Risk Assessment

of

Rancona 450 FS (L10899)/Lumiflex (L11112)

containing active ingredient

Ipconazole

for Agricultural use

as seed treatment fungicide

for

Derogation application

October 2024

DISCLAIMER

This Independent Toxicological Review is prepared by Professor Mary Gulumian to assist in the derogation of **Rancona 450 FS/Lumiflex,** containing active ingredient **Ipconazole** for Agricultural use: seed treatment **fungicide** as per Guidelines on the data and documents required for derogation of agricultural remedies in South Africa. The purpose of this Toxicological Review is to inform the Department of Agriculture, Land Reform and Rural Development (DALRRD) and therefore this report is not a decision on the application. Mention of trade names or commercial products do not constitute endorsement of the product.

Professor Mary Gulumian

Signature ----------

Date 29.10.2024 ----------

Contents

Abbreviations

AAOEL	Acute acceptable operator exposure level
ACR	Acute to Chronic Ratio
ADI	Acceptable daily intake
a.i.	Active ingredient
AOEL	Acceptable operator exposure level
AR	Applied radioactivity
ARfD	Acute reference dose
a.s.	Active substance
bw	Body weight
°C	Degree Celsius (centigrade)
$CaCl_2$	Calcium chloride
cc	cis-cis isomer
ct	cis-trans isomer
cc:ct	cis-cis: cis-trans isomer
cm	Centimetre
$^{14}CO_2$	Radioactive Carbon dioxide
CHO	Chinese hamster ovary cells
d	Day
DALRRD	Department of Agriculture, Land Reform and Rural Development
DAT	Days after treatment
DDD	daily dietary dose
DEEM-FCID	Dietary Exposure Evaluation Model software with Food Commodity Intake Database
$DissT_{50}$	The dissipation parameter
DMI	De-Methylation Inhibitors
DNA	Deoxyribonucleic acid
DT_{50}	Period required for 50% dissipation (define method of estimation)
EbC_{50}	Effective concentration (biomass)
ECHA	European Chemical Agency
EDSP	Endocrine Disruptor Screening Program
EECs	Estimated environmental concentrations
EC_{50}	Effective concentration
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
ErC_{50}	Effective concentration (growth rate)
EU	European Union
FIR	Food intake rate
FOCUS	**FO**rum for the **Co**-ordination of pesticide fate models and their **US**e
FOMC	First Order Multi-Compartment kinetics
FQPA	Food Quality Protection Act
FQPA SF	FQPA Safety Factor
FRAC	Fungicide Resistance Action Committee
g	Gram
ha	Hectare
HCl	Hydrochloric acid
HGPRT	Hypoxanthine phosphoribosyl transferase
HPLC-UV	High pressure liquid chromatography - Ultraviolet detector
ILV	Independent laboratory validation
IPM	Integrated pest management
IUPAC	International Union of Pure and Applied Chemistry
kg	Kilogram
K_{oc}	% Organic carbon to water partition coefficient
K_{ow}	Partition Coefficient between *n*-octanol and water
L	Litre
LC_{50}	Lethal concentration, median
LC/MS/MS	Liquid chromatography/mass spectrometry/mass spectrometry
LD_{50}	The dose required to kill 50% of the members of a tested population

LOAEC	Lowest-observed-adverse-effect level
LOAEL	Lowest observable adverse effect level
LOCs	level of concern
LOQ	limit of quantitation
MOE	Margins of exposure
mg	Milligram
MilliQ	Is water purified using a Millipore MilliQ lab water system
mN/m	Milli-Newton/meter
MoE	Margin of exposure
MRLs	Maximum residue limit or level
MS	Mass spectrometry
NaOH	Sodium hydroxide
NAR	Nominal application rate
ng	Nanogram
nm	Nanometre
NOAEC	No observed adverse effect concentration
NOAEL	No observed adverse effect level
NOEC	No observed effect concentration
NOEL	No observed effect level
Pa	Pascal
PAD	Population adjusted dose
aPAD	Acute population adjusted dose
cPAD	Chronic Population Adjusted Dose
PD	Proportion of different food types
PPE	Personal protective equipment
ppm	Parts per million (10^{-6})
PEC	Predicted environmental concentration
PEC_{air}	Predicted environmental concentration in air
PEC_{gw}	Predicted environmental concentration in ground water
PEC_{sed}	Predicted environmental concentration in sediment
PEC_{soil}	Predicted environmental concentration in soil
PEC_{sw}	Predicted environmental concentration in surface water
PRAPeR	Pesticides peer-review experts meetings
PRIMo	Pesticides Residue Intake Model
Q1* value	A pesticide's oncogenicity potency factor
r^2	Coefficient of determination
RAC	Raw agricultural commodity
REI	Restricted entry interval
RfD	Reference dose
RQs	Risk quotients
SF	Safety Factor
SFO	Single first-order
SIP	Screening Imbibition Program
SOP	Standard operation procedure
STIR	Screening Tool of Inhalation Risk
SWCC	Surface Water Concentration Calculator
$t_{1/2}$	Half-life (define method of estimation)
1,2,4-T	1,2,4-triazole
TA	Triazole alanine
TAA	Triazole acetic acid
TDMs	Triazole derivative metabolites
TDMG	Triazole Derivative Metabolite Group
TER	Toxicity exposure ratio
TER_{lt}	Long-term toxicity:exposure ratio
TGAI	Technical Grade Active Ingredient
TLA	1,2,4-triazole lactic acid
TMDI	Theoretical maximum daily intake/ maximum chronic dietary exposure
TWA	Time-weighted average
UF	Uncertainty factor
UF_A	Extrapolation from animal to human (interspecies)
UF_H	Potential variation in sensitivity among members of the human population (intraspecies)

µg	Microgram
UV	Ultraviolet
WPS	Worker Protection Standard
λ	Wavelength
ε	Decadic molar extinction coefficient

List of Tables

Executive Summary

From the review of the relevant documents citing work conducted on ipconazole by international agencies and those conducted specifically for South Africa, the following can be summarised:

Mammalian toxicology

- Acute exposure to ipconazole resulted in low toxicity via the oral, dermal and inhalation routes of exposure and it was classified as Category III for these routes. Ipconazole is classified as Category IV for dermal irritation, is a low to mild eye irritant and is not a dermal sensitizer.
- Ipconazole is not oncogenic.
- Developmental toxicity, suspected of damaging the unborn child. **Developmental effects were observed but only at the maternally toxic dose.**
- In multigeneration toxicity studies ipconazole did not show reproductive toxicity potential.
- Ipconazole did not show effects indicative of a neurotoxicity potential.
- Ipconazole testing indicate is not mutagenic.
- No effects were seen in the reproduction or teratology studies to indicate that ipconazole has no effect on the endocrine system.

Residue limits

- Tolerances/ Maximum residue limit (MRLs) at the limit of quantitation (LOQ, 0.0l Parts per million (ppm).

Ecotoxicology

- Ipconazole is persistent and bioaccumulative.
- No unacceptable risk of groundwater contamination is expected for the intended uses.
- No significant contamination of the air compartment is expected for the intended uses.

Risk assessment

Using the data generated from the aforementioned studies, risk assessment was conducted:

- ***Ecological risk assessment***

EPA analysis have indicated that because only low levels of ipconazole will be found in the environment following its use as a seed treatment.

  - On an acute exposure basis, Technical Grade Active Ingredient (TGAI) is moderately toxic to freshwater fish and estuarine/marine fish. Ipconazole is moderately toxic to freshwater invertebrates and very highly toxic to estuarine/marine invertebrates.
  - Chronic exposure studies with freshwater fish showed effects on post-hatch survival; however, for estuarine marine fish there were no treatment-related effects. The chronic study for daphnids was waived and an Acute to Chronic Ratio (ACR) was used to estimate the magnitude of toxicity; acute and chronic data for the mysid was compared to the acute value for the daphnid.
  - Based on the Toxicity Testing and Ecological Risk Assessment Guidance for Benthic Invertebrates, toxicity values for daphnids and mysids were used to estimate potential toxicity to benthic organisms.
  - Ipconazole is practically non-toxic to young adult honeybees on an acute contact and acute oral exposure basis; ipconazole is also practically non-toxic to honeybee larvae exposed *in vitro* on an acute exposure basis.
  - Due to a lack of treatment related effects, a No observed adverse effect level (NOAEL) could not be established for adult honeybees on a chronic exposure basis up. However,

a chronic study conducted using honeybee larvae showed effects on mortality and emergence.
  - Risk assessment for ipconazole assumed that granivorous birds feed exclusively on treated wheat or barley grains. A Lethal concentration, median (LC_{50}) could not be determined in the acute-dietary avian study due to a lack of a dose-response curve. In a 21-week reproductive toxicity study on the Northern bobwhite quail, the No observed adverse effect concentration (NOAEC) and Lowest-observed-adverse-effect level (LOAEC) were based on a 45% reduction in hatchling survival.
  - For birds and mammals, a high risk was only identified for small granivorous birds at long-term scale.
  - Terrestrial plant data for ipconazole was waived because the EPA does not currently have a standard method for quantifying and assessing risk to terrestrial plants based on exposure from dust-off due to seed treatment applications; additionally, other exposure pathways that could affect terrestrial plants are incomplete.

- ***Dietary exposure***
  - EFSA Pesticides Residues Intake Model (PRIMo) indicated that:
    - The Theoretical maximum chronic dietary exposure (TMDI) for wheat and barley is less than 1% of the Acceptable daily intake (ADI) of 0.015 mg/kg bw per day for ipconazole. In an acute consumer risk assessment, the calculated maximum exposure was less than 1 % of the Acute reference dose (ARfD) of 0.015 mg/kg bw for all cereal commodities for ipconazole.
    - Therefore, an exceedence of the current MRL of 0.01* mg/kg for ipconazole is not expected. The chronic and short-term intakes of ipconazole residues subsequently are unlikely to present a public health concern.
  - EPA has estimated chronic dietary exposures utilizing the Dietary Exposure Evaluation Model software with Food Commodity Intake Database (DEEM-FCID) version 3.15.
    - The chronic dietary exposure to the U.S. population (total) was 0.000043 mg/kg/day or 0.3% of the Chronic Population Adjusted Dose (cPAD),
    - The chronic dietary exposure to infants was 0.000068 mg/kg bw/day, or 0.5% of the cPAD.
    - The chronic dietary exposure to children 1 - 2 years old, the most sensitive group, was 0.000108 mg/kg bw/day, or 0.7% of the cPAD.
    - Therefore, chronic aggregate exposure from ipconazole is not expected to exceed the cPAD.
  - With aggregate cancer risk for U.S. population. Ipconazole has been classified as not likely to be carcinogenic and is not expected to pose a cancer risk to humans.
  - Based on these risk assessments, EPA concludes that:
    - **There is a reasonable certainty that no harm will result to the general population or to infants and children from aggregate exposure from dietary, drinking water, and non-occupational exposure assessments to ipconazole residues**.

- ***Occupational exposure***
  - EFSA (2013) with both French SeedTropex model and UK SeedTropex has reported on exposure of occupational and bystander exposure scenarios with acceptable exposure levels.

  - EPA assessing exposure found that:
    - In an occupational setting, exposure to ipconazole may occur during the seed treatment process as well as during activities associated with planting treated

seed. The occupational exposures may occur via dermal and/or inhalation routes.
        - All margin of exposure (MOEs) for seed handlers and seed planters found to be greater than the level of concern (LOC) of 100 for dermal exposure and 300 for inhalation exposure and therefore are not of concern to the EPA.
        - EPA: Ipconazole is registered as a non-agricultural seed treatment for turf grass and ornamental flowers and is not expected to result in residential exposures. Therefore, the Agency did not assess residential exposure or risk for ipconazole.
    - In South Africa, assessing exposure was found that:
        - Rancona 450 FS, containing the active ingredient ipconazole, is intended ONLY for use by commercial seed treatment applicators.
        - Workers handling Rancona 450 FS are required to wear chemical-resistant gloves and other Personal protective equipment (PPE) in common use for many seed treatment products, Within commercial treatment, exposure is minimized through the use of modern high-capacity treatment systems with bulk loading of product, dust aspiration, and PPE. Due to the nature of the use, post-application and bystander exposure are expected to be negligible.
        - The Margins of Exposure for planting maize seed treated with Ipconazole 452 FS are well above the LOC of 300 for both dermal and inhalation routes of exposure, indicating acceptable risks for planting maize seed treated with ipconazole.
        - Use of ipconazole as a seed treatment is therefore expected to result in low occupational exposure and negligible risk.

Registration of ipconazole in different countries

- ***Those Implementing risk-based approach***:
    - USEPA:
        - First registered in 2004 and still registered with the assessment of its benefits.
        - Canada.
        - Australia.
        - Japan.

Those Implementing hazard-based approach:

- EFSA/ European Union:
    - Was approved in 2014.
    - ECHA adopted an Opinion that ipconazole meets the criteria to be classified as toxic for reproduction, category 1B (R1B) in 2018.
    - European Commission has withdrawn its approval in 2023.

Approval on risk-based approach:

- South Africa:
    - The Rancona 450 FS (Ipconazole) dossier was first submitted in Dec 2017.
    - Occupational exposure to ipconazole was assessed and no occupational exposure to ipconazole was foreseen.
    - In 2024, Present application for derogation.

The Applicant

Corteva Agriscience RSA Crop Solutions
SA Proprietary Limited
(REG NO: 1991/003030/071967/007147/07)
Block A, Second Floor, Lakefield Office Park
272 West Avenue, Centurion, Pretoria, 0157 South Africa
TEL NO: +27(0)12 683-5700

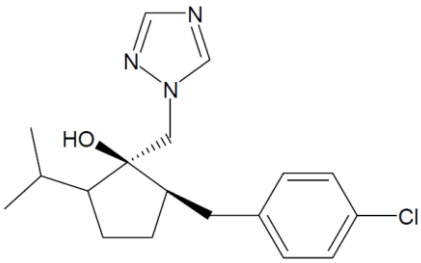
Formulation

Rancona 450 FS/Lumiflex	Minimum purity of the active ingredient as manufactured (g/kg): 944g/kg min
Function:	For plant protection products: Fungicide

Active ingredient

The following documents were reviewed for the information summarised in this section: (EPA 2008), (EPA 2012), (EFSA 2013), (EPA 2015a), (EPA 2021), and (EFSA 2022).

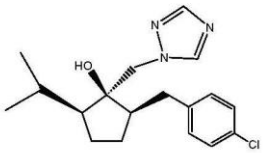
Active ingredient Common Name:	**Ipconazole**
Chemical name (IUPAC):	(1RS, 2SR, 5RS;1RS, 2SR, 5SR)-2-(4-chlorobenzyl)-5-isopropyl-1-(1*H*-1,2,4-triazol-1-ylmethyl) cyclopentanol
Chemical name (CA):	2-[(4-chlorophenyl)methyl]-5-(1-methylethyl)-1-(1H-1,2,4-triazol-1-ylmethyl) cyclopentanol 2-[(4-Chlorophenyl) methyl]-5-(1 -methylethyl)-1-(1 *H*- 1, 2, 4-triazol-1-y1metyl) cyclopentanol
CIPAC No:	798
CAS No:	125225-28-7 (mixture of diastereoisomers) 115850-69-6 (ipconazole cc, cis isomer) 115937-89-8 (ipconazole ct, trans isomer)
Minimum purity of the active substance As manufactured:	955 g/kg Ipconazole cc: 875 – 930 g/kg Ipconazole ct: 65-95 g/kg
• Molecular formula:	$C_{18}H_{24}ClN_3O$
Molecular Mass	333.861 g/mol
Structural formula:	



Ipconazole isomers:

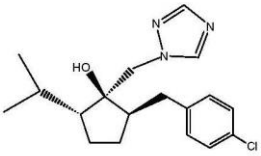
Ipconazole consists of a 9:1 cis-,cis-,:cis-,trans-mixture of isomers that have significantly different physical properties. The physical properties of the isomers are different enough that they will move through the environment at different rates. It is unknown whether just one or both isomers that are present in technical grade ipconazole are biologically active, or the extent to which they differ in biological activity. The toxicity data were developed on tests performed with technical grade ipconazole

.



Ipconazole *cc*
(*cis-cis* isomer)

(*1RS,2SR,5RS*)-2-(4-chlorobenzyl)-5-isopropyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol



Ipconazole *ct*
(*cis-trans* isomer)

(*1RS,2SR,5SR*)-2-(4-chlorobenzyl)-5-isopropyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol

Melting point (state purity):	81-89 °C (99.7 % pure)
Boiling point (state purity):	> 400 ± 0.5 °C (99.7 % pure cc) > 400 ± 0.5 °C (99.7 % pure ct)
Density:	1.2 g/mL at 20°C
Appearance (state purity):	White crystalline powder (99.3 % pure cc) White fine powder (98.3 % pure ct) White powder (98.1 % tech)
Vapor Pressure (25 °C)	3 x 10^{-6} Tor (99.7 % pure) cc-isomer: 1.6 x 10^{-8} torr ct-isomer: 4.5 x 10^{-9} torr Limited volatility from dry surfaces

Henry's Law Constant (25°C; Calculated)	3×10^{-5} atm.m^3 mol $^{-1}$ cc-isomer: 1.04×10^{-9} atm.m^3 mole^{-1} ct-isomer: 5.2×10^{-11} atm.m^3 mole^{-1} Calculated from solubility and vapor pressure vapor pressure; Limited volatility from water or wet surfaces
Aqueous Solubility (mg/L @ 20 °C)	a.i (9:1 cc/ct): 6.93 (99.2 % pure cc): 9.34 mg/L in pure water (Milli-Q ultrapure water) 9.86 mg/L in pH 5 buffer 8.68 mg/L in pH 7 buffer 9.13 mg/L in pH 9 buffer (99.0 % pure ct): 4.97 mg/L in pure water (Milli-Q ultrapure water) 5.79 mg/L in pH 5 buffer 4.60 mg/L in pH 7 buffer 4.71 mg/L in pH 9 buffer Relatively high solubility compared to expected environmental concentrations in the seed bed
Solubility in organic solvents:	98.1 % (tech) at 20 ± 0.5 °C: Acetone: 570.4 g/L 1,2-Dichloroethane: 424.8 g/L Dichloromethane: 583.1 g/L Ethyl acetate: 428.1 g/L Heptane: 1.90 g/L Methanol: 678.7 g/L n-Octanol: 229.6 g/L Toluene: 156.0 g/L Xylenes: 151.0 g/L
Surface tension: solution)	56.5 mN/m (Milli-Newton/meter) at 20 °C (90 % saturated (98.1 % tech)
n-Octanol/Water Partition Coefficient (K_{ow}) and (log K_{ow})	a.i (9:1 cc/ct): 4.21 cc-isomer: 4.49 at 20 °C (99.6 % pure cc) ct-isomer: 4.28 at 20 °C (100 % pure ct) Indicates possible bioaccumulation in aquatic organisms such as fish
UV/Vis absorption (max.) incl. ε:	(99.3 % pure cc): Neutral solution (water/acetonitrile; 3:2): λ max 276 nm; ε = 315 Acidic solution (HCl/acetonitrile; 3:2): λ max 276 nm, ε = 304 Basic solution (NaOH/acetonitrile; 3:2): λ max 276 nm, ε = 312 (98.3 % pure ct):

	Neutral solution (water/acetonitrile; 3:2): λ max 276 nm; ε = 312 Acidic solution (HCl/acetonitrile; 3:2): λ max 276 nm, ε = 293 Basic solution (NaOH/acetonitrile; 3:2): λ max 276 nm, ε = 305
Hydrolysis $t_{1/2}$ (25°C)	330 days in pH 5; 495 days in pH 7; and 257 days in pH 9 (No Transformation products detected & half-lives were extrapolated beyond the 30-day experiment duration) Data indicate the chemical is practically stable to hydrolysis
Aqueous Photolysis t ½ (25°C; continuous irradiation for 15 days)	64 days Major degradates: None Minor degradates: Hydroxyl-derivative of ipconazole (Max. 4% and its Isomer Max. 7% at end of study) Aqueous photolysis is not expected to be important degradation pathway for ipconazole

Analytical Enforcement Methodology

Adequate liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) enforcement methodology (AC/3020) is available to enforce the tolerance expression.

Methods of Analysis

Analytical methods for the active substance

Technical as (analytical technique):	HPLC-UV (detection at 220 nm)
Impurities in technical as (analytical technique):	HPLC-UV (detection at 220 nm)
Plant protection product (analytical technique):	HPLC-UV (detection at 220 nm)

Analytical methods for residues

Food of plant origin:	Ipconazole
Food of animal origin:	Not applicable
Soil:	Ipconazole and 1,2,4 triazole
Water surface:	Ipconazole and 1,2,4 triazole
Water drinking/ground:	Ipconazole
Air:	Ipconazole

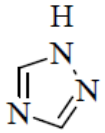
Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes):	LC-MS/MS (dry, high water, high acid and high oil crops). Independent laboratory validation (ILV) (dry crops) LOQ = 0.01 mg/kg The multi-residue method DFG S19 (dry, high water, high acid and high oil crops). ILV (dry crops)

	LOQ = 0.01 mg/kg
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes):	LC/MS/MS (meat, milk, eggs, fact, kidney, liver) LOQ = 0.01 mg/kg tissues and eggs. LOQ = 0.01 mg/L milk
Soil (analytical technique and LOQ):	LC-MS/MS (sandy loam and clay soils) LOQ = 0.001 mg/kg Open for 1,2,4 triazole
Water (analytical technique and LOQ):	LC-MS/MS (drinking, ground and surface water) LOQ = 0.05 μg/kg Open for 1,2,4 triazole in surface water
Air (analytical technique and LOQ):	LC-MS/MS LOQ = 0.0004 mg/m^3
Body fluids and tissues (analytical Technique and LOQ):	Not applicable

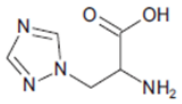
Triazole derivative metabolites

1,2,4-triazole (**1,2,4-T**)
IUPAC name/ notation: 1H-1,2,4-triazole
Structural formula

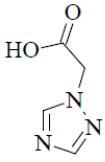


Triazole alanine (**TA**)
IUPAC name/ notation: 3-(1H-1,2,4-triazol-1-yl)-D,L-alanine
or
(RS)-2-amino-3-(1H-1,2,4 triazol-1-yl) propanoic acid

Structural formula

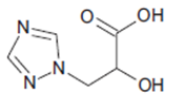


Triazole acetic acid (**TAA**)
IUPAC name/ notation: 1H-1,2,4-triazol-1-ylacetic acid
Structural formula

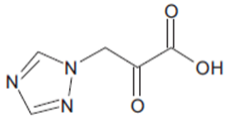


Triazole x`lactic acid or Triazolehydroxy propionic acid (**TLA**)
IUPAC name/ notation: (2RS)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl) propanoic acid

Structural formula:

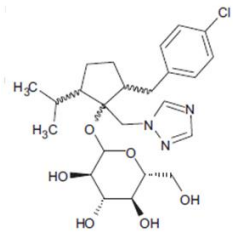


Triazolyl pyruvate
IUPAC name/ notation: 2-oxo-3-(1H-1,2,4-triazol-1-yl)propanoic acid
Structural formula:



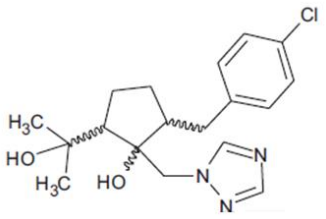
OH-IPC-glycoside
IUPAC name/ notation: 2-[(4-chlorophenyl)methyl]-5-(propan-2-yl)-1-[(1H-1,2,4-triazol-1-yl)methyl]cyclopentyl D-glucopyranoside

Structural formula:



tert-OH-isopropyl-IPC
IUPAC name/ notation: 2-[(4-chlorophenyl)methyl]-5-(2-hydroxypropan-2-yl)-1-[(1H-1,2,4-triazol-1-yl)methyl]cyclopentan-1-ol

Structural formula:



Introduction

The following documents were consulted for the preparation of the present derogation application: EFSA (2022), EPA (2004), EPA (2015a), EPA (2015b), EPA (2021), EPA (2022), and Russell (2024).

General information on Ipconazole

Ipconazole fungicide is a seed treatment that belongs to the triazole chemical group of De-Methylation Inhibitors (DMI) fungicides. Ipconazole has antifungal activity against many seed and soil-borne fungi. Ipconazole is a systemic and contact broad-spectrum seed treatment fungicide used to protect plants from soil borne and seed borne disease. Ipconazole fungicide seed treatments can reduce the effects of soil-borne or seed-borne pathogens, such as those that cause damping-off diseases (e.g., *Rhizoctonia solani*, *Fusarium* spp., *Sclerotinia* spp., *Pythium* spp., and *Phytophthora* spp.). *Rhizoctonia*, Fusarium, and *Phomopsis* are the targeted major soil and seed borne pathogens, which are responsible for important damping-off diseases. In addition, *Mucor*, *Rhizopus*, *Aspergillus*, *Penicillium*, *Alternaria*, and *Cladosporium* would likely be inhibited. Ipconazole is not active against *Phytophthora* spp. or *Pythium* spp. but would be used in combination with metalaxyl or mefanoxam where applicable.

Ipconazole is structurally similar to many other triazole compounds used as pesticides. Ipconazole exerts its effect by inhibiting sterol synthesis in fungi. Based on the radiotracer studies, residues on crops are non-existent and no tolerances have been proposed or established for ipconazole residues of concern in/on plant and animal commodities.

Ipconazole is registered as an on-farm and commercial seed treatment for a variety of crops including root and tuber vegetables, leafy (non-brassica) and brassica (cole crop) vegetables, cucurbit vegetables, cereal grains (barley, buckwheat, corn, millet, oats, rye, triticale, sorghum, and wheat), mustard, rape, canola, cotton, beans/peas (dried or succulent), peanuts, soybean, sunflower, and ornamentals (conifers, plants, turfgrass). Ipconazole is formulated into liquid (ready- to-use solutions and emulsifiable, flowable, and soluble concentrates) and dust (peanut seed treatment) products. Ipconazole is one of several chemicals included in standard seed treatment packages used by major seed suppliers.

Rancona 450 FS is a flowable concentrate for seed treatment formulation containing 452 g/ℓ of the active ingredient ipconazole. A use on maize seed at up to 8.14 grams ipconazole/100 kg seed is required to treat corn head smut disease.

Hazard Assessment

The documents consulted for the hazard assessment of ipconazole include, ECHA (2018), EPA (2004), EPA (2008), EPA (2012), EPA (2021), EFSA (2013), and Russell (2024).

Absorption, distribution, excretion and metabolism (toxicokinetics)

Rate and extent of oral absorption:	>90% based mostly on biliary excretion within 48h (oral dose of 2 mg/kg bw).
Distribution:	At 120h, widely distributed with highest residues in liver.
Potential for accumulation:	Limited accumulation on repeat dosing.
Rate and extent of excretion:	>70% excreted within 24h (mostly in faeces).

Metabolism in animals:	Extensively metabolised (max of 2% of dose excreted unchanged) with large number of metabolite fractions (each mostly <10 % of dose).
Toxicologically relevant compounds: (animals and plants)	Parent and the following metabolites: Triazole alanine (plants) Triazole acetic acid (plants)
Toxicologically relevant compounds: (environment)	None

Acute toxicity

Acute oral (rat) LD_{50}	M = 1338 mg/kg F = 888 mg/kg	Category IV
Acute oral (mice) LD_{50}	M = 537 mg/kg bw F = 468 mg/kg bw	Category IV
Acute dermal (rat) LD_{50}	>2000 mg/kg bw (both sexes)	Category IV
Acute inhalation (rat) LC_{50}	>1.88 mg/ℓ (both sexes)	Category III
Acute skin irritation (rabbit)	Primary irritation index = 0.08 Non-irritating to the skin of rabbits	Category IV
Acute eye irritation	Eye irritation present at 24 hours, cleared by day 7/ Mildly irritating to rabbit eyes	Category III
Skin sensitization (guinea pig)	Not a Sensitizer Non-sensitizing on the skin of guinea pigs	NA

Subchronic Toxicity

Inhalation

28–Day Rats:	NOAEL for systemic toxicity was 30 mg/m^3 NOAEL for upper respiratory tract and upper digestive tract (portal of entry) was < 30 mg/m^3 LOAEL (Lowest observable adverse effect level) = 78.3 mg/kg/day, based on decreased body weight, body weight gain, and food consumption in males; clinical findings, such as alopecia, in males and/or females; meta/ hyperplasia and inflammatory cells in the respiration tract in males and/or females; and increased.	

Oral

28-day Rat:	NOAEL: 30.5 mg/kg bw/day	Category II
28-day Mouse:	NOAEL: ≥ 44.8 / 53.4 mg/kg bw/d	
28-day oral (capsule) Dog	Lowest dose: 24 mg/kg bw/d	

90-day oral (capsule) dog:	NOAEL: 2 mg/kg bw/day H373 "May cause damage to organs through prolonged or repeated oral exposure)
90-day mouse:	NOAEL: 4.4 mg/kg bw per day in males and 5.1 mg/kg/day in females.
90-day rat:	NOAEL: 5.8 mg/kg/day in males and 7.0 mg/kg/day in females.

.

Dermal

28–Day Dermal Toxicity Study in Rats:	NOAEL = 150 mg/kg/day LOAEL = 1,000 mg/kg/day, based on decreased body weight, body weight gain, and food consumption, as well as increased incidences of dermal irritation

Dermal Absorption

Based on ipconazole *in-vitro* dermal absorption studies (total amount of absorbable ipconazole on human skin to be between 0.32% and 0.99%), the EPA comparison of dermal NOAEL to oral LOAEL which indicates 3% dermal absorption, and the United Kingdom Chemicals Regulation Directorate choosing a dermal absorption value of 5%, it is conservatively proposed that a value of **5% dermal absorption** be used in the occupational risk assessments for workers exposed to Ipconazole.

Target organs

Proposed classification of ipconazole as H373 - May cause damage to organs (eyes, skin, liver, gastrointestinal tract) through prolonged or repeated exposure.

Chronic Feeding/Oncogenicity Study

Target/critical effect:	Liver histopathology No relevant effects (rat); forestomach lesions in rat not relevant to humans
18-month Mouse	NOAEL 1.9 mg/kg/day in males and 2.3 mg/kg/day in females
2-year, rat	13.3 mg/kg/day males and 12.6 mg/kg/day females)
1-year oral (capsule) dog:	NOAEL: 1.5 mg/kg bw per day (***used by EPA for chronic Reference dose (RfD) calculation***) Ipconazole is not oncogenic.

Developmental Toxicity

Developmental target / critical effect:	*Rat*: Parental: reduced bw gain and food consumption

	Developmental: malformations of eyes and major blood vessels in presence of moderate maternal toxicity (main study); malformations of eyes and tail in presence of marked maternal toxicity. *Rabbit*: Parental: reduced bw gain Developmental: skeletal abnormalities indicative of foetal toxicity in presence of moderate maternal toxicity (main study); malformations of tail in presence of marked maternal toxicity (prelim study)
Relevant maternal NOAEL:	10 mg/kg bw per day, rat 10 mg/kg bw per day, rabbit (***used by EPA for acute aRfD calculation***)
Relevant developmental NOAEL:	3 mg/kg bw per day, rat 10 mg/kg bw per day, rabbit
The developmental toxicity LOAEL:	30 mg/kg/day based on decreased foetal body weight and increased incidences of visceral and skeletal variations. The classification as R63* ("Possible risk of harm to the unborn child" or H361d "**Suspected of damaging the unborn child**").

Reproductive Toxicity

Reproduction target / critical effect:	Parental: reduced bw gain Reproductive: no adverse effects Offspring: reduced bw gain, delayed vaginal opening
Relevant parental NOAEL:	9 mg/kg bw per day
Relevant reproductive NOAEL:	22 mg/kg bw per day
Relevant offspring NOAEL:	8 mg/kg bw per day In multigeneration toxicity studies ipconazole did not show reproductive toxicity potential.

Neurotoxicity

Acute neurotoxicity:	Not required since registration is limited to non-food uses not required
Repeated neurotoxicity:	No effect, 90-day rat (NOAEL 33 mg/kg bw per day)
Delayed neurotoxicity:	not required Ipconazole did not show effects indicative of a neurotoxicity potential.

Mutagenicity

Ipconazole testing indicate is not mutagenic. Ipconazole Technical was evaluated and found to be negative

in the Ames Reverse Mutation, Chinese hamster ovary (CHO) cells hypoxanthine phosphoribosyl transferase (HGPRT) Mammalian mutation, *Bacillus subtilis* DNA Repair, Chinese Hamster Lung Chromosome Aberration and Mouse Micronucleus assays.

Metabolite toxicology

Metabolites from the goat metabolism study essentially matched those produced in the rat. In addition to triazole, intact ipconazole metabolites were characterized as further oxidized and conjugated. In addition, cyclization occurred to produce both hemiacetals and lactones.

In plants, intact ipconazole metabolites were also found in the rat. In addition to intact metabolites, wheat and soybean produced triazole conjugates - triazolylalanine, triazolylpyruvic acid and triazolylacetic acid.

Although not produced in the rat, triazolylalanine, triazolylacetic acid, and by inference, triazolylpyruvic acid, have been evaluated in a recent human health risk assessment for triazole-derived fungicides. **It was concluded that the risk from these metabolites was below the level of concern**.

Endocrine disruption

There are no known reported adverse reproductive or developmental effects in domestic animals or wildlife as a result of exposure to this chemical. A standard battery of required toxicity tests has been conducted on ipconazole. No effects were seen in the reproduction or teratology studies to indicate that ipconazole has an effect on the endocrine system.

However, EFSA (2013) indicated that the risk to birds from potential endocrine mediated effects needs to be further addressed.

Hazard statement and classification

Information obtained from EFSA (2013) and Rapporteur Report (2018) on **RANCONA 450 FS Active substance: ipconazole, 452 g/L** is summarised as follows:

Hazard statement	H361d	Suspected of damaging the unborn child
	H373	May cause damage to organs through prolonged or repeated exposure
	H410	Very toxic to aquatic life with long-lasting effects

Classification and labelling in accordance with Regulation (EC) No1272/2008

Health hazards:	Reproductive toxicity	Category IB (R1B) (May damage the unborn child)
	Specific target organ toxicity after repeated exposure	Category II
Environmental hazards:	Hazardous to the aquatic environment, Chronic Hazard	Category I

Toxicological reference values

The following documents were consulted for the determined toxicological reference values: EFSA (2013), PVMA (2017), and EPA (2008).

Endpoints used in risk assessment by EFSA, EPA and Australia. EPA has however indicated that in support of a choice of a Safety Factor (SF) for infants and children of x1, is justified for the following reasons:

- *Prenatal and postnatal sensitivity*. Offspring effects only occurred in the presence of maternal toxicity; offspring effects were not considered more severe than the parental effects. Therefore, HED concluded that there is no quantitative or qualitative evidence of increased susceptibility to rat or rabbit foetuses exposed *in utero* and/or postnatally to ipconazole.

- *Conclusion*. EPA has determined that reliable data show the safety of infants and children would be adequately protected if the Food Quality Protection Act Safety Factor (FQPA SF) were reduced to 1X. That decision is based on the following findings:
    - The toxicity database for ipconazole is adequate for the purposes of this risk assessment.
    - There is no indication that ipconazole is a neurotoxic chemical and there is no need for a developmental neurotoxicity study or additional uncertainty factors (UFs) to account for neurotoxicity.
    - There is no evidence that ipconazole results in increased susceptibility in *in utero* rats or rabbits in the prenatal developmental studies or in young rats in the 2-generation reproduction study.
    - There are no residual uncertainties identified in the exposure databases. EPA made conservative (protective) assumptions in the ground and surface water modeling used to assess exposure to ipconazole in drinking water. EPA used similarly conservative assumptions to assess post-application exposure of children as well as incidental oral exposure of toddlers. These assessments will not underestimate the exposure and risks posed by ipconazole. The toxicological reference values are presented in **Table 1.**

Table 1: The toxicological reference values for the active substance ipconazole.

Active substance: ipconazole
European Union

Endpoint	Value	Study	Safety factor
ADI	0.015 mg kg bw/d	Based on the subchronic (1-year) NOAEL of 1.5 mg/kg bw per day in dogs	100
AOEL	0.015 mg/kg bw/d	Rat developmental	200*
ARfD	0.015 mg/kg bw/d	Rat developmental	200*
*The UF was increased to have the same margin as with the ADI between the reference values and the teratogenic effects occurring at 10 mg/kg bw per day			
Australia			
ADI	0.015 (mg/kg bw/d)	1-year oral (gelatine capsule) dog study; a NOAEL of 1.5 mg/kg bw/d based on increased incidence and severity of bile duct proliferation and increased incidence in centrilobular hepatocyte hypertrophy at the next higher dose	100
EPA			
Acute RfD	0.1 mg/kg/day	NOAEL = 10 mg/kg/day Developmental Toxicity Studies in Rats and Rabbits	UF_A = 10x UF_H = 10x FQPA SF = 1x
Acute population adjusted dose (aPAD)	0.1 mg/kg/day		
Chronic RfD = mg/kg/day	0.015	Chronic Toxicity Study in Dogs NOAEL = 1.5 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x
Chronic population adjusted dose (cPAD)	0.015 mg/kg/day		

ADI = Acceptable daily intake
AOEL = Acceptable operator exposure level
ARfD = Acute reference dose
RfD = reference dose.
PAD = population adjusted dose (a = acute, c = chronic).
cPad = Chronic Population Adjusted Dose
UF_A = extrapolation from animal to human (interspecies).
UF_H = potential variation in sensitivity among members of the human population (intraspecies).
FQPA = Food Quality Safety Act
FQPA SF = FQPA Safety Factor

Residues

The following documents were consulted for residues of ipconazole: (EFSA 2013), (EPA 2012), and (Rapporteur Report (2018)).

Residue Chemistry

Plant metabolism

The metabolism of ipconazole was investigated in wheat following seed treatment and foliar application of ^{14}C-benzyl methylene or ^{14}C-triazole labelled ipconazole, and in addition in soybean with seed treatment application of ^{14}C-triazole labelled ipconazole. The metabolism of ipconazole was also investigated in rotational crops wheat, lettuce, and carrots.

Plant groups covered: Wheat (cereal), Soybean (pulse/oilseed) seed treatment

Rotational crops: Wheat (cereal), lettuce (leafy) and carrot (root)
Metabolism in rotational crops

similar to metabolism in primary crops?	Yes
Processed commodities:	Not applicable, study not triggered
Residue pattern in processed Commodities similar to residue pattern in raw commodities?	Not applicable
Plant residue definition for Monitoring	Ipconazole
Plant residue definition for risk assessment:	1) Ipconazole 2) Triazole derivative metabolites (TDMs) which are for consideration in EU only, not by EPA, pending further detailing when a harmonised assessment approach for triazole compounds and TDMs has been agreed.
Conversion factor (monitoring to risk assessment):	Not applicable

Metabolism in livestock

Animals covered: Not applicable (animal intakes < 0.1 mg/kg)

Residues in succeeding crops

Based on the total radioactive residues in the rotational crop metabolism study it is unlikely that significant residues (> 0.01 mg/kg) would result from the intended use.

Stability of residues

Ipconazole was stable for up to 13 months in wheat (grain, forage, hay and straw) and maize (cobs, forage and straw).

Residues from livestock feeding studies

Not applicable

Summary of residues data according to the representative uses on raw agricultural commodities and feeding stuffs

MRL estimated from trials according to the representative use: 0.01 mg/kg (wheat and barley)

As residues of ipconazole do not exceed the trigger values, **there is no need to investigate the effect of industrial and/or household processing**. **Further investigation of residues, as well as the modification of MRLs in commodities of animal origin, are not necessary.**

Magnitude of residues

Crop residue trials were conducted in the US on soybeans at an exaggerated treatment rate of 5X, at five seed with pod, succulent seed without pod, and soybean seed were analysed for ipconazole.. No quantifiable residues of ipconazole were found in any of the raw agricultural commodities (RACs), at a limit of quantitation of 0.01 ppm. A tolerance of 0.01 ppm was already established for soybeans; the US

field trials support that tolerance. A petition to EPA (2013) requesting that residues of the fungicide ipconazole in or on legume vegetables, succulent or dried, crop group 6 to be established at 0.01 ppm.

International Residue Limits (MRLS)

The following documents were consulted for tolerances and MRLs: (EFSA 2013), (EPA 2008), (EPA 2012), and (EPA 2021).

EPA Tolerances

Tolerances at the LOQ, 0.0l ppm have been established for residues of ipconazole, including its metabolites and degradates, in or on the commodities listed in the **Table 2** below. Compliance with the tolerance levels specified below is to be determined by measuring only ipconazole (2-[(4-chlorophenyl)methyl]-5-(1-methylethyl)-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol) in or on the commodity (EPA 2008, EPA 2012, EPA 2021).

Table 2: Tolerances of ipconazole in certain commodities.

Commodity	Parts per million
Cotton, gin byproducts	0.01
Cotton, undelinted seed	0.01
Grain, cereal, forage, fodder and straw, group 16, except rice	0.01
Grain, cereal group 15, except rice	0.01
Peanut	0.01
Soybean, forage	0.01
Vegetable, legume, group 6	0.01

International MRLS

EFSA

Proposed MRLs 0.01 mg/kg using PRIMo rev. 3 model (EFSA 2020).

Codex Alimentarius

No Codex MRLs have been established for the requested uses.

Canada

Canada has established an MRL of 0.01 ppm for dried shelled pea and bean, except soybean (Crop Subgroup 6C); cereal grains (Crop Group 15, except rice); dry soybeans and peanuts.

Environmental fate and behaviour

EPA

The following data were developed for the technical grade ipconazole as described in EPA (2020).

Aerobic Soil Metabolism

Aerobic soil metabolism results (half-lives ranged from 181 to 1,960 days at 20°C in six soils) indicate that ipconazole is highly persistent based on the Goring persistence scale (Goring *et al.*, 1975).

- Non-persistent less than 15 days
- Slightly persistent for 15-45 days
- Moderately persistent for 45-180 days, and
- Persistent for greater than 180 days

Ipconazole is also persistent in aerobic aquatic systems (half-lives were 245 and 507 days at 20°C in two water: sediment systems). Study data indicate that ipconazole is practically stable to hydrolysis at pH 5, 7, and 9, and photolysis (half-life 64 days) is not considered to be an important degradation pathway (**Table 3**).

Table 3: Environmental degradation of ipconazole

Study	System Details	Representative Half-life (days)[1]
Aerobic Soil Metabolism	Sandy loam, 20°C	1960 (SFO)
	ND Sandy loam, 20C	466.7 (SFO)
	UK Sandy loam, pH 6.0, 20°C	318 (SFO)
	UK Sandy clay loam, pH 7.7, 20°C	181 (SFO)
	UK Silt loam, pH 6.1, 20°C	257 (SFO)
	UK Clay loam, pH 7.1, 20°C	184 (SFO)
Aerobic Aquatic Metabolism	UK Pond Sandy clay loam, water pH 6.98, sediment pH 7.7, 20°C	245 (SFO)
	UK Lake Loamy sand, water pH 7.23, sediment pH 6.4, 20°C	507 (SFO)

[1] The value used to estimate a model input value is the calculated SFO DT50. The model chosen is consistent with that recommended using the, *Guidance for Evaluating and Calculating Degradation Kinetics in Environmental Media* (NAFTA, 2012).

Anaerobic metabolism and terrestrial field dissipation studies

Anaerobic aquatic metabolism study data was not submitted and therefore stability will be assumed in modeling.

Adsorption-Desorption

Residues of ipconazole, at a nominal concentration of 0.1 µg/g, were incubated in sandy loam soil for 30 days. No radiolabelled residues were identified during the incubation period. After incubation, aged residues were placed on a 30 cm column of sandy loam soil and then leached at rate of 0.8 mL/hour with 0.01 M Calcium chloride ($CaCl_2$) over a 2-day period. Aged, radiolabelled residues in the soil column were identified as ipconazole. Radiolabelled residues were predominately detected (>96.6% of applied) in the 0-5 cm soil column segment. Radioactivity in leachate and volatility traps account for <0.01% of applied.

Ipconazole, at soil concentrations from 0.9 to 90 mg a.i./kg:
Freundlich adsorption coefficients were:

- 90 (1/n= 0.78; K_{oc} = 3214) in a Dock Road sandy loam soil.

- 107 (1/n=0.81; K_{oc}=1911) in a EL7 sandy loam soil.
- 108 (1/n=0.80; K_{oc}=2512) in German Hatzenbeler clay loam soil.
- 45 (1/n=0.81; K_{oc}=2513) in a Mutchler sandy loam soil.
- 47 (1/n=0.86; K_{oc}=2813) in an Oregon silt loam soil.

Freundlich desorption coefficients were:

- 113 (1/n= 0.80; K_{oc}=4036) in a Dock Road sandy loam soil.
- 118 (1/n=0.78; K_{oc}=2107) in a EL7 sandy loam soil.
- 146 (1/n=0.83; K_{oc}=3938) in German Hatzenbeler clay loam soil.
- 63 (1/n=0.84; K_{oc}=3938) in a Mutchler sandy loam soil.
- 59 (1/n=0.86; K_{oc}=3026) in an Oregon silt loam soil.

Hydrolysis

Ipconazole degraded with half-lives of 330 days in pH 5 buffer, 495 days in pH 7 buffer, and 257 days in a buffered pH 9 solution at 25°C. Ipconazole is stable to hydrolysis and is expected to be slightly affected by photolysis especially in shallow/clear water bodies. Photolysis in such water bodies cause the chemical to degrade to hydroxyl-derivative of ipconazole and hydroxyl-derivative isomer (maximum forming 4 and 7%, respectively). Photolysis is not expected to be an important dissipation pathway for ipconazole.

Aqueous Photolysis

The half-life for ipconazole at 3 µg/ml in a buffered (pH 5) solution under a continuous Xenon lamp irradiated (pH 5) solution is 32 days (equivalent to ca. 64 days of natural sunlight). No degradation was detected in dark control samples.

Spray drift

No ipconazole-specific studies were reviewed or required. Droplet size spectrum and drift field evaluation studies are not required since ipconazole is a seed treatment and will not be applied aerially. Drift may be considered minimal with seed treatment uses.

Summary

- Ipconazole is expected to be readily soluble when applied with the seeds in an expected moist seed bed. Volatilization of ipconazole into the air from dry/wet soils and water is expected to be limited due to its relatively low vapor pressure and Henry's low constant.
- Ipconazole is persistent and bioaccumulative. **The log K_{ow} is >3**, thus it can be considered potentially bioaccumulative. **Possible bioaccumulation in fish and aquatic organisms is suggested by the relatively high log K_{ow} of the isomer mixture** (4.21) although the value for one of the isomers, the ct-isomer is less (3.8).
- Ipconazole is **persistent** and degradation in soil is highly variable ($t_{1/2}$ = 330 days to 1386 days) and relatively **immobile** (K_f = 45 to 108 ml/g) in terrestrial and aquatic environments.
- Triazole was identified as the only major aerobic soil degradation product (>10%) of ipconazole. As a result of the abiotic and biotic process, low concentrations of 1, 2, 4-triazole degradate may form which appears to decline with time.

EFSA

The following data were developed for the technical grade ipconazole as described in the following EFSA documents: EFSA (2013), and (Rapporteur Report (2018)) (**Table 4**).

Aerobic route and rate of degradation

It should be noted that ipconazole used in the environmental fate and behaviour studies is present as two isomers, cis-cis (cc) and cis-trans (ct). The methods of analyses used in the radio labelled soil and water studies were able to distinguish between the isomers and there was no evidence of significant change in isomer ratio over the duration of the studies.

Aerobic soil metabolism studies used sandy loam, sandy clay loam, silt loam, and clay loam soils from Europe and one sandy loam soil from the United States. The submitted aerobic aquatic metabolism study used sandy clay loam and loamy sand sediments.

Aerobic route and rate of degradation studies on four soils were conducted with the active substance radio-labelled in the triazole and in the benzyl methylene positions. In these studies, mineralisation was limited with up to 9.8% at 122 days, indicative of the slow degradation under standard laboratory conditions. Aerobic degradation led to the formation of a number of minor metabolites, none of which exceeded 5% AR at any sampling time. The metabolite 1,2,4-triazole was 23.7% AR at 31 days after treatment in the sandy loam soil tested.

Ipconazole exhibited high to very high persistence in soil and metabolite 1,2,4 triazole exhibited persistence in the US soil. The extent of degradation of ipconazole under anaerobic conditions was slightly less than seen under aerobic conditions, but no novel metabolites were observed. A study investigating photolytic route of degradation of ipconazole on a single soil was also conducted using both radio labelled positions. Apparently greater degradation of ipconazole was seen during the course of this study than under dark conditions, with one major photolysis product (1,2,4-triazole) formed at a maximum of 10.4% AR on day 8. The representative use of ipconazole is as a cereal seed treatment, so, **residues of ipconazole are unlikely to be present on the soil surface**. Thus, **the photolytic route of degradation for ipconazole is not relevant to the exposure assessment for this use**. **Ipconazole exhibited low to slight mobility in soil and no pH influence on soil adsorption was detected**.

In a dark water-sediment study conducted on 2 natural aerobic aquatic systems, ipconazole dissipated rapidly from the water phase and was found predominantly in the sediment phase of both systems. No major metabolites (> 10% AR) were detected in water or sediment. In the natural sediment water systems, ipconazole exhibited high persistence. No data are required on aqueous photolysis, as there is no significant absorption of ipconazole at wavelengths greater than 220 nm.

Route of degradation (aerobic) in soil

Mineralization after 100 days:	0.2 – 4.3% applied radioactivity (AR) after 120 - 122 d, [^{14}C-triazole]-label (n= 4) 9.8% AR after 122 d, [^{14}C-benzyl methylene]-label (n= 1) 12.4% AR after 119 days, eqimolar mixture of [^{14}Ctriazole] and [^{14}C-benzyl methylene]-labels
Non-extractable residues after 100 days:	14.2 – 33.2% AR after 120-122 d, [^{14}C-triazole]-label (n= 4) 13.8% AR after 122 d, [^{14}C-benzyl methylene]-label (n= 1) 22.7% AR after 119 days, equimolar mixture of [^{14}Ctriazole] and [^{14}C-benzyl methylene]-labels

Metabolites requiring further consideration: None trigger assessment from EU studies. KNF-317-M-1 and KNF-317-M-11 <5% AR.
1,2,4-triazole 23.7% AR at 31 d in US study

Anaerobic degradation in soil

Mineralization after 100 days: 0.6% AR after 120 d, [^{14}C-triazole]-label (n= 1)
3.6% AR after 120 d, [^{14}C-benzyl methylene]-label (n= 1)

Non-extractable residues after 100 days: 12.3% AR after 120 d, [^{14}C-triazole]-label (n= 1)
11.7% AR after 120 d, [^{14}C-benzyl methylene]-label (n= 1).

Soil photolysis

Metabolites that may require further consideration for risk assessment – name and/or code, % of applied (range and maximum): 1,2,4-triazole – 10.4 % AR at 8 d (equiv. to 32.6 days 40°N summer sunlight) (n = 1)
4-chlorobenzaldehyde – 6.3 % AR at 8 d (equiv. to 32.5 days 40°N summer sunlight) (n = 1).

Table 4: Rate of degradation in soil

Laboratory studies							
Parent	**Aerobic conditions**						
Soil type	X[8]	pH (CaCl2)	t. °C / % MWHC	DT_{50} /DT_{90} (d)	DT_{50} (d) 20°C pF2/10kPa	St. (χ2)	Method of calculation
Sandy loam[1]		5.3	20°C / pF2	294 / 977	294	2.8	SFO
Sandy clay loam[1]		7.2	20°C / pF2	170 / 564	170	3.5	SFO
Silt loam[1]		5.4	20°C / pF2	225 / 748	225	4.1	SFO
Clay loam[1]		6.5	20°C / pF2	184 / 612	184	5.6	SFO
Sandy loam[2]		7.7[3]	25°C / 75% 1/3 bar	194 / 998	391	2.5	DFOP (SFO for 20°C)
Geometric mean/median					240		SFO
Sandy clay loam		7.2	10°C / pF2	593 / 1969		1.7	SFO
[1] = EU soil, [2] = US soil, [3] = pH measured in water							
Parent	**Anaerobic conditions**						
Sandy loam (anaerobic part of study only)		5.6	20°C	779 / 2587		0.5	SFO
Geometric mean/median			n.a.				
Parent	**Soil photolysis**						
Sandy loam		5.3	20°C, dry	147 / 490[a]		3.7	SFO
[a] = DT_{50} and DT_{90} are equivalent days under 40°N summer sunlight, assuming 12-hour day/night cycles							

Mobility in soil

Results are presented in **Table 5** below**.**

Soil adsorption/desorption

Table 5: Results of soil adsorption/desorption for Ipconazole

Parent							
Soil Type	OC %	Soil pH	Kd (mL/g)	K_{oc} (mL/g)	K_f (mL/g)	K_{foc} (mL/g)	1/n
Sandy loam	2.8	5.2			90	3214	0.7842
Sandy loam	5.6	7.1			107	1911	0.8073
Clay loam	4.3	7.1			108	2512	0.8077
Sandy loam	1.6	5.9			45	2813	0.8121
Silt loam	1.95	5.9			47	2410	0.8582
Loamy sand	0.3	6.2			5.2	1724	0.792
Arithmetic mean/median					67/68.5	2431/2461	0.81/0.81
pH dependence, Yes or No			No				
Metabolite 1,2-4 triazole (Endpoints derived from the Triazole Derivative Metabolite Group database, January 2013)							
Silty clay	0.70	8.8			0.833	120	0.897
Clay loam	1.74	6.9			0.748	43	0.827
Sand	0.12	4.8			0.234	202	0.8851
Silty clay loam	0.70	7.0			0.722	104	0.922
Sandy loam	0.81	6.9			0.720	89	1.016
Arithmetic mean (of 4 values excluding the very low OC sand that was considered not representative of agricultural soils)					0.756	89	0.9155
pH dependence (yes or no)			No				
K_{doc} organic carbon linear adsorption coefficient K_{Foc} Freundlich organic carbon adsorption coefficient Kd MWHC maximum water holding capacity K_f 1/n slope of Freundlich isotherm							

Column leaching: Not required.
Lysimeter/ field leaching studies: Not required

Route and rate of degradation in water

Hydrolytic degradation of the active Substance and metabolites > 10 %:

pH 4 or 5: *stable at 25°C and 50°C*
Parent: 90.9 %AR (30 d, 25°C, pH 5),
95.3 %AR (7 d, 50°C, pH 4)
No relevant metabolites >10%
pH 7: *stable at 25°C and 50°C*
Parent: 96.4 %AR (30 d, 25°C),
101.5 %AR (7 d, 50°C)
No relevant metabolites >10%
pH 9: *stable at 25°C and 50°C*
Parent: 92.1 %AR (30 d, 25°C),
97.5 %AR (7 d, 50°C)
No relevant metabolites >10%

Photolytic degradation of active substance and metabolites above 10 %: No data required, as there is no significant

absorption of ipconazole at wavelengths above 290 nm

Readily biodegradable: No

Results are presented in **Table 6** below.

Table 6: Degradation in water / sediment of Ipconazole

Parent	Distribution (eg max in water 92.3 %AR after 0 d. Max. sed 87.7 %AR after 30 d)									
Water / sediment system	**pH water phase**	**pH sed**	**t. °C**	**DT_{50}-DT_{90} whole sys.**	**St. (r^2)**	**DT_{50}-DT_{90}* water**	**St. (r^2)**	**DT_{50}-DT_{90} sed**	**St. (r^2)**	**Method of calculation**
Clay loam (Bury Pond)	7.44	7.7	20	241 799	0.93	2.0 17.6	>0.99	244 810	0.99	SFO
Sandy loam (Emperor Lake)	7.72	6.4	20	490 1628	0.85	2.8 19.3	>0.99	441 1466	>0.99	
Geometric mean/median			-	344 1141		2.4 18.4		328 1098		

* represents dissipation from water phase, calculated using First Order Multi-Compartment (FOMC) kinetics. $\chi 2$ values not available.
Pseudo SFO DT_{50} (FOMC DT_{90}/3.322) for water phase dissipation are 5.3 days (clay loam) and 5.8 days (sandy loam)

Field dissipation studies

Field dissipation studies were conducted in Germany (two sites), Italy and Spain (one site each). Applications were made in December/January period and the bare soil applications were immediately incorporated, presumably to mimic application as a seed treatment and to minimise any soil surface losses by photolysis and volatilisation. Only ipconazole was analysed for. With the exception of the Spanish field dissipation result, the field dissipation values are all considerably shorter than those seen in the laboratory studies, indicating that ipconazole exhibits medium to high persistence under field conditions. Based on the endpoints provided by the Triazole Derivative Metabolite Group (TDMG) evaluation, metabolite 1,2,4 triazole exhibits moderate to high persistence (derived from best fit kinetics of the dissipation parameter, $DissT_{50}$ values from 4 dissipation field trials in Germany, UK, Italy and Spain).

Direct photolysis in air

None are required, based on intended use of ipconazole as a seed treatment, limiting exposure to air.

Volatilisation

No data submitted. None are required, based on vapour pressure of 3 x 10^{-6} Pa at 25°C, Henry's Law constant of 3 x 10^{-5} $Pa.m^3.mol^{-1}$ and intended use of ipconazole as a seed treatment.

Predicted environmental concentration (PEC)

The fate and behaviour in the environment have therefore been evaluated. Appropriate endpoints from the EU conclusions were used to calculate predicted environmental concentration (PEC) values for the active substance and its metabolite for the intended use patterns. In cases where deviations from the EU

agreed endpoints were considered appropriate (for example when additional studies are provided), such deviations were highlighted and justified accordingly. The PEC values of ipconazole and its metabolite in soil, surface water and groundwater have been assessed according to FOCUS guidance documents (FOCUS, 2001) step 1 and step 2 approach (version 1.1 of the Steps 1-2 in FOCUS calculator). For the active substance ipconazole, satisfactory step 3 calculations were also available, with standard FOCUS scenarios to obtain outputs from the FOCUS models, and the endpoints established in the EU conclusions or agreed in the assessment based on new data provided.

The necessary surface water and sediment exposure assessments (PEC calculations) were carried out for parent ipconazole and the metabolite 1,2,4-triazole using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 1.1 of the Steps 1-2 in FOCUS calculator). For the active substance ipconazole, satisfactory step 3 calculations were also available. As the study performed to investigate toxicity of ipconazole to sediment dwelling organisms was dosed by spiking in the water phase and the No observed effect concentration (NOEC) expressed as a water concentration (mg/L), pseudo PEC_{sw} values were also calculated. As degradation of ipconazole in sediment occurs slowly, the potential for accumulation of residues in this compartment was also considered and evaluated using these pseudo PEC_{sw} values.

Appropriate groundwater exposure assessments for ipconazole and its soil metabolite 1,2,4-triazole were available. Input parameters for degradation and soil adsorption of 1,2,4-triazole were obtained from the TDMG database. The 80th percentile annual average PEC_{gw} concentrations for ipconazole and 1,2,4-triazole at 1 m soil depth were $\leq$ 0.001 µg/L for all the scenarios simulated using FOCUSPEARL v.4.4.4.

PEC_{soil} (soil)

Parent ipconazole:	DT_{50} (d): 391 days
Method of calculation:	Kinetics: SFO (Single first-order)
Metabolite 1,2,4-triazole:	Calculated with Escape v 2.0 Parent DT_{50} 391 days (SFO, worst case lab) or 228 days (SFO worst case field)*

PEC_{sw} ($PEC_{surface\ water}$) and PEC sediment

PEC_{sw} max 0.5501 µg/l, PEC_{sed} max 13.3739 µg/kg

Potential for ipconazole accumulation in sediment

As degradation of ipconazole in sediment occurs slowly, (geometric mean DT_{50} of 328 days), the potential for accumulation of residues in this compartment needs to be considered.

PEC_{gw} ($PEC_{ground\ water}$)

Ipconazole: <0.001 µg/L
Metabolite 1,2,4-triazole: <0.001 µg/l

PEC_{air}

PEC_{air} not calculated, nor required. Expert judgement, based on low vapour pressure, dimensionless Henry's Law Constant and intended use of ipconazole as a seed treatment.

PEC soil and PECsw values derived for ipconazole, and its metabolite are used for the ecotoxicological risk assessment. PECgw values for ipconazole and its metabolite do not occur at levels exceeding those mentioned in Regulation (EC) No 1107/2009 and guidance document SANCO 221/2000 on the relevance of metabolites in groundwater. Therefore, **no unacceptable risk of groundwater contamination is**

expected for the intended uses. Based on vapour pressure, information on volatilisation from plants and soil, and DT_{50} calculation, **no significant contamination of the air compartment is expected for the intended uses**.

Risk assessment

Using the provided same or additional data summarised above, ecotoxicological and human risk assessment of ipconazole were conducted by EFSA and EPA keeping in mind that a direct comparison of EPA and EFSA may not be possible as different crops and use rates were evaluated using different risk assessments schemes. As risk assessment by EPA are in agreement with the targeted use of seed treatment, risk assessment by EPA may also be of relevance to South Africa.

Ecological risk assessment by EFSA

Studies and risk assessment conducted by EFSA were summarised as reported in EFSA (2013). The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of ipconazole as a fungicide for seed treatment of wheat and barley as proposed by the applicant. As the study performed to investigate toxicity of ipconazole to sediment dwelling organisms was dosed by spiking in the water phase and the NOEC expressed as a water concentration (mg/L), pseudo PECsw values were also calculated. As degradation of ipconazole in sediment occurs slowly, the potential for accumulation of residues in this compartment was also considered and evaluated using these pseudo PECsw values.

Appropriate groundwater exposure assessments for ipconazole and its soil metabolite 1,2,4-triazole were available. Input parameters for degradation and soil adsorption of 1,2,4-triazole were obtained from the TDMG database. The 80th percentile annual average PECgw concentrations for ipconazole and 1,2,4-triazole at 1 m soil depth were $\leq$ 0.001 µg/L for all the scenarios simulated using FOCUS PEARL v.4.4.4. As a result, a high risk was only identified for small granivorous birds at long-term scale and a data gap was concluded for all of the representative uses for this scenario. For the relevant plant metabolite, a low risk to birds and mammals was concluded.

It is noted that although there was no evidence of significant change in the cis/trans isomeric ratio of ipconazole in the environment, the possible impact of each individual enantiomer on the environment was not evaluated. The toxicity endpoints were determined but also the necessary surface water and sediment exposure assessments (PEC calculations) were carried out for parent ipconazole and the metabolite 1,2,4-triazole using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 1.1 of the Steps 1-2 in FOCUS calculator). The Toxicity/exposure ratios for terrestrial vertebrates are presented in **Table 7**.

Table 7: Toxicity/exposure ratios for terrestrial vertebrates

Tier 1 (Birds)

Time scale	Toxicity endpoint (mg a.s./kg bw/day)	DDD Daily dietary dose (mg a.s./kg bw/day)	TER[1] Toxicity exposure ratio	Annex VI Trigger
Granivorous bird				
Acute	LD_{50} 962	6	160	10

Herbivorous bird				
Acute	LD_{50} 962	2	481	10
Granivorous bird				
Long-term	NOEL: 4.3	6	**0.717**	5
Herbivorous bird[2]				
Long-term	NOEL: 4.3	2	**2.15**	5
Earthworm-eating bird[2]				
Long-term	NOEL: 4.3	0.232	18.5	5
Fish-eating bird[2]				
Long-term	NOEL: 4.3	0.0248	174	5
Higher tier refinement: risk to granivorous and herbivorous birds				
Granivorous bird (refined TWA and geometric mean endpoint)				
Long-term	NOEL: 10.8	1.30	8.29	5
Granivorous bird (refined TWA and lowest endpoint)				
Long-term	NOEL: 4.3	1.30	**3.30**	5
Skylark (refined TWA, FIR/bw and PD) [3]				
Long-term	NOEL: 4.3	0.358	12.0	5
Woodpigeon (refined TWA, FIR/bw)				
Long-term	NOEL: 4.3	0.577	7.45	5
Yellowhammer (refined TWA, FIR/bw and PD) [3]				
Long-term	NOEL: 4.3	1.25	**3.44**	5
Herbivorous bird (refined residue value) [2]				
Long-term	NOEL: 4.3	0.01	430	5
Tier 1 (Mammals)				
Granivorous mammal				
Acute	468	4.8	97.5	10
Granivorous mammal				
Long-term	8	4.8	**1.67**	5
Herbivorous mammal				
Acute	468	0.96	488	10
Herbivorous mammal [2]				
Long-term	8	0.96	8.33	5
Earthworm-eating mammal [2]				
Long-term	8	0.283	28.3	5
Fish-eating mammal [2]				
Long-term	8	0.0221	362	5

Higher tier refinement (Mammals)				
Granivorous mammal (refined TWA)				
Long-term	8	1.04	7.68	5

[1] TERs highlighted in **bold** are less than the respective Annex VI trigger value
[2] No TWA was considered in the risk assessment for earthworm-eating, fish-eating and herbivorous birds and mammals.
[3] Residues in other feed items such as seedlings were not considered.
TWA = time weighted average
FIR = Food intake rate
PD = proportion of different food types

The **Tier 1** risk assessment for ipconazole assumed that granivorous birds feed exclusively on treated wheat or barley grains (may also apply to mammals). Toxicity:exposure ratio (TER) values for both crops were below the trigger value of 5, resulting in a high risk via long-term dietary exposure for the representative uses of ipconazole in barley and wheat (EFSA, 2013a). The conducted risk assessment is specific for the intended use in cereals as specified in the use pattern in EFSA (2013).

Results of Toxicity exposure ratios (TERs) for the most sensitive aquatic organisms FOCUS Step1are presented in **Table 8**, and hazard quotients for honeybees are presented in **Table 9**.

Table 8: TER of 7 g a.s./ha application rate as a seed treatment to winter and spring sown cereals

Time scale	Toxicity endpoint µg a.s./L (mg/L 1,24- triazole)	FOCUS Step 1 initial PEC µg a.s./L	TER	Annex VI trigger value
Test substance: ipconazole				
Fish				
Acute	LC_{50}: 1300	0.5501	2363.2	100
Chronic	NOEC: 0.44	0.5501	**0.8**	10
Aquatic invertebrate				
Acute	EC_{50}: 1700	0.5501	3090.3	100
Chronic	NOEC: 10.9	0.5501	19.8	10
Algae				
	EbC_{50}: 620	0.5501	1127.1	10
	ErC_{50}: >2200	0.5501	3999.3	10
Test substance: 1,2,4-triazole				
Fish				
Acute	LC_{50}: 498[1]	0.1023	4868035	100
Chronic	NOEC: 3.2[1]	0.1023	31281	10
Aquatic invertebrates				
Acute	EC_{50} > 100[1]	0.1023	977517	100
Algae				
	EbC_{50}: 8.2[1]	0.1023	80156	10
	ErC_{50}: 22.5[1]	0.1023	219941	10

TERs highlighted in **bold** are less than the respective Annex VI trigger value
[1]: endpoints derived from **Pesticides peer-review experts meetings** (PRAPeR) expert meeting 13 (2007)
EC_{50} = Effective concentration
EbC_{50} = Effective concentration (biomass)
ErC_{50} = Effective concentration (growth rate)
LC_{50} = Lethal concentration, median

Table 9: Hazard quotients for honeybees

Test substance ipconazole			
	Route	Hazard quotient	Annex VI Trigger
Honeybees			
	Contact	n/a[1]	50
	oral	n/a[1]	50

[1] Calculation of hazard quotients not suitable for a.s. which are proposed only for seed treatment use

Toxicity/exposure ratios for soil organisms are presented in **Table 10**.

Table 10: TER after seed treatment to spring and winter sown cereals at equivalent to 7 g a.s./ha

Time scale	**Initial soil PEC mg a.s./kg dw soil**	**TER**	**Trigger**
Earthworms			
Test substance: ipconazole			
Acute	0.02	14925	10
Chronic	0.02	19.5	5
Test substance: 1,2,4-triazole[1]			
Acute	0.00001	1000000000	10
Chronic	0.00001	100000	5
Collembola			
Chronic	0.00001	180000	5

[1]:toxicological endpoints derived from **Pesticides peer-review experts meetings** (PRAPeR) expert meeting 13 (2007)

Ecotoxicologically relevant compounds

Soil:	ipconazole
Water:	ipconazole
Sediment:	ipconazole

Classification and proposed labelling with regard to ecotoxicological data

Active substance:	N R50 R53, H410

From tables above, the first-tier risk assessments for granivorous and herbivorous birds and for granivorous mammals, soil organisms, honeybees, and aquatic organisms resulted in:

- A high risk via long-term dietary exposure. Therefore, higher tier risk assessments were performed for these scenarios. As a result, a high risk was only identified for small granivorous birds at long-term scale. For the relevant plant metabolite, a low risk to birds and mammals was concluded.
- The risk assessment using the available data resulted in a low risk for aquatic organisms. The only exception was the chronic risk to fish in the case of one of the surface water scenarios (R4) for the winter cereal uses. A low risk to aquatic organisms was concluded for the metabolite 1,2,4-triazole.
- A low risk to bees was concluded on the basis of the available data on foliar residues and degradation, the representative uses and the low toxicity of ipconazole to bees. The available assessments using the standard tier 1 test species as well as additional species, indicated a low risk to non-target arthropods for the representative uses of ipconazole.
- A low risk to earthworms and soil micro organisms was concluded for ipconazole. However, considering the persistence of ipconazole, further consideration for soil organisms was triggered. On the basis of the available information, a low risk for soil organisms was concluded for the metabolite 1,2,4-triazole.
- A low risk was concluded for non-target plants and organisms involved in biological methods for sewage treatment on the bases of the available data and the low exposure

The refined risk assessment for granivorous birds by EFSA (2022a) considering a TWA factor of 0.46 or 0.36 based on a DT_{50} of 2.67 from residue decline trials on treated grains and averaging times of 7 or 10 days, respectively, resulted in a high risk via long-term dietary exposure for the representative uses of ipconazole in barley and wheat (**Table 11**).

Table 11: Refined long-term risk assessment for granivorous birds for the representative uses of ipconazole on barley and wheat using a time-weighted average factor of 0.46 and 0.36.

Crop	NAR (mg/kg seed)	FIR/bw	TWA	DDD (mg/kg bw/day)	NOEL (mg/kg bw/day)	TER_{lt}	Trigger value
Barley	20	0.3	0.46	2.77	4.3	**1.6**	5
Wheat	20			2.07		**2.1**	
Barley	15		0.36	2.14		**2.0**	
Wheat	15			1.60		**2.7**	

DDD: daily dietary dose.
FIR: food intake rate.
NAR: nominal application rate.
NOEL: no observed effect level.
TER_{lt}: long-term toxicity:exposure ratio.
Values in **bold** indicate a high risk.

The conclusion of non-acceptable risk to birds however remained even with additional data to conduct refined long-term risk assessment for granivorous birds.

The risk assessment using the available data resulted in a low risk for aquatic organisms. The only exception was the chronic risk to fish in the case of one of the surface water scenarios (R4) for the winter cereal uses (at FOCUS step 3). Therefore, a data gap was concluded to further address the risk for the

European situations represented by the R4 FOCUS surface water scenario for the winter cereal uses. A low risk to aquatic organisms was concluded for the metabolite 1,2,4-triazole.

Ecological risk assessment by EPA

Studies and risk assessment conducted by EPA were summarised as reported in EPA (2004) and (EPA 2015a), (EPA 2020), and (EPA 2021).

- ## Effects to Aquatic Organisms

EPA assessed the effect of ipconazole on aquatic and terrestrial organisms from the determined toxicity endpoints on aquatic and terrestrial organisms.

A summary of the aquatic toxicity data has been provided in **Table 12.** Ipconazole ranges from moderately toxic to highly toxic for freshwater fish and is moderately toxic on an acute basis to freshwater invertebrates.

Table 12: Toxicity data for Ipconazole (ppm ai)

Acute Freshwater Fish (flow-through)

Rainbow Trout (*Oncorhynchus mykiss)*

96-h LC_{50} = 1,530 µg a.i./L

Moderately Toxic

NOAEC for mortality/immobilization was 0.76 ppm ai
NOAEC for sublethal effects was 0.34 ppm ai

Bluegill Sunfish (*Lepomis macrochirus)*

96-h LC_{50} > 730 µg a.i./L

NA

NOAEC 0.73 ppm a.i.and LOAEC 1.8 ppm a.i.
observed for mortality and sublethal effects, respectively

Chronic Freshwater Fish

Fathead Minnow (*Pimephales promelas*)

22-weeks NOAEC = 0.18 µg a.i./L
LOAEC = 0.44 µg a.i./L

Acute Estuarine/Marine Fish (Surrogates for Vertebrates)

Sheepshead Minnow (*Cyprinodon variegatus*)

96-h LC_{50} = 2,000 µg a.i./L

Moderately Toxic

Chronic Estuarine/Marine Fish (Surrogates for Vertebrates)

Sheepshead Minnow (Cyprinodon variegatus)

5-weeks NOAEC = 1.03 µg a.i./L
LOAEC > 1.03 µg a.i./L
No treatment related effects

Acute Estuarine/Marine Invertebrates (Water-Column Exposure)

Mysid (*Americamysis bahia*)
96-h LC_{50} = 220 µg a.i./L
Slightly toxic

Chronic Estuarine/Marine Invertebrates (Water-Column Exposure)
Mysid (*Americamysis bahia*)
4-week NOAEC = 3.93 µg a.i./L
LOAEC = 7.45 µg a.i./L
Most sensitive endpoint based on male/female length and mortality

Chronic Freshwater Invertebrate (Spiked Water Exposure)
Midge (*Chironomus riparius*)
28-day NOAEC = 77 µg a.i./L
LOAEC = 17 µg a.i./L
No mortality was observed

Acute Freshwater Invertebrates (Water-Column Exposure)
Daphnid (*Daphnia magna*)
48-h LC_{50} = 1,700 µg a.i./L
Moderately toxic
Chronic Freshwater Invertebrates (Water-Column Exposure)
Daphnid (*Daphnia magna*)
NOAEC = 30.4 µg a.i./L

Aquatic Plants and Algae
Non-vascular Green Algae (*Pseudokirchneriella subcapitata*)
EC_{50} = 650 µg a.i./L
NOAEC = 210 µg a.i./L
Vascular Duckweed (*Lemna gibba*)
EC_{50} = 350 µg a.i./L
NOAEC = 5.8 µg a.i./L

- **Effects to Terrestrial Organisms**

A summary of the terrestrial toxicity data has been provided in **Table 13.** On a dietary basis, ipconazole is practically nontoxic to birds. For mammals on an acute basis, ipconazole is moderately toxic.

Table 13: Summary of Most Sensitive Endpoints for Terrestrial Organisms to Ipconazole

---
Birds (Surrogates for Terrestrial Amphibians and Reptiles)
Acute Oral
Bobwhite Quail (*Colinus virginianus*)
14-day LD_{50} = 962 mg a.i./kg-bw
Slightly toxic
Zebra Finch (*Taeniopygia guttata*)
14-day LD_{50} = 28 mg a.i./kg-bw
Highly toxic
Sub-acute dietary

Bobwhite Quail (*Colinus virginianus*)
8-days LC_{50} > 5,710 mg a.i./kg-diet
Up the 33% mortality was seen in 587, 1,760, and 2,990 ppm treatment groups.

Chronic
Mallard (*Anas platyrhynchus*)
21-weeks NOAEC = 197 mg a.i./kg-diet
LOAEC > 197 mg a.i./kg-diet
No clinical signs of toxicity or treatment related effects observed in study
Bobwhite Quail (*Colinus virginianus*)
21-weeks NOAEC = 48.5 mg a.i./kg-diet
LOAEC = 97.6 mg a.i./kg-diet
45% reduction in hatchling survival at 97.6 mg a.i./kg-diet

Mammals
Acute Oral
Rat (*Rattus norvegicus*)
LD_{50} = 1,338 mg a.i./kg-bw/day
Moderately toxic

Chronic (2-generation reproduction)
Rat (*Rattus norvegicus*)
2-gen NOAEL = 8.2 mg/kg-be/day
LOAEL = 25.6 mg a.i./kg-bw/day
Based on 12% reduction in food consumption.
8% reduction gestational body weight gains.
15% reduction pup body weight.

Terrestrial Invertebrates
Acute contact (adult)
Honey bee (*Apis mellifera* L.)
LD_{50} > 10 µg a.i./bee
Practically non-toxic

Acute oral (adult)
Honey bee (*Apis mellifera* L.)
LD_{50} > 10 µg a.i./bee
Practically non-toxic

Chronic oral (adult)
Honey bee (*Apis mellifera* L.)
NOAEC = 62 µg a.i/bee/day
LOAEC > 62 µg a.i./bee/day
Mortality ranged from 0 to 17%

Acute oral (larval)
Honey bee (*Apis mellifera* L.)
LD_{50} = 22 µg a.i./larvae
Practically non-toxic
Chronic oral (larval)
Honey bee (*Apis mellifera* L.)

NOAEC = 8.5 µg a.i./larvae
LOAEC = 25.0 µg a.i./larvae
Percent emergence is most sensitive endpoint

Terrestrial and Wetland Plants
Seedling Emergence
Data waived in response to waiver requests

Vegetative Vigor
Data waived in response to waiver requests

Exposure Pathways of Concern

As a seed-treatment fungicide, ingestion of treated seed placed in soil and seed dropped on soil surface at the time of planting is the primary pathway through which exposure may occur for terrestrial wildlife. The environmental fate and transport properties and use patterns of ipconazole indicate that runoff with eroded soil and water represent the important transport mechanisms of the chemical to aquatic and terrestrial organisms. Routes of exposure such as dermal contact with treated seed and soil will not be taken into account based on currently available models.

Inhalation of pesticide vapours is estimated using the Screening Tool of Inhalation Risk (STIR). STIR estimates inhalation-type exposure based on pesticide specific information. Physical properties of each chemical, such as molecular weight and vapor pressure, are used to estimate vapor phase exposure. STIR also estimate spray droplet exposure using the application method (e.g. ground versus aerial spray) and rate and then compares these exposure estimates to avian and mammalian toxicity data. Based on the molecular weight, vapor pressure and application rate, inhalation exposure is not likely to be significant for ipconazole.

Screening Imbibition Program (SIP) is used to provide an upper bound estimate of exposure of birds and mammals to pesticides through drinking water alone. It is used to determine whether or not drinking water exposure alone is a potential pathway of concern; it does not aggregate drinking water exposure with other exposure routes. The results of SIP conclude that drinking water exposure alone is not a potential concern for mammals on an acute basis or chronic basis. For avian species, it concludes that exposure through drinking water alone is not a potential concern on an acute or chronic basis.

Measures of Exposure

EFED will use the latest standard available models to evaluate potential exposures to aquatic and terrestrial organisms as described at http://www.epa.gov/pesticides/science/models_db.htm. The parent ipconazole will be assessed for terrestrial and aquatic exposures.

Aquatic exposure estimates will be based on estimated environmental concentrations (EECs) generated using the Surface Water Concentration Calculator (SWCC) model to simulate a waterbody that is considered representative of vulnerable aquatic environment (*e.g.*, ponds and streams in headwater watersheds). Currently, terrestrial exposure will be estimated using a model (T-REX version 1.5.2; March 22, 2012, for Calculating Pesticide Residues on Avian and Mammalian Food Items) and the seed treatment functions available within the model. Exposure to terrestrial plants will be estimated using a model (TerrPlant; version 1.2.2; December 26, 2006, for Pesticide Exposure to Terrestrial Plants) that assumes ipconazole drifts or moves with runoff to adjacent habitats. At the time of risk assessment, seed treatments will be assessed based on the models available at that time. Please note that spray drift's

contribution of exposure with ipconazole seed treatment uses is expected to be negligible and therefore, no spray drift will be assumed for all aquatic and terrestrial exposure assessments.

Environmental Risk Summary

Mammals and Birds: The estimated risk quotients (RQs) for **mammals and birds do not exceed the LOCs**, therefore, **there are no anticipated risks of concern.**

Terrestrial Invertebrates (honeybees): **Based on the highest labelled application rates for ipconazole, there were no acute or chronic risk quotients that exceed their LOC.** Given the lack of acute or chronic risk concerns to individual bees based on Tier I data and current registered uses, **additional higher-tier toxicity and/or exposure data are not needed at this time.** Contact exposure is not considered for seed treatment applications. However, exposure may occur via dust-off during seed planting.

Terrestrial Plants: Ipconazole **exposure to terrestrial plants is expected to be low based on the registered use pattern.** The EPA does not currently have a standard method for quantifying and assessing risk to terrestrial plants based on exposure from dust-off due to seed treatment applications, therefore, **terrestrial plant data for ipconazole was waived.**

Aquatic Risks: **No acute or chronic risks were identified** for freshwater fish. **No acute or chronic risk concerns for sediment dwelling invertebrates.** Therefore, risk to benthic organisms via exposure to ipconazole **in pore water is considered to be low.**

EPA analysis have therefore indicated that because only low levels of ipconazole will be found in the environment following its use as a seed treatment, there is no direct acute or chronic risk to endangered or non-endangered terrestrial vertebrate species of any phyla.

- ## Dietary risk assessment by EFSA

The following documents were consulted for the dietary risk assessment by EFSA (EFSA 2013, EFSA (2022b) and (Rapporteur Report (2018)).

For the active substance ipconazole, the assessment of negligible exposure has been triggered by its harmonised classification as Reproductive toxicant **category 1B** (May damage the unborn child).

For the representative uses of ipconazole, residue concentrations of the active substance ipconazole in grain and straw of wheat and barley, in potential succeeding crops and in food items of animal origin were determined by data or can be reasonably expected to be less than 0.01 mg/kg. The consumer risk assessment performed with the EFSA PRIMo indicated that the TMDI for wheat and barley is less than 1 % of the ADI of 0.015 mg/kg bw per day for ipconazole. In an acute consumer risk assessment, the calculated maximum exposure was less than 1 % of the ARfD of 0.015 mg/kg bw for all cereal commodities for ipconazole. Therefore, an exceedence of the current MRL of 0.01* mg/kg for ipconazole is not expected. The chronic and short-term intakes of ipconazole residues subsequently are unlikely to present a public health concern.

Consumer exposure to ipconazole via drinking water is also unlikely for the representative uses, based on the peer-reviewed groundwater exposure assessments (EFSA, 2013; EFSA 2022).

Based on the qualitative and quantitative information on primary and rotational crops to support the representative uses, significant livestock exposure to ipconazole and carry over of ipconazole-derived residues in animal matrices is not expected.

• Dietary risk assessment by EPA

Dietary exposure from food and drinking water was assessed by EPA (2008) and (2012).

Chronic dietary exposures were estimated utilizing the Dietary Exposure Evaluation Model software with DEEM-FCID version 3.15. The cPAD of 0.015 mg/kg bw/day was based on the NOAEL of 1.5 mg/kg/day from the 1-year dog study and a 100x uncertainty factor and a 1x FQPA safety factor. The chronic dietary exposure to the U.S. population (total) was 0.000043 mg/kg/day or 0.3% of the cPAD.

The chronic dietary exposure to infants was 0.000068 mg/kg bw/day, or 0.5% of the cPAD. The chronic dietary exposure to children 1 - 2 years old, the most sensitive group, was 0.000108 mg/kg bw/day, or 0.7% of the cPAD. Therefore, chronic aggregate exposure from ipconazole is not expected to exceed the cPAD.

Exposure to ipconazole and potential residues in drinking water is expected to be negligible.

Aggregate cancer risk for U.S. population. Ipconazole has been classified as not likely to be carcinogenic and is not expected to pose a cancer risk to humans. Ipconazole is not registered for any use patterns that would result in short-term and intermediate-term residential exposure. Therefore, the short-term and intermediate-term aggregate risk, individually is the sum of the risk from exposure to ipconazole through food and water, which has already been addressed, and will not be greater than the chronic aggregate risk.

Based on these risk assessments, EPA concludes that there is a reasonable certainty that no harm will result to the general population or to infants and children from aggregate exposure from dietary, drinking water, and non-occupational exposure assessments to ipconazole residues.

The currently proposed uses for ipconazole encompass only non-food uses. Therefore, no aggregate dietary exposure analysis was performed. Since the triazole contribution to groundwater from ipconazole will be insignificant due to the very low use rate for a seed treatment, the EPA concludes that no surface water or groundwater risk assessment is required for ipconazole.

• Risk assessment from Occupational exposure by EPA

Risk assessment from occupational exposure conducted by EPA is summarised below EPA (2021).

EPA has registered products containing ipconazole for agricultural use as a seed treatment on barley, beans, buckwheat, wheat, canola, cole crops, conifers, corn, cotton, cucurbits, leafy vegetables, legume vegetables, millet, mustard, oats, peanuts, peas, root and tuber vegetables, rye, sorghum, sunflower and triticale, and as a nonagricultural seed treatment for turf grass and ornamental flowers. Therefore, only occupational exposure is anticipated, and no residential exposure is expected.

Occupational Handler and Post-Application Risks

In an occupational setting, exposure to ipconazole may occur during the seed treatment process as well as during activities associated with planting treated seed. The occupational exposures may occur via

dermal and/or inhalation routes. Occupational exposure and risk estimates were based on a PPE level of baseline clothing (long sleeve shirt, pants, socks and shoes) plus chemical resistant gloves.

All MOEs for seed handlers and seed planters are greater than the LOC of 100 for dermal exposure and 300 for inhalation exposure and are not of concern to EPA. The LOC for all inhalation occupational scenarios is equal to an MOE of 300, based on the combined uncertainty factors: 10X for lack of a no NOAEL in the inhalation study, 10X for intraspecies variability, and a 3X uncertainty factor for interspecies variability. MOEs range from 41,000 to 140,000 for dermal exposure and from 2,000 to 20,000 for inhalation exposure.

Dermal Post-Application Risk

Occupational post-application dermal exposures from seed treatment uses are not anticipated. The potential for post-application exposures following the planting of treated seeds is unlikely because sustained levels of contact with treated seed after it has been placed in the soil or other planting media would not be expected because no routine cultural practice required for the production of agricultural commodities involves such an activity, as defined in the no/low contact criteria in the Worker Protection Standard (WPS).

Human Health Risks: Risk Summary and Characterization

- *Dietary (Food + Water) Risks, Residential **Handler** Risks, Residential Post-Application Risks, Bystander Risks, Aggregate Risks and Cumulative Risks*

EPA concluded that there are no risks of concern related to dietary, residential, aggregate, or cumulative exposures (EPA 2021). Dietary risk estimates for ipconazole are well below the EPA's LOC of 100% of the population adjusted dose (PAD) at less than 1% of the PAD for both acute and chronic exposures for all population subgroups.

Ipconazole is registered as a non-agricultural seed treatment for turf grass and ornamental flowers and is not expected to result in residential exposures. Therefore, the EPA did not assess residential exposure or risk for ipconazole. Since there are no residential exposures for ipconazole, all aggregate exposures are equivalent to dietary exposure estimates, which **are not of concern to the EPA**.

- *Occupational **Handler** and Post-Application Risks*

In an occupational setting (EPA 2021), exposure to ipconazole may occur during the seed treatment process as well as during activities associated with planting treated seed. The occupational exposures may occur via dermal and/or inhalation routes. Occupational exposure and risk estimates were based on a personal protective equipment (PPE) level of baseline clothing (long sleeve shirt, pants, socks and shoes) plus chemical resistant gloves.

A low MOE represents a greater risk than a higher MOE. The LOC for all inhalation occupational scenarios is equal to a MOE of 300, based on the combined uncertainty factors: 10X for lack of a NOAEL in the inhalation study, 10X for intraspecies variability, and a 3X uncertainty factor for interspecies variability. MOEs range from 41,000 to 140,000 for dermal exposure and from 2,000 to 20,000 for inhalation exposure. All MOEs for seed handlers and seed planters are therefore greater than the LOC of 100 for dermal exposure and 300 for inhalation exposure and therefore **are not of concern to the EPA**. EPA has conducted assessments of risk to farmworkers who handle ipconazole or may be exposed to ipconazole when working in treated seeds and have found no risks of concern.

The current restricted entry interval (REI) of 12 hours is supported by the acute toxicity categories. However, due to ipconazole use being for seed treatment only, exposure during post-application

activities, such as scouting, irrigating, and harvesting, is not expected, therefore EPA did not assess this route of exposure.

Human Incidents and Epidemiology
Based on the low frequency and severity of incident cases reported for there does not appear to be a concern at this time that would warrant further investigation (EPA 2021).

- **Risk assessment from Occupational exposure by EFSA**

Worker Exposure/Risk

EFSA (2013) with both French SeedTropex model and UK SeedTropex has reported the following exposure levels for the following scenarios:

For Operators:	French SeedTropex model (70th percentile values) of exposure for operators treating seeds with Crusoe (micro-emulsion seed treatment containing 15 g ipconazole/L) are within acceptable levels for operators wearing gloves for all tasks except bagging: 90% of AOEL, Scenario 2 UK SeedTropex: gloves worn during the calibration, mixing/loading and cleaning tasks and coveralls are worn during bagging: 18% and 27% of the AOEL. Sowing treated seed worker wearing coverall: 23% of the AOEL.
For Bystanders:	During Seed Treatment <1% to <4% of the AOEL During seed sowing 39% of systemic AOEL
Bystander and resident Exposure	Four pathways of bystander and resident exposure are considered: exposure to dust drift, vapour exposure, exposure to surface deposits and entry into treated crops. The following can be considered for the overall exposure assessment: **1.** Exposure to dust drift during seed sowing can be estimated based on the submitted study. **2.** Due to the low vapour pressure of ipconazole (3 x 10^{-6} Pa, EFSA, 2013a), it can be considered as a low volatile compound, and it can be assumed that vapour exposure is also included in the inhalation exposure data from the study. **3.** Exposure to surface deposits can be calculated using the measured residues deposited in the Petri dishes at the feet of the adult mannequins during the study. In total, three Petri dishes were used, and residues were below the limit of detection for two of them and at 0.01 µg/100 cm² in the other one. This corresponds to surface deposits of 10^{-7} mg/cm^2, which leads to very low predicted exposure estimates.

4. Entry into treated crops: In the absence of crop foliage, no dermal exposure is foreseen. There might be the case of a child picking up and ingesting treated seeds; however, children are expected to be under the supervision of adults and not left unattended; thus, such a scenario is considered quite unlikely.
5. **Based on the above, exposure to the sum of all pathways is practically exposure to the dust drift as calculated using the study data.**

The overall results of negligible exposure assessment for the residents and **bystanders**, **the predicted exposure levels were below 1% of the (A)AOEL with a margin of exposure higher than 100,000**. It should also be taken into account that some uncertainties (e.g. limited number of mannequins, lack of data for the dosimeters (see details in Annex), different formulation type and seed type compared to representative use) could not be fully addressed by the current assessment **but are not likely to impact significantly on the negligible exposure assessment**

Workers For the concerned scenario, no re-entry exposure is anticipated (based on this also the potential exposure to isomers formed in the environment after application has no relevance).

Substance classified: (ipconazole) R22, R48/22, Toxic to reproduction Category 3 R63
Acute tox 4 H302, STOT-RE 2, H373, Repro cat 2 H361d

With regard to the dermal absorption, a value of **5%** was agreed for both the concentrate and the dilution of the representative formulation Rancona 15ME. However, EFSA in a more recent review of approval of the active substance ipconazole (EFSA, 2022) for the non-dietary exposure of operators, workers, residents and bystanders, the assessment has included the newly available field studies performed with the formulation Rancona 450 FS but stressing the point that the results of the newly submitted study are not with the representative formulation Rancona 15ME**.** EFSA has therefore provided additional considerations/calculations to align the assessment of these field studies with the critical representative use of 'Rancona 15ME'.

Operators: For operators, based on the submitted data, the total systemic exposure is predicted to be **less than 1% of the (A)AOEL** for an operator wearing normal workwear, gloves and FFP2 mask (with a margin of exposure higher than 1,000) EFSA (2022).

No adverse reactions in any operator handling either ipconazole technical or the formulated product have been recorded to date (agricultural and industry workers)**.** The estimated exposure for the operator and for the bystander during seed treatment and seed sowing is below the AOEL.

- **Risk assessment from Occupational exposure: South Africa**

Most recently, operator and worker risk assessments in South Africa was also conducted for Rancona 450 FS containing ipconazole 452 g/ℓ, which is the formulation of the present derogation application to DALRRD (Russell (2024)). Rancona 450 FS, containing the active ingredient ipconazole, is currently registered in South Africa for use as a seed treatment on corn seed at an application rate up to 18 ml / 100 kg seed (delivering **8.14 grams ipconazole per 100 kg seed**). It is intended ONLY for use by commercial seed treatment applicators. Applicators may employ transfer/pumping from containers (such as drums, totes, kegs), or employ closed mixing/loading equipment. Open pouring (such as pouring from a jug into a tank) is not permitted in commercial settings. In general, work shifts are 8 hours but may increase to 12 hours during the height of the season.

Occupational exposure in South Africa

In South Africa, occupational exposure to ipconazole can occur to workers treating maize seed and planting treated maize seeds. Commercial treatment equipment may vary in engineering, but it is becoming increasingly automated and enclosed as treatment facilities grow in scale, both to increase uniformity and efficiency of treatment and to decrease exposure potential and losses of product. These facilities typically treat a specific crop variety with a specific product through durations of a few hours to a week or more, after which the equipment is thoroughly cleaned before treatment of a different variety with a different product. Thus, the proportion of the treatment season during which workers are exposed to a specific active ingredient should approximate its market share, while the absolute duration of that exposure may vary. In general, work shifts are 8 hours but may increase to 12 hours during the height of the season.

Handler exposure

The term handlers are to describe those individuals who are involved in the pesticide application process. There are distinct job functions or tasks related to applications, and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses. Typically, for large-scale commercial seed treatments, workers perform only specific individual tasks; however, it is assumed that workers also may perform multiple activities throughout the day. As a result, a “multiple activities” scenario (i.e., where one worker performs all seed treatment tasks such as loading/applying, bagging, cleaning, calibration, repair, forklift driver, etc.) was addressed.

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Mixing, loading, applying liquid formulations for commercially treated seeds.
- Multiple activities.
- Planting treated seed.

Exposure Data, and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler (seed treatment and planting) risk assessments. Each assumption and factor are detailed below on an individual basis.

- **Application Rate**

The maximum application rate listed on the proposed label was used for all exposure assessments. The maximum rate is 18 mℓ / 100 kg seed (delivering 8.14 grams ipconazole per 100 kg seed).

- **Unit Exposures**

The best available data is used to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include US-EPA Exposure SAC Policy 14: SOPs for Seed Treatment. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the SOP 14. In summary, treated seed is defined as seed that is given an application of pesticide to reduce, control or repel disease organisms, insects, or other pests that attack seed or seedlings. This definition includes control of pests while the seed is in storage and after planting. Seeds commonly treated are corn, small grains, or cereals (barley, oats, rye, wheat, and rice), sorghum, millets, soybeans, sugar beets, sunflowers, cotton, and flax. Seed treatment pesticides are applied as either dusts, slurries, or liquids. This seed treatment standard operation procedure (SOP) contains all known scenarios associated with seed treatment facilities and planting treated seed. The data contained in this document are for worker exposure estimation and are mostly generated by the industry. Exposure estimates are from actual seed treatment studies and are based on physical factors of a handler scenario (e.g., commercial seed treatment, on-farm seed treatment, planters, etc.).

Fourteen studies were initially considered for use in this document. For all selected seed treatment studies, replicates were combined into sets of equivalent job functions. This process resulted in 4 categories of commercial seed treatment activities, plus the planter and on farm seed treater categories.

Commercial Seed Treatment - This section describes how this guide could be used to assess exposure related to various activities in a commercial seed treatment facility. This section is divided in to four parts, based on a specific activity. These activities are:
1) loader/applicator
2) bagger
3) sewer stitching bags of seed
4) multiple activities

Exposure for these activities were measured using liquid formulations and wettable powders packed in water soluble bags.

Planting Treated Seed - This section describes the procedure to measure the exposure of the workers to treated seed as it is being planted. It provides exposure measurements for workers loading treated seed into plant hoppers and driving a tractor to pull the planter around the field.

Table 14 summarises the dermal and inhalation exposure values with different types of PPE for activities related to seed treatment and planting treated seed.

Table 14: Summary of exposure values for seed treatment and seed planters

Type	Exposure Scenario	Dermal Unit Exposure (mg / kg a.i.)	Inhalation Unit Exposure* (ug / kg a.i.)	PPE
Commercial	Loader / Applicator	0.051	0.75	single layer, glove
	Loader / Applicator	0.040	0.75	single layer, glove, coverall
	Sewer	0.014	0.51	single layer, no glove

	Bagger	0.020	0.35	single layer, no glove
	Multiple Activities	0.093	3.5	single layer, glove
Planters	Seed Planters	0.55	7.5	single layer, glove**
* Inhalation unit exposure represents no respirator ** glove used for loading only				

- **Amount of Treated Seed Handled**

The US-EPA Guidance (SOP 15.1) "Amount of Commercial Seed Treated Per Day" provides updated additional information regarding these throughput data. Since the AHETF surveys only include information for the five major field crops (canola, corn, rice, soybean, and wheat), throughput values for non-surveyed crops are assigned based on a combination of "best professional judgement;" similarity of seed size to that of the surveyed crops; and general knowledge of each crop and its production. In summary, SOP 15.1 was created to assure consistency in the standard values used for the amount of seed treated per day in commercial seed treatment facilities, during on-farm seed treatments and when planting treated seed. This guide can be used as a reference by exposure assessors when there are no acceptable data available regarding the amount of seed treated or planted per day with a specific pesticide. It provides a broad range of standard values for seed treatment activities and planting treated seed.

This SOP was revised in 2022 and is divided into the following sections as presented in **Table 15**:
1. Amount of Seed Treated
2. Amount of Seed Planted per day

Table 15: Amount of Seed Treated per Day in Commercial Seed Treatment Facility and Amount of Seed Planted Per Day

Seed type	**Amount treated per day**				
Corn	163994 kg				
	Amount of seed planted per day				
	Number of seeds /kg	Seeds/hectare	Hectares planted per day	Amount of seed planted per day (kg)	Seeding rate (kg seed/hectare)
	617	99460	81	2681	34

Worker Exposure

Occupational exposure to ipconazole can occur to workers **treating maize seed** and **planting treated maize seeds**.

- **Commercial Seed Treatment**

Exposure of commercial seed treatment workers treating maize seed is expected to be of short- to intermediate-term duration and to occur via the dermal and inhalation routes of exposure. Based on ipconazole *in-vitro* dermal absorption studies (total amount of absorbable ipconazole on human skin to be between 0.32% and 0.99%), the EPA comparison of dermal NOAEL to oral LOAEL which indicates 3% dermal absorption, and the United Kingdom Chemicals Regulation Directorate choosing a dermal absorption value of 5%, it is conservatively proposed that a value of 5% dermal absorption be used in the occupational risk assessments for workers exposed to Ipconazole

The following assumptions were used in the risk assessment:

Application rate 18 mℓ ipconazole 450 FS/100 kg seed

8.14 g ipconazole/100 kg seed
Amount of seed treated per day`153994 kg
Average body weight = 60 kg
Dermal absorption = 5%

Since the dermal and inhalation endpoints are based on different toxicological effects (decreased foetal weights and increased malformations for dermal exposure and irritation of the respiratory tract for inhalation exposure) it is not considered appropriate to combine MOEs from the dermal and inhalation routes of exposure. Therefore, the LOC for dermal risk assessments is a MOE of 100, based on the combined interspecies (10X) and intraspecies (10X) uncertainty factors. The LOC for all inhalation occupational scenarios is equal to an MOE of 300, based on the combined uncertainty factors: 10X for lack of a NOAEL in the inhalation study, 10X for intraspecies variability, and a 3X uncertainty factor for interspecies variability. The outcome of the estimation is presented in **Table 16**. The target MOE for occupational risk is 300 for dermal and inhalation. MOEs greater than 300 do not exceed the level of concern.

Table 16: Summary of Exposure and Risk Estimates for Workers Treating Maize Seed with ipconazole at Commercial Seed Treatment Facilities

Work Function	PPE	Dermal Unit Exposure[1] (mg/kg a.i. handled)	Inhalation Unit Exposure[1] (µg/kg a.i.)	Amount a.i. handled[2] (kg)	Dermal Exposure[3] (mg/kg bw/day)	InhalationExposure[4] (mg/kg bw/day)	Dermal MOE	Inhal. MOE
Loader/Applicator	single layer, glove	0.051	0.75	15.59	0.00066	0.000195	15091	41048
Sewer	single layer, no glove	0.014	0.51	15.59	0.00018	0.000133	54975	60364
Bagger	single layer, no glove	0.02	0.35	15.59	0.00026	0.000091	38482	87959
Multiple Activities	single layer, glove	0.093	3.5	15.59	0.00121	0.000910	8276	8796

[1] US-EPA Policy 14
[2] Based on an application rate of 8.14 ipconazole/100 kg seed × 153994 kg seed treated/day.
[3] Dermal exposure (mg/kg bw/day) = kg a.i. handled/day × unit exposure (mg/kg a.i. handled) × 5% dermal penetration/60 kg bw
[4] Inhalation exposure (mg/kg bw/day) = kg a.i. handled/day × unit exposure (µg/kg a.i. handled) × 1000 µg/1 mg × 100% inhalation penetration /60.6 kg bw
[5] Based on an oral NOAEL of 10 mg/kg bw/day for dermal exposure and an inhalation LOAEL of 8 mg/kg bw/day. The UF for both dermal and inhalation exposure is 300

The Margins of Exposure for commercial seed treatment workers treating maize seed with Rancona 452 FS are well above the Level of Concern of 300 for both dermal and inhalation routes of exposure, indicating acceptable risks for commercial treatment with ipconazole. The unit exposure values are based

on a worker wearing a single layer of clothing and gloves. The Rancona 450 FS label requires PPE of long-sleeved shirt, long trousers, chemical-resistant gloves, and protective eyewear.

- **Planting Treated Seed Exposure Evaluation**

Exposure of workers planting treating maize seed is expected be of short- to intermediate-term duration and to occur via the dermal and inhalation routes of exposure (**Table 17**).

The following assumptions were used in the risk assessment:

Application rate	18 ml Ipconazole 452 FS /100 kg seed 8.14 g ipconazole/100 kg seed
Amount of seed planted per day	2681 kg
Average body weight	60 kg
Dermal absorption	5%
Clothing	Long-sleeved shirt, long trousers, chemical-resistant gloves (gloves during loading only)

Table 17: Summary of Exposure and Risk Estimates for Workers Planting Treated Maize Seed with ipconazole

Work Function	Dermal Unit Exposure[1] (mg/kg a.i. handled)	Inhalation Unit Exposure[1] (µg/kg a.i.)	Amount a.i. handled[2] (kg)	Dermal Exposure[3] (mg/kg bw/day)	Inhalation Exposure[4] (mg/kg bw/day)	Dermal MOE[5]	Inhal. MOE[5]
Planters	0.55	7.5	0.27	0.00012	0.000034	80386	64309

[1] US-EPA Policy 14
[2] Based on an application rate of 8.14 g ipconazole/100 kg seed × 2681 kg seed treated/day.
[3] Dermal exposure (mg/kg bw/day) = kg a.i. handled/day × unit exposure (mg/kg a.i. handled) × 5% dermal penetration/60 kg bw
[4] Inhalation exposure (mg/kg bw/day) = kg a.i. handled/day × unit exposure (µg/kg a.i. handled) × 1000 µg/1 mg × 100% inhalation penetration /60 kg bw
[5] Based on an oral NOAEL of 10 mg/kg bw/day for dermal exposure and an inhalation LOAEL of 8 mg/kg bw/day. The UF for both dermal and inhalation exposure is 300

The Margins of Exposure for planting maize seed treated with Ipconazole 452 FS are well above the Level of Concern of 300 for both dermal and inhalation routes of exposure, indicating acceptable risks for planting maize seed treated with ipconazole. The unit exposure values are based on a worker wearing a single layer of clothing and gloves (during loading only). The Ipconazole 452 FS label requires PPE of long-sleeved shirt, long trousers, chemical-resistant gloves for protection.

In conclusion, US-EPA seed treatment standard operation procedures Policy 14 and Policy 15 were used for surrogate unit exposure values and application/planting rate data to estimate exposure to commercial seed treatment workers treating maize seed with Rancona 450 FS, and workers planting seed treated with Rancona 450 FS.

In all cases, the calculated Margins of Exposure for ipconazole were well above the Level of Concern of 300, indicating acceptable risks for all workers. Use of ipconazole as a seed treatment is therefore expected to result in low occupational exposure and negligible risk.

Workers handling Rancona 450 FS will be required to wear chemical-resistant gloves and other PPE in common use for many seed treatment products. Within commercial treatment, exposure is minimized through the use of modern high-capacity treatment systems with bulk loading of product, dust aspiration, and PPE. Due to the nature of the use, post-application and bystander exposure are expected to be negligible. Use of ipconazole as a seed treatment is therefore expected to result in low occupational exposure and negligible risk.

Precautionary statements on product labels registered in South Africa include:

- Wear protective gloves, protective clothing, eye protection, and face protection.
- Avoid release to the environment.
- Collect spillage.
- Seek medical advice/attention if you feel unwell.

Registration of Ipconazole, in chronological order internationally and nationally

USEPA

Ipconazole fungicide was first registered in the U.S. in 2004 (USEPA, 2004) and therefore was not subject to reregistration. There are 19 registered end-use products formulated as liquid and liquid suspensions, as well as one product formulated as dust for peanut seed treatment only. EPA has registered products containing ipconazole for agricultural use as a seed treatment on barley, beans, buckwheat, wheat, canola, cole crops, conifers, corn, cotton, cucurbits, leafy vegetables, legume vegetables, millet, mustard, oats, peanuts, peas, root and tuber vegetables, rye, sorghum, sunflower and triticale, and as a non-agricultural seed treatment for turf grass and ornamental flowers. Therefore, **only occupational exposure is anticipated, and no residential exposure is expected**. The EPA has proposed tolerances for ipconazole in 2008 (EPA 2008) and the registration was reviewed in 2015 (EPA 2015a) and also in 2021 (EPA 2021). In 2024, notice of registration was issued (EPA 2022) and in 2024, EPA has accepted Label Amendment – Adding labelled pest and definitions to crop tables (EPA 2024).

With benefits assessment, it could be shown that Ipconazole protects germinating seeds and emerging seedlings from a broad spectrum of fungi during crop establishment (EPA 2021). Extension literature from Wisconsin, for example, rates ipconazole as providing good control for *Phomopsis* and *Rhizoctonia* spp. and it is rated as excellent for control of *Fusarium* spp. as a seed treatment in soybean (WSU, 2017).

- ***Interim Registration Review Decision***

The EPA has reviewed the risks, benefits, and uses of ipconazole. EPA has determined that (EPA 2021):

  - there are **no human health or ecological risks of concern from registered ipconazole uses**.
  - Given the uses of ipconazole solely as a seed treatment and its environmental fate properties, there is a **low likelihood of ipconazole exposure to non-target terrestrial and/or aquatic organisms**.
  - EPA has determined that updating glove language to promote consistency among pesticide labels is necessary.
  - Ipconazole has a **medium risk of resistance development in fungi**, and EPA has determined that **resistance management is necessary**.
  - The EPA has determined that **a seed treatment Environmental Hazards statement is necessary to be added to all labels**.

- ***Pesticide Resistance Management***

Ipconazole belongs to the triazole chemical group of DMI fungicides. It belongs to group 3 of Fungicide Resistance Action Committee (FRAC) based on mode of action of fungicides. These fungicides have **medium risk of resistance development in fungi**, and EPA has determined that resistance management is necessary. To combat pesticide resistance, resistance management experts recommend using pesticides with different chemical modes (or mechanisms) of action against the same target pest population as part of integrated pest management (IPM) programs. This approach may prevent or delay target pest populations from developing resistance to a particular mode (or mechanism) of action without resorting to increased rates and frequency of application, possibly prolonging the useful life of pesticides (EPA 2021).

Seed Treatment Environmental Hazard Statement

If a pesticide product contains directions for use in seed treatment, the EPA requires the following Environmental Hazards statements (EPA 2021):

- "*Treated seed exposed on soil surface may be hazardous to wildlife. Cover or collect seeds spilled during loading and planting*".

EPA Interim Registration Review Decision

The EPA has reviewed the risk and benefits of ipconazole in developing risk mitigation for ipconazole use (EPA 2021). EPA has determined that:

- There are no human health or ecological risks of concern from registered ipconazole uses.
- Given the uses of ipconazole solely as a seed treatment and its environmental fate properties, there is a low likelihood of ipconazole exposure to non-target terrestrial and/or aquatic organisms.
- EPA has determined that updating glove statements to promote consistency among pesticide labels is necessary.
- Ipconazole has a medium risk of resistance development in fungi, and EPA has determined that resistance is necessary.
- The EPA has determined that a seed treatment Environmental Hazards statement is necessary to be added to all labels.
- EPA has determined that there is no human dietary risk from registered uses of ipconazole.
- Taking into consideration the available information on toxicity and exposure, EPA assessed ipconazole's potential aggregate risks, including dietary (food and water) and non-occupational residential exposures, and found no risks exceeding the EPA's levels of concern.
- EPA has determined that there is a reasonable certainty that no harm will result from aggregate exposure to ipconazole, including all anticipated dietary exposures and all other exposures for which there is reliable information.
- Therefore, ipconazole's residues do not present human dietary risk and EPA intends to leave the modified tolerances in place because EPA's analysis indicates that those tolerances are safe.
- EPA is not making any human health or environmental safety findings associated with the Endocrine Disruptor Screening Program (EDSP) screening of ipconazole.

EPA also determined that continuing to register ipconazole provides the benefit of protecting germinating seeds and emerging seedlings from a broad spectrum of fungi during crop establishment.

European Commission

The registration of Ipconazole was approved much later than its approval by EPA with the following documented dates:

02 April 2013 (EFSA 2013)

- EFSA reviewed mammalian toxicology, residues, fate and behaviour and ecotoxicology of ipconazole.

1 September 2014

- Ipconazole was approved on with the provision that the applicant to submit to the European Commission confirmatory information on:
    - a) the acceptability of the long-term risk to granivorous birds.
    - b) the acceptability of the risk to soil macro-organisms.
    - c) the risk of enantioselective metabolisation or degradation.
    - d) the potential endocrine disrupting properties of ipconazole for birds and fish.
- The information under (a) and (b) was required by 31 August 2016, the information under (c) within 2 years after adoption of the pertinent guidance document on evaluation of isomer mixtures and the information under (d) within 2 years.

19 June 2017 (EFSA 2017)

- The risk to soil macroorganisms was low.
- However, the quantitative risk assessment still indicated a high long-term risk to granivorous birds

9 March 2018 (ECHA 2018)

- The Committee for Risk Assessment of the European Chemicals Agency adopted an Opinion that ipconazole meets the criteria to be classified as toxic for reproduction, **category 1B (R1B)**.

9 December 2020 (EFSA 2020)

- EFSA was required to provide a reasoned opinion on the review of the existing maximum residue levels (MRLs) for that active substance.

26 January 2022 (EFSA 2022)

- New data on residue dissipation from seeds treated with ipconazole and some ecological data were made available to refine the risk to granivorous focal species.
- Considering these data, the quantitative risk assessment still indicated a high long-term risk to granivorous birds. Nevertheless, overall, it was considered that the confirmatory data did not resolve the long-term risk to granivorous birds.
- As regards soil macro-organisms, new studies were available, and the updated risk assessment indicated a low risk

10 May 2023 (EU 2023)

- European Commission has withdrawn its approval of the active substance ipconazole due to concerns about its impact on the environment and risks to agricultural workers. EU Member States must withdraw authorisations for products containing ipconazole by 31 August 2023.
- Reasons for its withdrawal include: Ipconazole Health Hazards: Toxic to the reproductive system: clear evidence connected to malformations in offspring (Classified “R1B”). Adverse health risks were also connected to effects on the liver, and the thymus gland, impacting the immune system.

Registration in other countries

Australia

APVMA 2020:

- The Australian Pesticides and Veterinary Medicines Authority. Rancona C Seed Treatment, containing ipconazole (20 g/L) and cypermethrin (4g/L).

New Zealand

New Zealand 2015:

- Environmental Protection Authority, New Zealand. Rancona Dimension contains 25g/L ipconazole and 20g/L metalaxyl as a micro emulsion.

Japan

Ipconazole was firstly introduced in 1993 in Japan as a seed disinfectant for rice (trade name: Techlead®) and it had been globally registered and being used as a seed disinfectant for cereals, corn, cotton and other kinds of corps in more than 20 countries by 2014. (Tateishi et al., 1998). Now produced by number of Japanese companies such as Hayashi Pure Chemical Ind.,Ltd.

Canada

27 March 2018: "Under the authority of the Pest Control Products Act, Health Canada's Pest Management Regulatory Agency (PMRA) has concluded that the registration of the new end-use product Rancona V 100 Pro FS Fungicide, containing technical grade ipconazole and carboxin; and the addition of new uses on various commodities to the product labels of Rancona V RS Fungicide, containing technical grade ipconazole and carboxin, and Rancona 3.8 FS Fungicide, containing technical grade ipconazole, are acceptable. The evaluation of these ipconazole applications indicated that the end-use products have value, and the human health and environmental risks associated with the new uses are acceptable".

South Africa

Rancona 450 FS, containing the active ingredient ipconazole, is currently registered in South Africa for use as a seed treatment on corn seed at an application rate up to 18 mℓ / 100 kg seed (delivering 8.14 grams ipconazole per 100 kg seed). It is intended ONLY for use by commercial seed treatment applications.

However, as per DALRRD (2024) "Regulations relating to agricultural remedies" of 25 August 2023, ipconazole may be considered as a Substance of Concern for its classification as reproductive toxicity categories 1A or 1B of the GHS. As per DALRRD (2024), Registrar may grant or renew a registration of an implicated agricultural remedy when the following conditions are met where the risk to humans, animals or the environment from exposure to the active substance in an agricultural remedy, under realistic worst-case conditions of use, is negligible.

The present risk assessment subsequently addresses the material concerns associated with the use of ipconazole in South Africa.

Discrepancy in the registration of ipconazole in different countries

To ensure the safety of pesticides, hazard- and risk-based approaches are implemented. In hazard-based approaches, simply the presence of a potentially harmful agent is used as a basis for legislation and/or risk management action. Risk-based approaches allow consideration of exposure in assessing whether there may be unacceptable risks to health. Problems can arise when both types of approach are used in regulation by separate agencies that address different aspects of the same pesticides. This separation of decision-making can result in hazard-based restrictions on marketing and use, whereas risk-based assessments for those exposed show there is reasonable certainty no harm will result. This in turn can lead to contradictory, confusing and ultimately unnecessary actions. Use of hazard-based approaches also means that comparisons with benefits cannot be undertaken. This has the potential to lead to bias in the overall conclusions of regulators and risk managers, who may not have been presented with the benefits of pesticide. The value of risk-based approaches is therefore becoming increasingly recognised.

The European Union uses a hazard-based approach, meaning they first screen out the most hazardous chemicals based on their hazards. However, those not eliminated based on hazard will be assessed based on risk assessments. Therefore, in Europe, a classification as a 1A or 1B CMR (carcinogenic, mutagenic, or toxic for reproduction), or a classification as an endocrine disruptor, is used to automatically triggers legislative restrictions on approval, manufacture, marketing, and use, irrespective of the outcome of any risk assessment of those exposed.

EPA on the other hand, relies on a risk-based approach where they do not ban chemicals based on hazard but rather on risk assessments. A risk-based approach does not automatically ban hazardous chemicals. Instead, it places greater emphasis on assessing and managing the risks of the chemical. A substance can still be banned, but only if all measures and steps to prevent exposure have been considered and evaluated and shown to be inadequate at keeping risks below acceptable levels.

Summary and Recommendations

- The present document has reviewed the existing internationally available documents and could present evidence that the risk to humans, animals or the environment from exposure to the active substance ipconazole in an agricultural remedy, under realistic worst-case conditions of use, is negligible

- As per Criterion 3 of the Guideline (2024) with regards to the “Application for a Derogation for an Agricultural Remedy identified as a Substance of Concern” ipconazole meets the criteria of reproductive toxicity category 1B of the GHS.

- Using latest available data, a risk-based approach implemented by EPA could however confirm that “*the risk to humans, animals or the environment from exposure to the active substance ipconazole in an agricultural remedy, under realistic worst-case conditions of use, is negligible*”.

- EPA also determined that continuing to register ipconazole provides the benefit of protecting germinating seeds and emerging seedlings from a broad spectrum of fungi during crop establishment.

- Using a similar risk-based approach implemented by EPA, studies in South Africa confirm that Use of ipconazole as a seed treatment is therefore expected to result in low occupational exposure and negligible risk.

- Based on negligible risk, it could be recommended that DALRRD may grant derogations for the use of ipconazole in seed treatment as intended.

Bibliography

APVMA 2020. Public Release Summary on The Evaluation Of The New Active Ipconazole In The Product Rancona C Seed Treatment APVMA Product Number 63309. March 2010.

DALRRD (2024). Department of Agriculture, land reform and Rural Development (DALRRD). Guideline For the Application for A Derogation for An Agricultural Remedy Identified as A Substance of Concern Issued by The Registrar: Act No 36 Of 1947, Private Bag X343, Pretoria, 0001 Republic Of South Africa. April 2024.

ECHA 2018. ECHA. Committee for Risk Assessment RAC Opinion proposing harmonised classification and labelling at EU level of ipconazole. CLH-O-0000001412-86-198/F Adopted 9 March 2018.

EFSA 2013. European Food Safety Authority; Conclusion on the peer review of the pesticide risk assessment of the active substance [ipconazole]. EFSA Journal 2013;11(4):3181. [76 pp.] doi:10.2903/j.efsa.2013.3181.

EFSA 2017. EFSA (European Food Safety Authority), 2017. Technical report on the outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment for ipconazole in light of confirmatory data. EFSA supporting publication 2017:EN-1260. 24 pp.

EFSA 2020. Reasoned Opinion on the review of the existing maximum residue levels for ipconazole according to Article 12 of Regulation (EC) No 396/2005. EFSA Journal 2020;18(1):5961, 53 pp.

EFSA 2022. European Food Safety Authority (EFSA). Statement concerning the review of the approval of the active substance ipconazole. EFSA J. 2022 Aug 26;20(8):e07133.

EPA 2013. Ipconazole. Petition to Establish Permanent Tolerances for Residues of the Fungicide Resulting from Food Use on Legume Vegetables, Group 6. Summary of Analytical Chemistry and Residue Data. D406708; EPA-HQ-OPP-2012-0796-0008

EPA 2004. EPA 2004. Pesticide Fact Sheet. Name of Chemical: Ipconazole Reason for Issuance: Conditional Registration Date Issued: September, 2004 Office of Prevention, Pesticides and Toxic Substances (7505C).

EPA 2008. EPA 2008. Federal Register /Vol. 73, No. 224 /Wednesday, November 19, 2008 /Rules and Regulations 69557. 40 CFR Part 180 EPA-HQ-OPP-2007-0226; FRL-8389-1. Ipconazole; Pesticide Tolerances. Final rule. 11/19/2008.

EPA 2012. EPA Registration Division Company Notice of Filing for Pesticide Petitions Published in The Federal Register.

EPA 2015a. EFED Registration Review Problem Formulation for Ipconazole. PC Code: 125618 DP Barcode: 0428127 Date: December 9, 2015.

EPA 2015b. BEAD Chemical Profile (BCP) for Registration Review: Ipconazole (125618).

EPA 2020. Ipconazole: Draft Ecological Risk Assessment for Registration Review. June 30, 2020. PC Code: 125618. MEMORANDUM DP Barcodes: 457154.

EPA 2021. EPA-HQ-OPP-2015-0590. Ipconazole Interim Registration Review Decision Case Number 7041 September 2021.

EPA 2022. Notice Of Pesticide: Registration. 12/15/22. Ipconazole 4l Ipconazole 40.7%.

EPA 2024. Label Amendment – Adding labelled pest and definitions to crop tables Product Name: Ipconazole 4L, EPA Registration Number: 45002-40, Application Date: September 14, 2023, Case Number: 489665.

EU 2023. Commission Implementing Regulation (EU) 2023/939 of 10 May 2023 withdrawing the approval of the active substance ipconazole in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council, amending Commission Implementing Regulation (EU) No 540/2011 and repealing Commission Implementing Regulation (EU) No 571/2014.

Goring, C. A. I., Laskowski, D. A., Hamaker, J. H., & Meikle, R. W. 1975. Principles of pesticide degradation in soil. In R. Haque & V. H. Freed (Eds.), *Environmental dynamics of pesticides.* NY: Plenum Press.

Guideline 2024. Guideline for The Application for a Derogation for an Agricultural Remedy Identified as a Substance of Concern Issued by the Registrar: ACT NO 36 of 1947, Private Bag X343, Pretoria, 0001 Republic of South Africa April 2024.

NAFTA. 2012. *Guidance for Evaluating and Calculating Degradation Kinetics in Environmental Media*. December 2012. NAFTA Technical Working Group on Pesticides

New Zealand 2015. Formulated substance name: Rancona Dimension.

PVMA 2017. Australian Pesticide and Veterinary Medicines Authority. Acceptable Daily Intakes (ADI) for Agricultural and Veterinary Chemicals Used in Food Producing Crops or Animals Edition 1 / 2017 current as of 31 March 2017.

Rapporteur Report 2018. Rapporteur Report 2018: Registration Report Part A Risk Management Product code: UBI 4336.01 Product name: RANCONA 450 FS Active substance: ipconazole, 452 g/L.

Russell 2024. Russell Roy W. Ipconazole: Operator and Worker Risk Assessments in South Africa Formulation Rancona 450 FS (ipconazole 452 g/ℓ). Report Number UPL/2023/1085. February 19, 2024.

Tateishi H, Saishoji T, Suzuki T, Chida T. Antifungal Properties of the Seed Disinfectant Ipconazole and Its Protection against “Bakanae” and Other Diseases of Rice. Japanese Journal of Phytopathology. 1998 Volume 64 Issue 5 Pages 443-450.

WSU, 2017. Management of Soybean Seedling Diseases: Fungicide Efficacy for Control of Soybean Seedling Diseases. University of Wisconsin. January 2017.