>)	96-h Acute	Paclobutrazol	0.126	LC ₅₀ > 24.3	10	> 2.43	< 0.052	No

Table 25 Refined risk assessment for non-target freshwater organisms

Organism	Exposure	Test substance	EEC (mg/L)	Endpoint value (mg/L)	UF	Effects metric (mg/L)	RQ	LOC of 1 exceeded?
6% Spray drift								
Fathead minnow (<i>Pimephales promelas</i>)	32-d ELS	Paclobutrazol	0.0076	NOEC = 0.049	1	0.049	0.15	No
Amphibian (<i>Xenopus laevis</i>)	21-d Amphibian metamorphosis	Paclobutrazol	0.040	NOEC = 0.028	1	0.028	1.44	Yes
Vascular plants (<i>Lemna gibba</i>)	7-d	Paclobutrazol	0.0076	EC ₅₀ = 0.00461	2	0.002	3.28	Yes
Runoff								
Fathead minnow (<i>Pimephales promelas</i>)	32-d ELS	Paclobutrazol	0.076	NOEC = 0.049	1	0.049	1.55	Yes
Amphibian (<i>Xenopus laevis</i>)	21-d Amphibian metamorphosis	Paclobutrazol	0.130	NOEC = 0.028	1	0.028	4.64	Yes
Vascular plants (<i>Lemna gibba</i>)	7-d	Paclobutrazol	0.076	EC ₅₀ = 0.00461	2	0.002	33.0	Yes

Table 26 List of Supported Uses

Items	Label claims that are supported
Application rate	0.45–1.12 L/ha, use lower rate and more frequent applications if turf discolouration cannot be tolerated. Ensure that the rates are measured accurately since excessive rate may cause undesirable turf growth control and discolour grass temporarily.
Efficacy claims	Reduces the frequency of mowing by regulating the growth of turfgrass. Suppresses <i>Poa annua</i> .
Hosts and use sites	Turfgrass on golf course fairways, greens, and tees.
Application method	Foliar spray in water volumes of 400–800 L/ha, to ensure thorough coverage. For best results, irrigate TRIMMIT into the soil but not to the point of runoff, prior to rain or within 24 hours after application to limit surface movement. For best residual activity, remove TRIMMIT from the leaf surface by irrigation or rainfall prior to mowing.
No. of applications	Multiple applications 7–21 days apart. Do not apply more than 4.05 L/ha/year.
Application timing	Growth suppression: Apply in spring after green-up and turfgrass has been mowed once or twice. Apply at least one month before onset of high air temperatures. In late summer/early fall, apply at least one month before anticipated first killing frost. Repeat applications can be made within the same growing season as long as the turf is actively growing. Suppression of <i>Poa annua</i>: Apply when the <i>Poa annua</i> is actively growing. In climates with a prolonged winter dormancy, fall applications can be made up to one month prior to anticipated first killing frost. Repeat application should be made as part of a <i>Poa annua</i> suppression program.

Table 27 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Paclobutrazol (parent)	CGA 149907 (major TP)	NOA 457654 (major TP)
CEPA toxic or CEPA toxic equivalent ¹	Yes	Yes	Yes	Yes
Predominantly anthropogenic ²	Yes	Yes	Yes	Yes

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Paclobutrazol (parent)	CGA 149907 (major TP)	NOA 457654 (major TP)
Persistence ³ :	Soil	Half-life ≥ 182 days	Aerobic soil: Yes (DT ₅₀ = 27.1 to 547 days) Anaerobic soil: Yes (stable)	Aerobic soil: No (DT ₅₀ = 55 and 101 days in parent-based study, and 23 to 72 days in TP-based study)	Aerobic soil: Yes (DT ₅₀ = 253 and 407 days in parent-based study, and 3 to 10 days in TP-based study)
	Water	Half-life ≥ 182 days	Yes (DT ₅₀ = 1.9 days to stable)	Not available	Not available
	Sediment	Half-life ≥ 365 days	Yes (DT ₅₀ = 357 days to stable)	Not available	Not available
	Air	Half-life ≥ 2 days or evidence of long-range transport	Not determined. The AOPWIN program (v1.92) in EPI Suite (v4.11) is not suited for predicting the atmospheric half-life of paclobutrazol given the large fraction expected to be sorbed to airborne particles.	Not available	Not available
Bioaccumulation ⁴	Log $K_{ow} \geq 5$		No (log K_{ow} = 3.11 to 3.18)	No ⁵ (log K_{ow} = 2.85)	No ⁵ (log K_{ow} = -0.49 (hydroxy); -1.36 (ketone))
	BCF ≥ 5000		No (BCF = 44)	Not available	Not available
	BAF ≥ 5000		Not available	Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No. Does not meet all TSMP Track 1 criteria.	No. Does not meet all TSMP Track 1 criteria.	No. Does not meet all TSMP Track 1 criteria.

¹ All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).

- 2 The policy considers a substance “predominantly anthropogenic” if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
- 3 If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air), then the persistence criterion is considered to be met.
- 4 Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, $\log K_{ow}$).
- 5 Estimated using the KOWWIN (version 1.68) module in EPI Suite version 4.11.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA

Document

Number

Reference

1241949	2006, Paclobutrazol Technical: Chemical and Physical Properties, DACO: 2.14.1, 2.14.10, 2.14.11, 2.14.12, 2.14.13, 2.14.14, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8, 2.14.9 CBI
3446852	2023, Paclobutrazol Technical (PP333) Validation of Analytical Method [CBI Removed] for [CBI Removed], DACO: 2.13.1 CBI
3446853	2023, [CBI Removed] Determination of [CBI Removed] in Paclobutrazol (PP333G) technical active ingredient by [CBI Removed], DACO: 2.13.1 CBI
3116813	2008, Paclobutrazol - Residue Analytical Method for the Determination of Paclobutrazol and its Ketone Metabolite (R79105) in Soil. Final Determination by LC-MS/MS, DACO: 8.2.2.1
3116814	2008, Paclobutrazol - Residue Analytical Method for the Determination of Paclobutrazol and its Ketone Metabolite (R79105) in Water. Final Determination by LC-MS/MS., DACO: 8.2.2.3
3116815	2018, Paclobutrazol - Independent Laboratory Validation of Residue Analytical Method GRM028.02A for the Determination of Paclobutrazol and its Ketone Metabolite (R79105) in Water, DACO: 8.2.2.3
3116760	2019, A8164F - Physico-Chemical Studies of the Formulation, DACO: 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.14, 3.5.2, 3.5.3, 3.5.6, 3.5.7, 3.5.8, 3.5.9, 3.7 CBI
3116754	2019, A8164F - Document J - Confidential Information, DACO: 2.2, 3.1.2, 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.3.2, 3.4.2, 4.8 CBI
3116757	2019, Analytical Method SF-556/1 - Paclobutrazol in Formulation SC (250) By capillary GC (fast GC), DACO: 3.4.1 CBI
3116759	2019, A8164F - Validation of Analytical Method SF-556/1, DACO: 3.4.1 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
3277879	2006, Paclobutrazol Technical - Acute Oral Up-and-Down Procedures in Rats, DACO: 4.2.1
3277880	2006, Paclobutrazol Technical - Acute Dermal Toxicity in Rats, DACO: 4.2.2
3280224	2006, Paclobutrazol Technical - 4 Hour Acute Inhalation Study in the Rat, DACO: 4.2.3
3277881	2006, Paclobutrazol Technical - Primary Eye Irritation in Rabbits, DACO: 4.2.4
3277882	2006, Paclobutrazol Technical - Primary Skin Irritation in Rabbits, DACO: 4.2.5
3277883	2006, Paclobutrazol Technical - Skin Sensitisation (Local Lymph Node Assay in the Mouse), DACO: 4.2.6
3277884	1987, Paclobutrazol - 90 Day Oral Dosing Study in Dogs, DACO: 4.3.2
3277887	2013, Paclobutrazol - Acute Oral (Gavage) Neurotoxicity Study in the Wistar Rat, DACO: 4.5.12
3277888	2007, Evaluation of Triazole Lactic Acid In An In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes, DACO: 4.8
3277889	2007, Evaluation of Triazole Lactic Acid in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay, DACO: 4.8
3277890	2006, Triazole Lactic acid (CGA 205369): Acute oral toxicity in the rat - up and down procedure, DACO: 4.8
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3260413	2021, Paclobutrazol technical - Screening for the Potential to Modulate Steroidogenesis <i>in Vitro</i> using the Human H295R Adreno-Carcinoma Cell Line, DACO: 4.8
3260442	2021, Paclobutrazol technical - In Vitro Aromatase Inhibition using Human Recombinant Microsomes Final Report, DACO: 4.8
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3396823	1984, Paclobutrazol - 4 Week Oral (Dietary Administration) Dose Range-Finding Study in the Mouse, DACO: 4.3.3
3396822	1984, Paclobutrazol - 4 Week Oral (Dietary Administration) Dose Range-Finding Study in the Rat, DACO: 4.3.3
1231115	Paclobutrazol (PP333): 90 Day Feeding Study in Rats (CTL/P/760), DACO: 4.3.1
1231122	1986, Paclobutrazol: 104 Week (Dietary Administration) Combined Toxicity & Carcinogenicity Study in the Rat with a 52 Week Interim Kill (5055-72/273) DACO: 4.4.2

1231138	1986, Paclobutrazol: 104 Week (Dietary Administration) Combined Toxicity & Carcinogenicity Study in the Mouse with a 52 Week Interim Kill (5014-72/274) DACO: 4.4.1,4.4.2
1231142	Paclobutrazol: Two Generation Reproduction Study in Rats (CTL/P/1496), DACO: 4.5.1
1231134	1983, Paclobutrazol: Teratogenicity Study in the Rat (CTL/P/842), DACO: 4.5.2
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1232576	Paclobutrazol: Teratogenicity Study in the Rabbit (CTL/P/861), DACO: 4.5.2
1232601	Paclobutrazol: Second Teratogenicity Study in Rabbit (CTL/P/1460), DACO: 4.5.2

3.0 Environment

PMRA

Document Number	Reference
1232571	PP333: Hydrolysis in water at pH 4, 7 & 9 (RJ0316B), DACO: 8.2.1
1232573	Paclobutrazol: Photolytic stability on a soil surface (RJ0601B), DACO: 8.2.3.3.2
1232575	PP333: Photolysis in aqueous solution (RJ0317B), DACO: 8.2.1
1232578	Paclobutrazol: Adsorption & desorption equilibria in soils (TMJ2377B), DACO: 8.2.4.1
1232579	PP333: Leaching in soil (RJ0244B), DACO: 8.2.4.1
1232580	Paclobutrazol: Mobility of paclobutrazol & its degradation products in soil columns (RJ 0495B), DACO: 8.2.4.1
1232581	PP333; Degradation in soil (RJ0256BR), DACO: 8.3.2.3
1232582	Paclobutrazol: Degradation in aerobic & flooded soils (RJ0370B), DACO: 8.2.3.1
1232583	Paclobutrazol: Degradation in sediment-water systems (RJ0538B), DACO: 8.2.3.1
1232586	The acute oral toxicity (LD50) of PP333 to the mallard duck (ICI/252WL/781176), DACO: 9.6.2.1
1232587	The acute oral toxicity of paclobutrazol to the Japanese quail (ISN 147BT/871054), DACO: 9.6.2.1
1232589	The subacute dietary toxicity (LC50) of PP333 to the mallard duck (ICI 417 WL/82629), DACO: 9.6.2.1
1232590	The subacute dietary toxicity (LC50) of PP333 to the bobwhite quail (ICI 418/82661), DACO: 9.6.2.1
1232591	Determination of the acute toxicity of PP333 to rainbow trout (BL/B/1935), DACO: 9.5.5
1232592	PP333: Determination of the acute toxicity to bluegill sunfish (BL/B/2209), DACO: 9.5.5
1232593	PP333: Toxicity of the technical material & formulation GFU 029 to first instar <i>Daphnia magna</i> (RJ 0282B), DACO: 9.3.1

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4.0 Value

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B. Additional Information Considered

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