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TOXICOLOGY ASSESSMENT OF PROPICONAZOLE AS AN ACTIVE SUBSTANCE IN THE PLANT PROTECTION PRODUCTS: PRINCIPLE 250 EC, Bumper 250 EC and Propin 250 EC

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Table of Contents

1. Executive Summary

Propiconazole is a systemic, broad-spectrum fungicide belonging to the class of triazoles used for the control of various plant diseases that acts as an ergosterol biosynthesis inhibitor.

In the Republic of South Africa regulatory jurisdiction, according to Regulation 8(1)(d) and 10(3)(e) respectively, the Registrar (Act 36 of 1947) may not grant or renew a registration after 1 June 2024 if a plant protection product contains substances of concern. In the European Union, propiconazole has been classified with respect to reproductive toxicity as Repr.1B H360D (May damage the unborn child) in accordance with Regulation (EC) No. 1272/2008, and as such would be considered a substance of concern. In exceptional circumstances, the Registrar may grant a registration for a product (i.e.: an agricultural remedy) containing a substance of concern, based on a risk assessment demonstrating the safe use of the product.

The Propiconazole Derogation Group is submitting a derogation for emulsifiable concentrate (EC) formulation products containing 250 g/L propiconazole that include dietary and non-dietary human health risk assessments to demonstrate safe use of these products. To support the derogation application and inform the human health risk assessment, a summary review of the toxicological profile of propiconazole has been carried out, considering recent and relevant authoritative regulatory evaluations and the derivation of health-based reference values. Toxicological information has been sourced from evaluations conducted by: the Joint Meeting on Pesticide Residues (JMPR), the expert *ad hoc* body administered jointly by the United Nations (UN) Food and Agriculture Organization (FAO) and the World Health Organization (WHO) and the European Union (EU) European Food Safety Authority (EFSA) and European Chemicals Agency (ECHA).

Propiconazole has low acute dermal and inhalation toxicity and is not a skin or an eye irritant. The substance has moderate acute oral toxicity and requires classification in GHS Cat 4. H302 (Harmful if swallowed) and is a skin sensitiser, requiring classification in GHS Cat 1. H317 (May cause an allergic skin reaction).

Propiconazole is not genotoxic based on the findings of a standard battery of *in vitro* and *in vivo* studies, is not neurotoxic and has not been considered as having endocrine disruption potential. Based on authoritative evaluations of the data, propiconazole is not considered to be carcinogenic in humans.

In studies of the repeated dose toxicity of propiconazole conducted in rodents via the oral, dermal and inhalation routes, decreased body-weight gain, frequently linked to reduced food consumption has been consistently observed in short- and long-term repeated dose toxicity studies and in studies of developmental and reproductive toxicity. The liver was the primary target organ for the toxicity attributable to propiconazole.

Propiconazole does not affect fertility, mating or gestation whereas reproductive effects (i.e.: decreased litter size and the number of viable pups) were observed at or above doses levels producing parental toxicity. Developmental effects in the available studies generally concurred with severe maternal toxicity. While a low incidence of cleft palate was observed in two rat studies only, and may be secondary to maternal toxicity, the authoritative reviews could not definitively rule out the findings as incidental or not relevant to humans, and taking into account other effects (i.e.: skeletal variations in rats study and resorptions, abortions and early deliveries in rabbits) propiconazole was classified as a reproductive toxicant Category 1B H360D (May damage the unborn child) in the EU.

Based on the review of the toxicological profile of propiconazole, the critical human health effects have been adequately identified and characterised. The following health-based

reference values are considered to be relevant to inform the dietary and non-dietary risk assessments for EC products containing 250 g/L propiconazole and are sufficiently conservatively protective in respect of human health:

Reference endpoint	**Derived value**	**Source**
ADI	**0-0.07 mg/kg bw/day**	JMPR (FAO and WHO, 2004)
Acute RfD	**0.3 mg/kg bw/day**	JMPR (FAO and WHO, 2004)
AOEL	**0.1 mg/kg bw/day**	EFSA (2017)
AAOEL	**0.1 mg/kg bw**	EFSA (2017)

2. Introduction

Propiconazole (CAS No. 60207-90-1, EC No. 262-104-4) is a systemic, broad-spectrum fungicide belonging to the class of triazoles used for the control of various plant diseases. It is a racemic mixture of 4 stereoisomers which are separated into cis- and trans-diastereomers, both exerting biological activities. The compound acts as an ergosterol biosynthesis inhibitor. The lack of normal sterol production slows or stops the growth of the fungus, preventing further infection of host tissues. The active substance is used against several fungal pathogens in several agricultural crops.

In the Republic of South Africa regulatory jurisdiction, according to Regulation 8(1)(d) and 10(3)(e) respectively, the Registrar (Act 36 of 1947) may not grant or renew a registration after 1 June 2024 if a plant protection product contains substances of concern. In the European Union, propiconazole has been classified with respect to reproductive toxicity as Repr.1B (H360D "May damage the unborn child") in accordance with Regulation (EC) No. 1272/2008, and as such would be considered a substance of concern. However, in exceptional circumstances, the Registrar may grant a registration for a product (i.e.: an agricultural remedy) containing a substance of concern and the Applicant can submit a derogation to achieve this. According to Section 2.1 of the *"Guideline for the Application for a Derogation for an Agricultural Remedy Identified as a Substance of Concern"* issued by the Registrar (DALLRD, 2024),

"Before commencing an application for derogation of an agricultural remedy, the applicant must conduct a risk assessment to evaluate the risks associated with the use of the remedy according to the proposed uses for which a derogation is sought and determine whether the associated risks can be sufficiently mitigated."

The Propiconazole Derogation Group, comprising of: ICA International Chemicals (Pty) Ltd, Sharda International Africa (Pty) Ltd. and Adama South Africa (Pty) Ltd, is submitting a derogation for the formulations: PRINCIPLE 250 EC, Bumper 250 EC and Propin 250 EC, emulsifiable concentrate (EC) formulations containing 250 g/L propiconazole.

As part of the derogation, dietary and non-dietary human health risk assessments have been carried out to demonstrate safe use of the products containing the active substance, propiconazole. To support the derogation application and inform the human health risk assessment, this report provides a summary review of the toxicological profile of propiconazole, considering recent and relevant authoritative regulatory evaluations, and the derivation of health-based reference values.

3. Regulatory evaluations of propiconazole

Sections 4 and 5 of this report provide a summary of the toxicological profile of propiconazole and the derived health-based reference values, respectively, sourced from recent and relevant authoritative regulatory evaluations of the toxicological data for the substance (i.e.: for its approval as a plant protection product active substance and the consideration of associated risks to human health).

These evaluations, and the regulatory context are summarised in the sections below.

It is noted that the triazole derivative metabolites (TDMs) toxicological profile is not in scope of this toxicological assessment. A comprehensive review was conducted by EFSA (EFSA Journal 2018;16(7):5376 amended in 2019.

3.1. Joint Meeting on Pesticide Residues (JMPR)

The Joint Meeting on Pesticide Residues (JMPR), the expert *ad hoc* body administered jointly by the United Nations (UN) Food and Agriculture Organization (FAO) and the World Health Organization (WHO), which harmonizes the requirement and the risk assessment on the pesticide residues, periodically undertakes active substance evaluations. The JMPR evaluated the toxicological profile of propiconazole in 2004 (FAO and WHO, 2004). As part of this evaluation, the JMPR conducted a comprehensive hazard assessment and characterisation for human health based on available, primarily proprietary toxicological studies and derived health-based reference values to inform dietary risk assessments.

Subsequent to the 2004 toxicological assessment of propiconazole, the JMPR has scrutinised the regulatory evaluations of other jurisdictions (i.e.: the European Union (EU)), and, on this basis have defended the hazard characterisation and conclusions made during the 2004 assessment (FAO and WHO, 2021). The 2004 JMPR evaluation of propiconazole has therefore been considered to be the primary source of toxicological information to support the derogation application.

It is however noted that while the JMPR and the EU regulatory authority, the European Food Safety Authority (EFSA) have largely reviewed the same toxicological datasets as part of their respective evaluations, their interpretation of the study findings diverges on several endpoints. Where applicable, these differences are discussed further in the sections below.

In addition, since the focus of the JMPR evaluation is the assessment of dietary risks arising from potential exposures to pesticide residues, the JMPR does not derive health-based reference values for non-dietary risk assessments and therefore relevant information from the EU evaluation has been sourced in this respect.

3.2. UN Food and Agriculture Organisation (FAO)

In 2019, the UN FAO evaluated toxicological data as part of establishing the specification for the technical material and related formulations of propiconazole as an agricultural pesticide (FAO, 2019). The FAO assessment was largely based on the toxicological dataset evaluated by the JMPR in 2004, but included some additional toxicological studies, conducted more recently but reported in limited detail only, that were not included in the JMPR evaluation. These additional studies are highlighted in Section 4.

3.3. European Union (EU) – EFSA evaluation of propiconazole as pesticide active substance

In the EU, propiconazole was evaluated in the framework of Directive 91/414/EEC with Finland being the designated rapporteur Member State (RMS). The representative uses supported for the peer review process included foliar applications to cereals, sugar beets, stone fruits and grass. Following the peer review, a decision on the inclusion of the active substance in Annex I to Directive 91/414/EEC was published by means of Commission Directive 2003/70/EC, entering into force on 1st June 2004. According to Regulation (EU) No 540/2011, propiconazole was deemed to have been approved under Regulation (EC) No 1107/2009.

An application for the renewal of the propiconazole as an active substance was subsequently submitted under Regulation (EC) No 1107/2009, in accordance with Article 1 of Commission Implementing Regulation (EU) No. 844/2012 and was evaluated by the RMS, Finland and co-RMS, the United Kingdom. EFSA published its conclusion on the peer review of the pesticide risk assessment of the active substance, propiconazole, on 12th July 2017 (EFSA, 2017).

Following the renewal evaluation, propiconazole was not approved under Regulation (EC) No. 1107/2009, in accordance with Commission Implementing Regulation (EC) 2018/1865 of

28th November 2018, on the grounds that the approval criteria in Article 4 of Regulation (EC) No 1107/2009 were not met. The non-approval took into account the classification of propiconazole as toxic for reproduction category 1B, adopted in accordance with Regulation (EC) No 1272/2008 (discussed in Section 3.4), as this classification for reproductive toxicity is a hazard-based "cut-off" criterion according to Regulation (EC) No. 1107/2009.

3.4. European Union (EU) – ECHA hazard identification and harmonised classification

Within the EU legislative framework, Regulation (EC) No. 1272/2008 on the Classification, Labelling and Packaging of Substances and Mixtures (referred to as the "CLP Regulation") serves as a hazard identification process, with direct risk management consequences, to ensure that the hazards presented by chemical substances are clearly communicated to workers and consumers in the European Union, across the supply chain. As such, the CLP Regulation does not facilitate the assessment of exposures to the chemical substances, the characterisation of the hazards (i.e.: via health-based reference values) or the assessment of health risks.

The harmonised hazard classification of propiconazole in accordance with the CLP Regulation has been reviewed with the Finnish Member State Competent Authority (MSCA) adopting the role of Dossier Submitter (DS). The Finnish DS submitted an intention to the Registry of Intentions (RoI) on 16th January 2015 and subsequently submitted a finalised Harmonised Classification and Labelling (CLH) dossier to the European Chemicals Agency (ECHA) on 27th November 2015, with a legal deadline for opinion adoption of 26th May 2017.

With respect to human health hazards, at the time of the classification review, propiconazole had harmonised classifications of Acute Tox. 4 (H302) and Skin Sens. 1 (H317). The CLH dossier proposed by Finland during the review initially included a new classification for reproductive toxicity: Repro. 2, with the hazard statement H361d – *"Suspected of damaging the unborn child."*

Following the public consultation, an assessment of the available evidence against the classification criteria and deliberation by the RAC CLH Working Group and Plenary meetings, the RAC adopted the opinion that propiconazole met the criteria for harmonised classification as: Repro. 1B, with the hazard statement H360D: *"May damage the unborn child."* The RAC opinion was adopted on 9th December 2016. ECHA subsequently forwarded the RAC opinion to the EC for a decision and the harmonised classification was included in Part 3, Annex VI of the CLP Regulation on 4th Oct 2018 (ATP13), with an adoption date of 1st May 2020.

4. Propiconazole: Summary of mammalian toxicity data

This section presents a summary of the mammalian toxicological profile of propiconazole based on the conclusions of authoritative regulatory evaluation conducted by the joint FAO/WHO JMPR, by EFSA and ECHA respectively, as part of evaluations in the EU.

4.1. Absorption, distribution, metabolism and excretion.

JMPR 2004

Based on the evaluation of toxicokinetic data, the JMPR noted that after oral administration of radiolabelled propiconazole to rats and mice, the radiolabel is rapidly (Cmax at 1h) and extensively (>80% of the administered dose) absorbed and widely distributed, with the highest concentrations being found in the liver and the kidneys.

Excretion of the radiolabel is rapid (80% in 24h) with significant amounts being found in the urine (39–81%) and the faeces (20–50%), the proportions varying with dose, species and sex.

There is a significant degree of biliary excretion and subsequent enterohepatic recirculation. There was no evidence for bioaccumulation, with tissue or carcass residues being typically <1% of the administered dose 6 days after dosing. Propiconazole is extensively metabolized and <5% of the dose remains as parent compound; however, many metabolites have not been identified.

While propiconazole is primarily metabolised via oxidation of the propyl sidechain on the dioxolane ring to give hydroxy or carboxylic acid derivatives, hydroxylation of the chlorophenyl and triazole rings followed by conjugation with sulfate or glucuronide has also been detected. There is evidence for only limited cleavage between the triazole and chlorophenyl rings. The extent of cleavage of the dioxolane ring varied significantly according to species and sex, representing about 60% of urinary radioactivity in male mice, 30% in female mice and 10–30% in male rats. In rats, propiconazole is readily absorbed after dermal application (about 30% within 10 hours).

EU – EFSA evaluation and conclusions

EFSA concluded that based on toxicokinetic studies, propioconazole was extensively and rapidly absorbed. Bioavailability was approximately 91 % and no evidence of accumulation was found. While excretion of the substance was primarily through the bile route, appreciable amounts were excreted in the urine. The main metabolic pathway identified was oxidation, cleavage and hydroxylation reactions.

4.2. Acute toxicity

JMPR 2004 and FAO 2019

The acute toxicity of propiconazole was evaluated by the JMPR in 2004 as part of the toxicological evaluation based on a number of pre-guideline and GLP studies (summarised in Table 4.1). Overall, the studies were considered to be adequate for assessing the acute toxicity of propiconazole.

The 2019 FAO review of propiconazole included additional, more recent OECD Test Guideline (TG) and GLP compliant acute toxicity studies including: an OECD TG 425 acute oral toxicity study; an OECD TG 402 acute dermal toxicity study; an OECD TG 404 skin irritation study and an OECD TG 405 eye irritation study.

Acute oral, dermal and inhalation toxicity

Propiconazole has moderate acute oral toxicity in rats and mice, based on LD_{50} values of 1517 and 1490 mg/kg bw respectively (Bathe (1978) and Bathe (1979a), cited in FAO and WHO, 2004).

In an OECD TG 425 acute oral toxicity study conducted in rats, the LD_{50} was determined to be 550 mg/kg bw (FAO, 2019). According to the Global Harmonised System for the Classification and Labelling of Chemicals (GHS; UN, 2023), propiconazole would meet the classification in Category 4 for acute oral toxicity (H302; Harmful if swallowed) based on the LD_{50} value lying between 300 and 2000 mg/kg bw.

Propiconazole has low acute dermal toxicity in rats and in rabbits: the respective LD_{50} values were >4000 mg/kg bw and >6000 mg/kg bw (Bathe (1979b) and Ullman (1979a), cited in FAO and WHO, 2004). In an OECD TG 402 acute dermal toxicity study conducted in rats, the LD_{50} was determined to be >5000 mg/kg bw, confirming that the substance has low acute dermal toxicity.

Propiconazole had low acute inhalation toxicity in a study in rat (LC_{50}, >5mg/l of air; Hartman and Gfeller (1988), cited in FAO and WHO, 2004).

Skin and eye irritation and skin sensitisation

Propiconazole was moderately irritating to rabbit skin (Ullmann, 1978a, cited in FAO and WHO, 2004) and produced only minimal irritation to rabbit eyes (Ullmann, 1978b, cited in FAO and WHO, 2004)). Propiconazole was found to be mildly irritating to the skin and eyes of rabbits in respective OECD TG 404 skin irritation and OECD TG 405 eye irritation studies, confirming that the substance is non-irritant.

Weak reactions were seen in 3 out of 19 guineapigs in an "optimization" test for skin sensitization (Ullmann, 1979b, cited in FAO and WHO, 2004)). A positive result was reported in a test for skin sensitization in guineapigs that was performed to a protocol for the Magnusson & Kligman maximization test (Sommer, 1999, cited in FAO and WHO, 2004). According to the Global Harmonised System for the Classification and Labelling of Chemicals (GHS; UN, 2023), propiconazole would meet the classification in Category 1 for skin sensitisation (H317; May cause an allergic reaction).

EU – EFSA evaluation and conclusions

Based on the evaluation of the acute toxicity dataset, EFSA concluded that propiconazole has low acute toxicity when administered dermally or by inhalation, moderate acute oral toxicity when administered to rats, is not a skin or an eye irritant but is a skin sensitiser (EFSA, 2017).

A summary of the acute toxicity of propiconazole is provided in the table below.

Table 4.1: Summary of acute toxicity studies using propiconazole

STUDY	SPECIES/STRAIN AND DOSES	LD_{50}/LC_{50}	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
Acute oral (No guideline; non GLP)	Rat (Tif:RAIf); (male and female) Dose levels 500, 1000, 3000 or 4000 mg/kg 14 day observation period	LD_{50} = 1517 mg/kg bw	Low toxicity	Bathe (1978) cited in FAO and WHO, 2004 [CGA64250/1528 FAO, 2019]
Acute oral (No guideline; non GLP)	Mouse (Tif:MAG); (males and females) Dose levels 800, 1500, 2500 or 3000 mg/kg 14 day observation period	LD_{50} = 1490 mg/kg bw	Low toxicity	Bathe (1979a) cited in FAO and WHO, 2004 [CGA64250/1529 FAO, 2019]
Acute oral toxicity, Up and Down Procedure (OECD 425, GLP)	Rat RjHan: WI female rats 2000, 550 or 175 mg/kg bw	LD_{50} = 550 mg/kg bw	GHS Acute oral toxicity Cat. 4 H302 (Harmful if swallowed)	CGA064250_10710 (2010) FAO, 2019: Additional study
Acute dermal (No guideline; non GLP)	Rat (Tif:RAIf); (male and female) Dose levels 3000 or 4000 mg/kg	LD_{50} = > 4000 mg/kg bw	Low toxicity	Bathe (1979b) cited in FAO and WHO, 2004 [CGA64250/1531 FAO, 2019]

STUDY	SPECIES/STRAIN AND DOSES	LD_{50}/LC_{50}	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
	14 day observation period			
Acute dermal (No guideline; non GLP)	Rabbit (NZW); (male and female) Dose levels 2000 or 6000 mg/kg 14 day observation period	LD_{50} = > 6000 mg/kg bw	Low toxicity	Ullman (1979a) cited in FAO and WHO, 2004 [CGA64250/1532 FAO, 2019]
Acute dermal (OECD 402, GLP)	Rat RjHan: WI (5/sex/group) 5000 mg/kg bw	LD_{50} = > 5000 mg/kg bw	Low toxicity	CGA064250_10706 (2010) FAO, 2019: Additional study
Acute inhalation (OECD 403 (1981); GLP)	Rat (Tif:RAIf); (male and female) 4h nose only exposure; MMAD approx.2.6 µm	LC_{50} = >5 mg/m^3	Low toxicity	Hartman and Gfeller (1988) cited in FAO and WHO, 2004 [CGA64250/1533 FAO, 2019]
Skin irritation (No guideline; non GLP)	Rabbit 7 day observation period	-	Moderate irritant	Ullman (1978a) cited in FAO and WHO, 2004 [CGA64250/1535 FAO, 2019]
Skin irritation OECD 404, GLP)	Rabbit NZW 3 male 0.5g	-	Mild irritant	CGA064250_10705 (2010) FAO, 2019: Additional study
Eye irritation (No guideline; non GLP)	Rabbit	-	Mild irritant	Ullman, 1978b; cited in FAO and WHO, 2004 CGA64250/1536 FAO, 2019
Eye irritation (OECD 405, GLP)	Rabbit NZW 3 male 0.1 mL	-	Mild irritant	CGA064250_10711 FAO, 2019 (2010): Additional study
Skin sensitisation (Optimisation test)	Guinea pigs	-	Weak reactions in 3/19 animals	Ullman (1979b) cited in FAO and WHO, 2004
Skin sensitisation (Magnusson and Kligman maximisation Test)	Guinea pigs	-	GHS Skin Sens. Cat 1, H317 (May cause an allergic skin reaction)	Sommer (1999) cited in FAO and WHO, 2004 [CGA64250/4197 FAO, 2019]

4.3. Short-term toxicity

JMPR 2004 and FAO 2019

The short-term, repeated dose toxicity of propiconazole studies evaluated by the JMPR in 2004 as part of the toxicological assessment included: oral 28-day and 90-day studies in rats; oral 13- and 17-week studies in mice; oral 90-day and 1-year studies in dogs; a dermal 21-day (15 exposures) study in rabbits and a 13-week (65 exposures) inhalation study performed in rats.

The 2019 FAO review of propiconazole included an additional GLP, OECD TG 410 repeated dermal toxicity study in rats.

In a non-guideline sub-acute, repeated oral dose toxicity study in which rats were given propiconazole at 0, 50, 150, 450 mg/kg bw per day for 28 days by gavage, treatment-related effects included reductions in body weight gain in males, and signs of clinical toxicity and a reduction of erythrocyte parameters in females. Both sexes had increased liver weights and hepatocyte hypertrophy, with hepatocyte necrosis also being seen in females. Increases in liver weight with hepatocyte hypertrophy observed at 150 mg/kg bw per day, were considered to be adaptive and not adverse. The NOAEL was determined to be 150 mg/kg bw/day, based on clinical signs of toxicity, liver necrosis and reduced erythrocyte parameters observed at 450 mg/kg bw/day (Baslet and Gfeller (1980), cited in FAO and WHO, 2004).

In a sub-acute, repeated dermal OECD TG 410 (pre-GLP) study in which rabbits were treated with propiconazole at 0, 200, 1000 or 5000 mg/kg bw/day for 3 weeks (five applications per week), skin lesions were noted in all treated groups and a NOAEL for local effects was not determined. The NOAEL for systemic toxicity was determined to be 200 mg/kg bw/day based on clinical signs (i.e.: tremor, dyspnoea and ataxia) observed at 1000 mg/kg bw/day (Sachsee *et al.* (1980), cited in FAO and WHO, 2004).

In a sub-acute GLP, repeated dermal OECD TG 410 study in which rats were treated with propiconazole at 0, 10, 100 or 1000 mg/kg bw/day for 28 days, the NOAEL was determined to be 1000 mg/kg bw/day i.e.: the highest dose tested (FAO, 2019).

In a sub-chronic, 90-day dietary study conducted according to OECD TG 408, in which rats were administered propiconazole at 0, 240, 1200 or 6000 ppm via the diet, reductions in body-weight gain, increased relative liver weight and increased γ-glutamyl transpeptidase activity were seen in both sexes treated at 6000 ppm. In females, erythrocyte parameters were reduced at this dose. Based on these findings, the NOAEL was determined to be 1200 ppm (equal to 76 mg/kg bw per day; Sacchsee *et al.* (1979a), cited in FAO and WHO, 2004).

In two respective, non-guideline, 13-week and 17-week sub-chronic studies, male mice were given diets containing propiconazole at 0, 20, 500, 850, 1450 or 2500 ppm whereas female mice were given diets containing propiconazole at 0, 20, 500 or 2500 ppm. In the 13-week study, increases in liver weight, hepatocyte necrosis and clinical chemistry parameters (serum activities of alanine aminotransferase and sorbitol dehydrogenase) were observed in rats treated at 850 ppm (121 mg/kg bw/day). In the 17-week study, treatment-related effects included changes in clinical chemistry parameters, increases in liver weight and histopathology findings were observed in male and female rats treated at 850 and 2500 ppm, respectively. The NOAEL was determined to be 500 ppm (equal to 65 and 71 mg/kg bw/day, respectively) in both studies (Potrepka and Turnier (1991 a, b), cited in FAO and WHO, 2004).

In two respective, GLP OECD TG 452 sub-chronic 90-day and 1-year repeated dose toxicity studies, dogs were administered propiconazole via the diet at 0, 50, 250 or 2500 ppm. In the studies, dogs appeared to be sensitive to the local effects of propiconazole as manifested by gastrointestinal tract irritation. The NOAELs for local effects were determined to be 250 ppm (equal to 6.9 mg/kg bw per day) after 90 days and 50 ppm (1.9 mg/kg bw/day) after 1 year. No systemic effects were seen in dogs receiving doses up to 250 ppm (equal to 8.4 mg/kg bw/day) for 1 year or up to 1250 ppm (equal to 35 mg/kg bw per day) for 90 days, the highest doses tested, in each study.

In a 13-week repeated dose inhalation study (comparable to OECD TG 413, pre-GLP), in which rats were exposed to air concentrations of propiconazole at 0, 21, 85 or 191 mg/m^3 for 5 days per week; 6 hours per day, reduced body-weight gain was seen in females treated at the top dose of 191 mg/m^3. The NOAEC for the sub-chronic inhalation toxicity of propiconazole was determined to be 85 mg/m^3 of air.

EU – EFSA evaluation and conclusions

Based on the evaluation of the short-term oral toxicity studies, EFSA concluded that the target organs for the systemic toxicity of propiconazole were the liver in rats and in mice and the pituitary gland in dogs. The relevant, short-term oral NOAEL was determined to be 2.7 mg/kg bw/day based on a 17-week repeated oral exposure study in mice (EFSA, 2017).

A summary of the short-term toxicity of propiconazole is provided in the table below.

Table 4.2: Summary of short-term toxicity studies using propiconazole

STUDY	SPECIES/STRAIN AND DOSES	NOAEL	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/STUDY NUMBER
28-Day repeated oral dose toxicity (No guideline)	Rat (m+f) RAIf rats Dose: 0, 50, 150, 450 mg/kg bw/day oral gavage	NOAEL = 150 mg/kg bw/d	450 mg/kg bw/day (f): Clinical signs of toxicity, liver necrosis and reduced erythrocyte parameters	Basler and Gfeller (1980) cited in JMPR, 2004 [CGA64250/1596 FAO, 2019]
21-Day repeated dermal toxicity (OECD 410 (prior to GLP))	Rabbit (m+f) NZW rabbits (10 males/ 10 females) Dose Levels: 0, 200, 1000 or 5000 mg/kg bw/ day	NOAEL (Local effects) – Not determined NOAEL (Systemic effects) = 200 mg/kg bw/day	Skin lesions noted in all treated groups 1000 mg/kg bw/day: Clinical signs (tremor, dyspnoea, ataxia)	Sachsse *et al.* (1980), cited in FAO and WHO, 2004 CGA64250/1595 FAO, 2019
28-Day repeated dermal toxicity (OECD 410, GLP)	Rats Hanlbm:WIST 10/sex/group Dose: 0, 10, 100, 1000 mg/kg bw/day	NOAEL: 1000 mg/kg bw/day	Not stated	CGA64250/4412 (2001) FAO: Additional data
90-Day repeated oral dose toxicity (OECD 408 (1981)	Rat (m+f) Tif:RAIf rats Dose: 0, 240, 1200, 6000 ppm via the diet	NOAEL = 1200 ppm (76 mg/kg bw/day)	6000 ppm: Reduced body-weight gain, increased liver weight and altered erythrocyte and clinical chemistry parameters	Sacchsse *et al*., (1979a) cited in FAO and WHO, 2004 [CGA64250/1538 FAO, 2019]
90-Day repeated oral dose toxicity (OECD 452 (1981), GLP)	Dog (m+f) Beagle dogs (4/sex/group) Dose: 0, 50, 250, 1250 ppm via the diet	NOAEL (Local effect) = 250 ppm (6.9 mg/kg bw/day) NOAEL (systemic	1250 ppm (Local effects): Lymphoid changes in the stomach No systemic toxicity observed	Sachsse *et al* (1980b), cited in FAO and WHO, 2004 CGA64250/1539 FAO, 2019

STUDY	SPECIES/STRAIN AND DOSES	NOAEL	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/STUDY NUMBER
		effects) = > 1250 ppm (> 35 mg/kg bw/day) i.e.: highest dose tested		
90-Day repeated inhalation toxicity (OECD 413 (prior to GLP)	Rats (m+f) RAIf rats (5/sex/group) Dose: 0, 21, 85,191 mg/m^3	NOAEC = 85 mg/m^3	191 mg/m^3 (f): reduced body weights	Sachsse *et al*., 1979b, cited in JMPR 2004 CGA64250/1593 FAO, 2019
13-week repeated oral dose toxicity (No guideline)	Mouse (m+f) CD1 (ICR) BR mice Dose: 0, 20, 500, 850, 1450, 2500 ppm (males); 0, 20, 500, 2500 ppm (females) via the diet	NOAEL = 500 ppm (71 mg/kg bw/day)	850 ppm (121 mg/kg bw/day: increases in liver weight, hepatocyte necrosis and serum activities of alanine aminotransferase and sorbitol dehydrogenase	Potrepka and Turnier (1991a) cited in FAO and WHO, 2004 CGA64250/2020 FAO, 2019
17-week repeated oral dose toxicity (No guideline)	Mouse (m+f) CD1 (ICR) BR mice Dose: 0, 20, 500, 850, 1450, 2500 ppm (males); 0, 20, 500, 2500 ppm (females) via the diet	NOAEL = 500 ppm (65 mg/kg bw/day)	850 ppm (m); 2500 ppm (f): changes in clinical chemistry, increases in liver weight and histopathology findings	Potrepka and Turnier (1991b) cited in FAO and WHO, 2004 CGA64250/2019 FAO, 2019
1 year repeated oral dose toxicity (OECD 452 (1981), GLP)	Dog (m+f) Beagle dogs (5/sex/group) Dose Levels: 0, 5, 50, 250 ppm via the diet	NOAEL (local effects) = 50 ppm (1.9 mg/kg bw/day) NOAEL (systemic effects) > 250 ppm (>8.4 mg/kg bw/day) i.e.: highest dose tested	250 ppm (Local effects): Hyperaemia of the gastrointestinal tract No systemic toxicity observed	Johnson *et al* (1985) cited in FAO and WHO, 2004 [CGA64250/1544 FAO, 2019]

Key: f-female; m-male, TG – Test Guideline

4.4. Genotoxicity

JMPR, 2004 and FAO, 2019

The JMPR evaluated a battery of *in vitro* and *in vivo* genotoxicity studies, as part of the toxicological assessment of propiconazole conducted in 2004. Studies conducted in vitro included: gene mutation assays conducted in bacteria and mammalian cells (mouse lymphoma L5178Y thymidine kinase (TK)+/- cell line), a transformation assay using BALB 3T3 mouse embryo cells, a mammalian cell chromosomal aberration assay using human peripheral lymphocytes and an unscheduled DNA synthesis assay in mammalian cells using rat hepatocytes.

Studies conducted *in vivo* included two respective micronucleus studies conducted according to GLP and OECD TG 474 in Chinese hamsters (dosed with propiconazole by gavage at 0, 307, 615 or 1230 mg/kg bw) or mice (dosed with propiconazole by gavage at 0, 165 or 495 mg/kg bw). Propiconazole has also been tested in an *in vivo* study of dominant lethal mutation in which mice were dosed with propiconazole by gavage at 0, 165 or 495 mg/kg bw. The highest concentrations used in these studies were justified on the basis of results of screening for toxicity/cytotoxicity.

While the *in vitro* studies pre-date and do not meet the current OECD test guidelines, the overall extent of the database was considered to be adequate for assessing the genotoxic potential of propiconazole.

The 2019 FAO review of propiconazole included an additional GLP, OECD TG 470 *in vitro* bacterial cell reverse mutation assay and an *in vitro* cell mutation assay at the TK locus in mouse lymphoma L5178Y cells (reported in limited detail only; FAO, 2019).

All the available *in vitro* and *in vivo* studies gave negative results, where applicable, in the presence and in the absence of a metabolic activation system. Based on the negative findings in an adequate battery of *in vitro* and *in vivo* genotoxicity studies, the JMPR concluded that propiconazole was unlikely to be genotoxic.

EU – EFSA and ECHA (RAC) evaluation and conclusions

Overall, EFSA concluded that there was no evidence of mutagenicity observed in the available *in vitro* and *in vivo* genotoxicity studies. EFSA however noted that there were some uncertainties regarding the clastogenic and aneugenic potential of propiconazole on the basis that the design of the *in vitro* clastogenicity assay was considered to have some limitations and the *in vivo* micronucleus test was not considered to have demonstrated clear evidence of sufficient exposure in the bone marrow (EFSA, 2017).

As part of the evaluation of the potential human health hazards of propiconazole in accordance with the CLP Regulation, the CLH Dossier Submitter, Finland and the ECHA RAC concurred that there was no evidence of genotoxicity observed in the *in vivo* and *in vitro* mutagenicity assays: the overall conclusion was that propiconazole is not genotoxic (Tukes, 2015; ECHA, 2016).

A summary of the genotoxicity studies conducted using propiconazole is provided in the table below.

Table 4.3: Summary of genotoxicity studies using propiconazole

STUDY	SPECIES/STRAIN AND DOSES	RESULTS	REFERENCE/STUDY NUMBER
In vitro bacterial reverse mutation assay (No guideline, non GLP)	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538) 20- 5120 µg/plate +/- S9 DMSO	Negative +/- S9	Deparade and Arni (1983), cited in JMPR 2004 CGA64250/1571 FAO, 2019
In vitro bacterial reverse mutation assay (OECD 471, GLP)	*Salmonella typhimurium* (TA1535, TA1537, TA98, TA100) and *Escherichia coli* (WP2 (pKM101), WP2 uvrA)	Negative	CGA064250_10884 (2014) FAO, 2019: Additional data

STUDY	SPECIES/STRAIN AND DOSES	RESULTS	REFERENCE/STUDY NUMBER
	0 to 5000 µg/plate, +/- activation		
In vitro mammalian gene mutation (No guideline, non GLP)	Mouse lymphoma L5178Y TK +/- cells 7.8-125 µg/mL +/-S9 in DMSO	Negative +/- S9	Strasser and Muller (1982a), cited in FAO AND WHO, 2004 CGA64250/1583 FAO, 2019
In vitro mammalian gene mutation (OECD/GLP – not stated)	Mouse lymphoma L5178Y TK +/- cells 0 to 90 µg/ml, - activation 0 to 70 µg/ml, + activation	Negative	CGA064250_10886 (2014) FAO, 2019: Additional data
In vitro cell transformation (No guideline, non GLP)	BALB 3T3 mouse embryo Cells 1.2-18.5 µg/mL +/-S9 in DMSO	Negative +/- S9	Strasser and Muller (1982b), cited in FAO and WHO, 2004 CGA64250/1582 FAO, 2019
In vitro chromosome aberration (No guideline, non GLP)	Human peripheral lymphocytes 1-180 µg/mL +/-S9 in DMSO	Negative +/- S9	Strasser and Arni (1984), cited in FAO and WHO, 2004 CGA64250/1576 FAO, 2019
In vitro unscheduled DNA synthesis (OECD 482 (1986), GLP	Tif:RAIf rat hepatocytes 0.7-83 ng/mL+/-S9 in DMSO	Negative	Puri and Muller (1982), cited in FAO and WHO, 2004 CGA64250/1581 FAO, 2019
In vivo micronucleus (OECD 474 (1997), GLP)	Chinese hamster 0, 307, 615 or 1230 mg/kg bw by gavage in arachis oil. 8 animals per sex per group	Negative	Strasser and Arni (1987), cited in FAO and WHO, 2004 CGA64250/860359 CGA64250/1584 FAO, 2019
In vivo micronucleus (OECD 474 (1997), GLP)	Mice (Ico:CD1) Dose: 0, 80, 1600, 3200 mg/kg bw by gavage in arachis oil 5 animals per sex per group	Negative	Deparade (1999), cited in FAO and WHO, 2004 CGA 64250/4268 FAO, 2019
Dominant lethal mutation	Mice (Tif:MAGf (SPF)) Dose: 0, 165, 495 mg/kg bw by gavage in methyl cellulose. Males	Negative	Hool and Muller (1979); Caressa (1988), cited in FAO and WHO, 2004 CGA64250/1569 CGA064250_10740 FAO, 2019

4.5. Chronic toxicity and oncogenicity

JMPR 2004

The long-term toxicity and carcinogenicity studies evaluated by the JMPR in 2004 as part of the toxicological assessment included: a 2-year (104 week) dietary study in male and female mice, an 18-month dietary study in male mice and a 2-year (109 week) dietary study in male and female rats.

In a non-guideline, long-term toxicity and carcinogenicity study, male and female mice were administered propiconazole at 0, 100, 500 or 2500 ppm (equivalent to 0, 10, 49 and 344 mg/kg bw/day in males and 0, 11, 56 and 340 mg/kg bw/day in females) for 104 weeks. In the study, the liver was considered to be the only target organ for the long-term toxicity of propiconazole. At doses at or above 500 ppm, decreases in body-weight gain and serum concentration of cholesterol, and increases in liver weight, hepatocellular hypertrophy and hepatocellular vacuolation were observed. The NOAEL for non-neoplastic effects was 100 ppm, equal to 10 mg/kg bw/day, on the basis of hepatocellular lesions at 500 ppm (Hunter *et al.* (1982a), cited in FAO and WHO, 2004).

A statistically significant (p = 0.0013) increase in the combined incidence of liver tumors (benign and malignant) was observed in male mice treated at the top dose of 2500 ppm. Based on these findings, the no-observed-effect level (NOEL) for neoplasia was determined to be 500 ppm (equal to 49 mg/kg bw/day; Hunter *et al*. (1982a), cited in FAO and WHO, 2004).

Comparable results were observed in another long-term toxicity and carcinogenicity study in which male mice were administered propiconazole via the diet at 0, 100, 500 or 800 ppm (equivalent to 0, 11, 59 and 108 mg/kg bw/day) for 18 months. The liver was identified as the target organ for toxicity. In the study, the NOAEL for non-neoplastic effects was determined to be 100 ppm (equal to 11mg/kg bw per day based on reduced cholesterol, reduced body-weight gain (10%) and increased liver weights/hypertrophy observed at 500 ppm. Fatty liver changes noted at 9 weeks in 2 out of 10 animals treated at 100 ppm did not progress and was not considered to be biologically significant (Gerspach (1987), cited in FAO and WHO, 2004).

Regarding neoplastic effects, the incidence of hepatocellular adenomas in male mice treated at 850 ppm was above historical and concurrent controls and was considered to be treatment related. The incidence of adenomas at 500 ppm (3 out of 50) was at the lower end of the control range of 6–18% reported in CD1 mice in the same test facility and was not considered to be biologically significant. Based on these findings, the NOAEL for tumours was determined to be 500 ppm (equal to 59 mg/kg bw per day) on the basis of a significant increase in the incidence of liver adenomas at 850 ppm (Gerspach (1987), cited in FAO and WHO, 2004).

In a GLP, long-term toxicity and carcinogenicity study conducted in accordance with OECD TG 453, rats were administered propiconazole at 0, 100, 500 or 2500 ppm (equivalent to 0, 3.6, 18 or 96 mg/kg bw/day in males and 0, 4.6, 23 or 131 mg/kg bw/day in females) for 109 weeks via the diet. Reductions in body-weight gain were observed in both sexes treated at 2500 ppm. Increased incidences of enlarged hepatocytes were present in males and increases in atrophy of the exocrine pancreas and dilation of the uterine lumen in females. Slight (<10%), transient reductions in body-weight gain, variations in clinical chemistry and haematology parameters that fell within physiological ranges at 500 ppm (equal to 18 mg/kg bw per day) were not considered to be adverse. In the study, the NOAEL for the long-term, systemic toxicity of propiconazole in rats was determined to be 500 ppm (equal to 18 mg/kg bw per day; Hunter *et al*. (1982b), cited in FAO and WHO, 2004).

No treatment-related tumours were observed in the study: liver cell tumors were slightly higher in animals at the highest dose but were within normal background ranges and when combined with the increased survival were not considered to indicate a tumourigenic response to propiconazole. Reticulum cell tumours of the pancreas were present in three animals in the satellite groups but were not seen in the main group and were not considered to indicate a carcinogenic response to propiconazole. Propiconazole was not therefore considered to be

carcinogenic in rats at doses of up to 2500 ppm (equal to 96 and 131 mg/kg bw per day in males and in females respectively (Hunter *et al.* (1982b), cited in FAO and WHO, 2004).

The long-term toxicity and carcinogenicity studies in rodents indicated that propiconazole was a hepatocarcinogen only in male mice, on the basis of significant increases in the incidence of liver tumours at ≥850 ppm (equal to 108 mg/kg bw/day), with a NOAEL of 500 ppm (equal to 59 mg/kg bw/day). Assays for hepatocyte proliferation (measured by bromodeoxyuridine incorporation) in mice showed qualitative similarities between propiconazole and phenobarbital. The doses that produced increases in tumour incidences (≥850ppm) also produced cell proliferation, increased liver weight and hepatocyte hypertrophy. Studies of liver enzyme induction in mice showed that propiconazole increased the activity of a number of cytochrome P450s enzymes, particularly Cyp2b, and exhibited similar characteristics to a phenobarbital type inducer of xenobiotic-metabolizing enzymes. The progression from P450 (Cyp2b) induction, initial mitogenic response, hepatocyte hypertrophy and increased liver weight to tumours is consistent with a mode of action similar to that of phenobarbital.

Based on consideration of liver tumours in male mice, the high doses required to induce the tumours, the likely mechanism of action, the absence of tumorigenicity in rats and the negative results obtained in genotoxicity studies, the JMPR concluded that propiconazole was unlikely to pose a carcinogenic risk to humans.

EU – EFSA and ECHA (RAC) evaluations and conclusions

Based on the evaluation of long-term toxicity and carcinogenicity studies, EFSA considered that the target organs for toxicity were the adrenals in rats and the liver in mice. The rat was considered to be the most sensitive species. The relevant long-term NOAELs were concluded to be 3.6 mg/kg bw/day for the rat and 10 mg/kg bw/day for the mouse (EFSA, 2017).

EFSA noted that propiconazole was found to induce liver tumours in male CD-1 mice at dose levels of 107.8 and 344.3 mg/kg bw/day (EFSA, 2017) and classification in respect of carcinogenicity was subsequently discussed by the ECHA RAC in the context of human health hazard criteria indicated in the CLP Regulation. The RAC concluded that the liver tumours observed in mice after exposure to propiconazole were not of concern for humans and no classification in respect of carcinogenicity was warranted (ECHA, 2016).

A summary of the chronic toxicity and oncogenicity of propiconazole is provided in the table below.

Table 4.4: Summary of chronic toxicity and oncogenicity studies using propiconazole

STUDY	SPECIES/ STRAIN AND DOSES	NOAEL	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
104-Week oral carcinogenicity (No guideline)	Mice (m+f) CD1 mice Dose: 0, 100, 500, 2500 ppm via the diet	NOAEL (Non-neoplastic effects) = 100 ppm (10 mg/kg bw/day) NOEL (tumours) = 500 ppm (49 mg/kg bw/day)	500 ppm (Non-neoplastic effects): Hepatocellular lesions (m/f) 2500 ppm (Neoplasia): Increased incidence of combined liver tumours (m)	Hunter et al., (1982a), cited in JMPR 2004 [CGA64250/1542 FAO, 2019]

STUDY	SPECIES/ STRAIN AND DOSES	NOAEL	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
18-Month oral carcinogenicity (Not conducted to OECD test guideline)	Mice (m) Crl:CD1 (ICR) BR (5/sex/group) Dose: 0, 500, 850 ppm via the diet	NOAEL (Non-neoplastic effects) = 100 ppm (11 mg/kg bw/day NOAEL (tumors) = 500 ppm (59 mg/kg bw/day)	500 ppm (No-neoplastic effects): Reduced cholesterol and body weight gain; increased liver weights and hypertrophy 850 ppm (Neoplastic effects): Increased incidence of hepatocellular adenomas	Gerspach (1987), cited in FAO and WHO, 2004 CGA64250/3142 FAO, 2019
109-Week oral carcinogenicity (OECD 453)	Rats (m+f) CD Sprague-Dawley Dose: 0, 100, 500, 2500 ppm via the diet	NOAEL (Non-neoplastic effects) = 500 ppm (18 mg/kg bw/day) NOAEL (tumors) = >2500 ppm (>96 (m); 131 (f) mg/kg bw/day (tumours)	2500 ppm (Non-neoplastic effects): Reduced body weight gain; variation in clinical chemistry and haematology parameters, hypertrophy (m), pancreatic atrophy, uterine dilation (f) No treatment-related tumours observed.	Hunter *et al.*, (1982b), cited in JMPR 2004 [CGA64250/1540 FAO, 2019]

4.6. Reproduction toxicity – Effects on fertility and sexual function

JMPR 2004

As part of the toxicological assessment conducted in 2004, the JMPR evaluated the reproductive toxicity of propiconazole based on the findings of a two-generational reproduction study (two litters per generation) conducted in rats according to GLP and OECD TG 416 (version 1983). The main deviations from the current OECD TG 416 (version 2001) were: oestrus cycle and sperm parameters were not determined, developmental landmarks of the offspring including parameters of sexual maturation were not evaluated, food consumption was only determined during the pre-mating period, only brain, ovary and testes weights were determined.

In the study, groups of CD rats (15 males and 30 females) received diets containing propiconazole at a concentration of 0, 100, 500 or 2500 ppm during the pre-mating, gestation, lactation and weaning periods. The equivalent doses, expressed in mg/kg bw/day, were reported in the 2004 JMPR toxicological assessment as: 0, 7, 35 and 175 mg/kg bw/day. Dosing was initiated 12 weeks before mating for the F1a and F2a litters. Animals were observed for mortality, clinical signs, body weight, food consumption, mating performance and reproductive outcomes. All P1 parental animals and 10 weanlings of each sex per group received a gross examination, brain and reproductive organs were weighed, and liver and reproductive organs were examined histopathologically (Borders *et al*. (1985), cited in FAO and WHO, 2004).

There were no signs of toxicity in P0 or P1 males other than a slight (10%) reduction in body weight gain was observed at the highest dose of 2500 ppm. Reduced body weight gain (20 %)

and reduced food consumption during most stages of the study was observed in females treated at 2500 ppm. Reduced body weight gain was also observed in females treated at the intermediate dose of 500 ppm (approximately 10 %; $p < 0.01$).

Reproductive parameters including mating performance, fertility and duration of gestation were comparable between the treated and the control groups although the degree of variation in values for controls hindered comparisons between the generation groups. Organ weights such as brain and testes/epididymides showed no consistent pattern between the generation groups, with reductions in absolute values or increases in relative values being secondary to body-weight changes. There were no treatment-related gross pathology findings. Histopathological examination of the reproductive organs found no notable effects of treatment.

Treatment-related changes (hepatocellular hypertrophy and vacuolization) were observed in the livers of both parental and weanling animals at 2500 ppm and in parents from groups treated at 500 ppm, indicating a consistent profile of liver toxicity observed in repeated dose toxicity studies.

While lower weights of pups on postnatal day (PND) 21 were typically associated with larger litters, the mean pup litter weights for F1a and the F1b generation groups treated at 2500 ppm were statistically significantly reduced by 26 % ($p < 0.05$) and 19 %, ($p < 0.01$), respectively. Comparable findings were observed in the second generation: the mean pup litter weights for the F2a and the F2b generation groups treated at 2500 ppm were statistically significantly reduced by 19 % ($p < 0.01$) and 26 % ($p < 0.01$), respectively and the mean litter size in both generation groups were also statistically significantly reduced by 20 % ($p < 0.01$) and 26% ($p < 0.01$) respectively. The mean pup weight in the F2b litter group was additionally reduced at 500 ppm (9 %, $p < 0.01$). The main effect on F2 litter size at 2500 ppm was poor survival during lactation: the mean number of viable pups was statistically significantly reduced on PND 0, 4 and 14 (26 % ($p < 0.01$), 15 % ($p < 0.01$), 21 % ($p < 0.01$) in the F2a group and on PND 14 (26 %, $p < 0.05$) in the F2b group.

Based on the findings of the study, the JMPR 2004 toxicological assessment concluded the following:

- The NOAEL for general parental toxicity was determined to be 100 ppm (equivalent to 7 mg/kg bw per day) the basis of reduced body weight gain in dams and hepatotoxicity observed at 500 ppm (35 mg/kg bw/day).

- The NOAEL for reproductive effects was determined to be 500 ppm (equivalent to 35 mg/kg bw per day) based on reduced pup survival observed at 2500 ppm (175 mg/kg bw/day) in the F2 generation.

- The NOAEL for offspring effects was determined to be 100 ppm (equivalent to 7 mg/kg bw per day) based on reduced pup body weights on PND 21 observed in the F2b litters in dams treated at 500 ppm (35 mg/kg bw/day).

EU evaluation and EFSA conclusions

In the EU, the two-generation reproductive toxicity study (Borders *et al.* (1985)) was evaluated as part of the consideration of the renewal of approval of the pesticide active substance propiconazole, submitted under Regulation (EC) No 1107/2009. According to the 2017 dRAR,

the equivalent doses in mg/kg bw/day for the doses used in the study i.e.: 100, 500 and 2500 ppm were reported as approximately: 8.4, 49 and 215 mg/kg bw/day for males and 9.7, 44 and 243 mg/kg bw/day for females.

Based on the evaluation of the study, the RMS (Finland) concluded the following:

- The NOAEL for parental toxicity was determined to be 100 ppm (8.4 mg/kg bw/day males and 9.7 mg/kg bw/day females) based on the liver effects at 500 ppm (49 mg/kg bw/day in males and 44 mg/kg bw/day in females).

- The NOAEL for reproductive effects was determined to be 500 ppm (app. 48.8 mg/kg bw/day males and 43.7 mg/kg bw/day females) based on decreased litter size, decreased number of pups delivered viable and increased number of runt pups at 2500 ppm.

- The NOAEL for fetal toxicity was determined to be 500 ppm (app. 48.8 mg/kg bw/day males and 43.7 mg/kg bw/day females) based on decreased testes plus epididymides weights of male offspring, decreased pup weights and histopathological changes in liver at 2500 ppm.

The EFSA conclusion concurred that in the two-generation study, propiconazole showed reproductive toxicity (i.e.: decreased litter size and decreased number of pups delivered viable) at higher dose levels than those producing parental toxicity. The agreed parental NOAEL was 8.4 mg/kg bw/ day (100 ppm), whereas the reproductive and offspring NOAELs were agreed at 43.7 mg/kg bw per day (500 ppm; EFSA, 2017).

The EU evaluation of the reproductive toxicity of propiconazole aligned with the conclusions of the JMPR 2004 evaluation in respect of parental toxicity and reproductive effects, but established a less conservative NOAEL for the effects on offspring, considering that only the effects in the highest dose tested may be treatment related.

RAC Evaluation of reproductive toxicity – Effects on fertility and sextual function

In the EU, the findings from the two-generation reproductive toxicity study by Borders *et al.* (1985) were additionally evaluated in the consideration of the harmonised classification and labelling for propiconazole in accordance with the CLP Regulation.

The Dossier Submitter (DS), Finland, proposed that the classification of propiconazole for effects on sexual function and fertility was not warranted based on the absence of treatment related effects on mating, fertility, gestation, female and male fertility indices and the average gestation length in a 2-generation reproduction study in rats and noted that the only effects on reproduction reported in the study were a reduction in in F1 pup weights, and reductions in F2 litter size, number of viable pups delivered, pup survival and increased number of runt pups at the highest dose.

The RAC concurred that the two-generation study showed no effects on mating, fertility, gestation, female and male fertility index and average of gestation length and noted the effects in F1 and F2 generations: reductions in body weight, hepatotoxicity, reductions in testes weight and reductions in mean number of live pups (only in F2). Since reductions in body weight and hepatotoxicity were consistently reported in the repeated dose toxicity studies, the RAC considered that the effects in the F1 and F2 generations may be due to systemic toxicity rather than a direct effect on reproduction.

As there were no corresponding histological assessments, no alterations in sexual and reproductive performance and comparable findings were not reported in the chronic toxicity

studies, the RAC questioned the biological significance of the reductions in the weight of the testes reported for the second litters of both generations and did not consider the effects relevant for classification.

In conclusion, the RAC supported the DS proposal for no classification of propiconazole for fertility effects.

A summary of the reproduction toxicity (effects on sexual function) propiconazole is provided in the table below.

Table 4.5: Summary of reproduction toxicity studies (effects on fertility and sexual function) using propiconazole

STUDY	SPECIES/STRAIN AND DOSES	NOAEL	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/STUDY NUMBER
Reproductive toxicity; 2 generation (OECD 416 (1983))	Rats Dietary, oral Dose levels: 0, 100, 500, 2500 ppm (0, 7, 35, 175 mg/kg bw/day)*	NOAEL (Parental): 100 ppm (7 mg/kg/bw/day) NOAEL (Reproductive effects): 500 ppm (35 mg/kg bw/day) NOAEL (Offspring effects): 100 ppm (7 mg/kg bw/day)	500 ppm (Parental effects): Reduced body-weight gain in dams; hepatotoxicity 2500 ppm (Reproductive effects): Reduced pup survival in the F2 generation 500 ppm (Offspring effects): Reduced pup body weights at day 21 in the F2b litters	Borders *et al*. (1985), cited in FAO AND WHO, 2004. CGA64250/1591 FAO, 2019

*Equivalent concentrations reported in the JMPR 2004 toxicological evaluation.

4.7. Reproduction toxicity - Developmental effects

JMPR 2004

As part of the toxicological assessment of propiconazole conducted in 2004, the JMPR evaluated three studies of developmental toxicity conducted in rats and one in rabbits.

In the first developmental study conducted in rats (pre-GLP and OECD test guidelines), groups of 25 mated female Tif:RaIf rats were administered propiconazole at doses of 0, 30, 100 or 300 mg/kg bw/ day by gavage in 2% carboxymethyl cellulose on days 6–15 of gestation (Fritz (1979), cited in FAO and WHO, 2004). One third of the fetuses were evaluated by Wilson sectioning, the rest were stained for skeletal investigation.

In the study, there was evidence of severe maternal toxicity in rats treated at the highest dose of 300 mg/kg bw/day and three dams in the group died. While no malformations were recorded at 300 mg/kg bw per day, two fetuses treated at the intermediate dose of 100 mg/kg bw/day had malformations. No cleft palates were recorded in the study. Delayed ossification, particularly of the phalangeal nuclei and calcaneum was seen at the highest dose. The level of detail in the report was insufficient to permit the JMPR to derive NOAEL values for maternal or developmental toxicity.

In the second developmental toxicity study conducted in rats according to GLP and OECD TG 414), groups of 24 mated female Crl:COBS CD(SD)BR VAF/Plus rats were administered

propiconazole at a doses of 0, 30, 90 or 360/300mg/kg bw/day by gavage in aqueous 3% corn starch + 0.5% Tween® on days 6–15 of gestation (Marcsisin *et al*. (1987), cited in FAO and WHO, 2004). Due to maternal toxicity after 3-5 doses, the highest dose was reduced from 360 to 300 mg/kg bw/ day. Dams were sacrificed on day 20 of gestation and fetuses were examined. Approximately half of the fetuses in each litter were examined for visceral abnormalities, the remainder were examined for skeletal abnormalities after staining with alizarin red.

One control female died due to complications associated with an early birth. Severe compound-related maternal toxicity, characterized by lethargy, ataxia, salivation and reductions in food consumption and body weight gain were observed at the highest dose during the first five days of dosing at 360 mg/kg bw per day. The reduced body-weight gain observed at 360 mg/kg bw/day persisted after the dose was reduced to 300 mg/kg bw/day. Reduced body-weight gain was also noted at the intermediate dose during the first days of dosing, but terminal body weights were similar to those of controls.

There were no effects on litter sizes, fetal viability, litter size, pup weight or sex ratio. One fetus from a dam treated at the intermediate dose of 90 mg/kg bw/day had multiple malformations (cleft lip and palate, micromelia and club foot), which were not considered to be clearly related to treatment. At the highest dose, one fetus had multiple malformations (anasarca, cleft palate, hydromelia and protruding tongue), another fetus at the highest dose had cleft palate. Overall, a low incidence of cleft palate was observed at 90 mg/kg bw/day (one fetus; 0.3%) and at 360/300mg/kg bw per day (two fetuses; 0.7%) in the presence of severe maternal toxicity. In the evaluation of these findings, the JMPR noted that cleft palate was very rare, but not unknown, in CD rats as incidence in controls ranged from 0% to 0.3%.

Evidence of delayed development of the urinary system was seen at the highest and intermediate doses, together with an increase in rudimentary ribs and unossified sternebrae. The JMPR concluded that it was uncertain if these findings were secondary to maternal toxicity as fetal weights were similar in all groups.

Based on the findings of the study, the JMPR 2004 toxicological assessment concluded the following:

- The NOAEL for maternal toxicity was determined to be 90 mg/kg bw/day based on severe signs of toxicity observed at 300 mg/kg bw per day. Although the maternal body-weight gains were significantly decreased at 90 mg/kg bw/day during days 6–8 of gestation only, this effect was considered to be temporary and secondary to reduced food consumption.

- The NOAEL for developmental toxicity was determined to be 30 mg/kg bw/day based on incomplete ossification of the sternebrae and the presence of rudimentary cervical ribs at 90 mg/kg bw per day.

The cleft palate finding was also seen at a low incidence in rats in an extensive study that specifically investigated the palate and jaw at a single dose of 300 mg/kg bw per day. The third GLP developmental toxicity study conducted by Mallows (1987), as cited in FAO and WHO, 2004, was specifically designed to investigate the incidence of cleft palate reported in the rat developmental toxicity study by Marcisin *et al.* (1987). In the study, mated female Crl:COBS CD(SD)BR VAF/Plus rats (178 controls; 189 test) were administered propiconazole at a doses of 0 or 300 mg/kg bw/day by gavage in aqueous 3% corn starch

+ 0.5% Tween® on days 6–15 of gestation. Dams were sacrificed on day 20 of gestation and the uterine contents were examined. Fetal examinations focused primarily on the palate. As the study was specifically designed to investigate cleft palate, it was not designed to determine a NOAEL.

In the study, marked maternal toxicity was observed throughout the period of treatment with propiconazole at 300 mg/kg bw/day, characterised: by reductions in food consumption and body-weight gain, clinical signs (ataxia, coma, lethargy, abnormal breathing, prostration and ptosis), and three treatment-related deaths occurred in 189 dams. There were no unusual findings at the necropsy examination. Fetal weight and litter size were reduced in the group receiving propiconazole.

Cleft palates were detected in 2 out of 2064 fetuses of treated animals from different litters (0.1%), versus none in the 2122 fetuses of controls, in the presence of severe maternal toxicity.

In the evaluation of the two rat developmental toxicity studies (by Marcisin *et al* (1987) and Mallows (1987), cited in FAO and WHO, 2004), the JMPR noted that the cleft palate was a very rare but occasional finding in control rats and that published data indicated that testing compounds at maternally toxic doses may be associated with the induction of a number of malformations, including cleft palate. Overall, the JMPR concluded that while the low incidences of cleft palates seen in the two rat developmental toxicity studies could not be discounted as being related to treatment with propiconazole, it was considered unlikely that these effects would to be seen in the absence of maternal toxicity.

The prenatal developmental toxicity of propiconazole has been investigated in rabbits in a study conducted according to GLP and OECD TG 414 (version 1981). In the study, groups of 19 inseminated, female New Zealand White rabbits were given propiconazole at doses of 0, 100, 250 or 400 mg/kg bw/day by gavage in aqueous 3% corn starch + 0.5% Tween® on days 7–19 of gestation (Raab *et al.* (1986), cited in FAO and WHO, 2004).

Dams were observed for clinical signs, mortality, body weight and food consumption, and sacrificed on day 29 of gestation; fetuses were examined after caesarean section. All fetuses were examined for visceral abnormalities by dissection and for skeletal abnormalities after staining with alizarin red. Owing to processing errors, a large number of fetuses (20–40%) were damaged (disarticulated) before skeletal examinations; the damaged fetuses were examined by experienced technicians for evidence of skeletal abnormalities.

Two does (one at the lowest dose and one at the intermediate dose) were found dead. One doe in the control group, one at the intermediate dose and five at the highest dose were sacrificed having aborted or delivered early. Maternal toxicity was evident at 400 mg/kg bw/day (reduced food consumption, body-weight loss; abnormal stools; abortion/early delivery) and to a lesser extent at 250 mg/kg bw/day (reduced feed consumption and body-weight loss). Slight, but consistent, reductions in food consumption and body-weight gain were evident at 100 mg/kg bw/day but were not associated with any adverse effects on fetuses. Food consumption and body weight gain in groups receiving propiconazole were greater than those of controls after cessation of dosing. There were no necropsy findings indicating treatment-related effects. One animal at the highest dose resorbed an entire litter. In does with viable fetuses, litter sizes and fetal weights were similar in all groups. One fetus at the intermediate dose had a number of abnormalities.

A treatment-related increased incidence of fully formed 13th ribs was observed at 400 mg/kg bw per day. An increase in the number of resorptions at 400 mg/kg bw/day was associated with resorption of an entire litter by one dam.

Based on the findings of the study, the JMPR 2004 toxicological assessment concluded the following:

- The NOAEL for maternal toxicity was determined to be 100 mg/kg bw/day based on reduced food consumption and body-weight loss at 250 mg/kg bw/day. The slight effects on food consumption and body-weight gain at 100 mg/kg bw per day were not considered to be adverse.

- The NOAEL for developmental toxicity was determined to be 250 mg/kg bw/day based on an increased incidence of the formation of 13th ribs at 400 mg/kg bw/day in the presence of maternal body-weight loss, signs of toxicity and abortions.

- Propiconazole was not considered to be teratogenic in rabbits: The NOAEL for teratogenicity was 400 mg/kg bw/day day i.e.: the highest dose tested.

EU – EFSA evaluation and conclusions

Based on the findings of the developmental toxicity studies, EFSA determined that the relevant maternal NOAELs were 30 mg/kg bw/day for the rat and 100 mg/kg bw/day for the rabbit. Based on skeletal variations and cleft palate in rat and the increased incidence of fully formed 13th rib, increased incidence of resorptions, abortions and early deliveries in rabbit, the developmental NOAELs were determined to be 30 mg/kg bw/ day for the rat and 250 mg/kg bw/day for the rabbit (EFSA, 2017).

It was considered that the findings warranted consideration in respect of hazard classification for reproductive toxicity: the harmonised classification of propiconazole was subsequently discussed by the ECHA RAC in the context of the human health hazard criteria indicated in the CLP Regulation (as discussed below).

EU - RAC Evaluation of developmental toxicity

The DS, Finland, proposed the classification of propiconazole for reproductive toxicity Category 2 H361d (Suspected of damaging the unborn child) on the basis of two different developmental studies in rats (Marcsism *et al*. (1987) and Mallow (1987)) showing incidences of cleft palates higher than controls and historical control data but always appearing concurrently with maternal toxicity.

The RAC evaluated the two developmental studies in rats reporting cases of cleft palate, noting: cleft palate occurred in 1/302 (0.33%) pups at 90 mg/kg bw/day without significant maternal toxicity, and 2 cases were seen at 360/300 mg/kg bw/day, together with severe maternal toxicity (clinical signs, ECHA, 2016). RAC noted that in the second independent study by Mallow (1987), cleft palate was again observed at 300 mg kg bw/day (also together with maternal clinical signs: 17% reduction in corrected maternal body weight gain and 2 mortalities) with an incidence of 2/2061 foetuses (0.097%) from 2/158 litters. The RAC noted that according to the CLH report, cleft palate had not been seen previously in the performing laboratory (incidence 0/5431 during 1983-1985) and according to data submitted by the registrant the observed incidences are also above the historical control data of other laboratories during 1983-1986 (4/25522, 0.016%).

The RAC considered that cleft palate is a serious malformation that should be taken into consideration for classification purposes and additionally considered other developmental effects reported in the rat studies including skeletal variations (rudimentary ribs and non-ossified sternebrae) and the increased incidence of urinary tract variations. The RAC noted that while the visceral findings appeared only at doses exerting maternal toxicity and might be attributable to a secondary consequence of it, the skeletal findings appeared with both maternal and non-maternal toxicity, following a dose-response pattern and were therefore considered for classification.

Other reported developmental effects were resorptions, abortions, early deliveries and increased incidence of fully formed 13th ribs in rabbits exposed at 400 mg/kg bw/day. The RAC noted that these effects appeared at doses causing maternal body weight gain reductions of 89% and 56% in the periods between 10-14 and 14-20 days of gestation, respectively and were additional concerns for classification for developmental toxicity.

The RAC considered that cleft palate is a severe malformation that can be induced by chemicals if the critical dose and timing of exposure are aligned but could also occur as a consequence of maternal toxicity. The RAC noted that cleft palate appeared with a low incidence, but in two independent studies and in different litters and although the finding appeared in the presence of severe maternal toxicity in the two studies, it was observed at 90 mg/kg bw/day in the absence of relevant maternal toxicity and following a dose-response pattern (0.33% at 90 mg/kg bw/day and 0.70% at 300 mg/kg bw/day). The RAC viewed that cleft palate could not be readily disregarded as a chance finding on the basis that it had been observed in two independent studies and a dose-response trend was observed. Furthermore, the RAC noted the increased incidence of cleft palates in rat has also been observed in response to exposure to other triazoles (e.g. cyproconazole and epoxiconazole).

The RAC postulated that while the mode of action of propiconazole in the observed developmental alterations is not known, the teratogenicity of triazoles may be related to altered embryonic retinoid acid catabolism, since abnormalities are confined to structures controlled by retinoid acid. There was no information available to the RAC evaluation showing that the mechanism is not relevant for humans and whether human sensitivity is more similar to rabbits (where no cases were reported) or to rats. RAC noted that while the cleft palate appeared only in rats and not in rabbit, some cases might be masked by the post-implantation loss and the reduced number of viable foetuses in the rabbit study.

In conclusion, the RAC considered the increases in cleft palate incidences found in both rat developmental studies as of human relevance. The following findings also contributed to the consideration of propiconazole as a presumable developmental toxicant for humans: skeletal variations at 90 mg/kg bw/day in the rat study and resorptions, abortions and early deliveries in rabbits exposed to 400 mg/kg bw/day. RAC consequently proposed propiconazole to be classified as a reproductive toxicant Category 1B H360D (May damage the unborn child): the harmonised classification was subsequently adopted on 1st May 2020.

A summary of the reproduction toxicity (developmental effects) of propiconazole is provided in the table below.

Table 4.6: Summary of reproduction toxicity studies (developmental effects) using propiconazole

STUDY	SPECIES/ STRAIN AND DOSES	NOAEL	TARGET ORGAN/ SIGNIFICANT EFFECTS/COMMENTS	REFERENCE/ STUDY NUMBER
Developmental toxicity (No guideline)	Rats Tif:RaIf rats Dose: 0, 30, 100, 300 mg/kg bw/day (oral gavage)	Level of detail insufficient to derive NOAEL	-	Fritz (1979), cited in FAO and WHO, 2004 CGA64250/1585 FAO, 2019
Developmental toxicity (OECD 414 (1981); GLP)	Rats Crl:COBS CD(SD) BR VAF/plus rats Dose: 0, 30, 90, 360/300 mg/kg bw/day (oral gavage)	NOAEL (Maternal): 90 mg/kg bw/day NOAEL (Developmental): 30 mg/kg bw/day	300 mg/kg bw/day (Maternal effects): Severe signs of toxicity 90 mg/kg bw/day (Developmental effects): Incomplete ossification the sternebrae and the presence of rudimentary cervical ribs Cleft palate: 90 mg/kg bw/day (1/302; 0.3%); 360/300mg/kg bw/day (2 fetuses; 0.7%) in the presence of severe maternal toxicity.	Marcsism *et al.* (1987), cited in FAO and WHO, 2004 CGA64250/1586 FAO, 2019
Developmental toxicity (No guideline required; GLP)	Rats Crl:COBS CD(SD) BR VAF/plus rats Dose: 0 or 300 mg/kg bw/day (oral gavage)	Study was not designed to determine a NOAEL	300 mg/kg bw/day: Cleft palates: 2/2064 fetuses (0.1%), in the presence of severe maternal toxicity versus 0/2122 fetuses of controls,	Mallow (1987), cited in FAO and WHO, 2004. CGA64250/1587 FAO, 2019
Developmental toxicity (OECD 414 (1981))	Rabbits New Zealand White Dose: 0, 100, 250, 400 mg/kg bw/day (oral gavage)	NOAEL (Maternal): 100 mg/kg bw/day NOAEL (Developmental): 250 mg/kg bw/day NOAEL (Teratogenicity): > 400 mg/kg bw/day (i.e.: highest	250 mg/kg bw/day (Maternal effects): Reduced food consumption, body weight loss 400 mg/kg bw/day (Developmental effects: Increases in fully formed 13th ribs and abortions	Raab *et al.* (1986), cited in FAO and WHO, 2004 CGA64250/1589 FAO, 2019

4.8. Neurotoxicity

No acute or short-term neurotoxicity studies were available during the toxicological assessment of propiconazole conducted by the JMPR in 2004. The JMPR nevertheless noted that there was no evidence of neurotoxicity apparent in the toxicological studies included in the assessment (FAO and WHO, 2004).

The 2019 FAO review of propiconazole included two neurotoxicity studies: an acute study and a 90-day repeated dose study conducted according to OECD TG 424 respectively

(summarised in the table below). While these studies are reported in limited detail only, no indications of neurotoxic potential were noted.

No neurotoxicity studies were submitted as part of the application for the renewal of propiconazole as a plant protection active substance in the EU. A justification for the non-submission of data was submitted on the grounds that no clinical signs or biochemical or histopathological changes have been observed in the available mammalian toxicology dataset to indicate that propiconazole has any neurotoxic potential (EFSA, 2017). This justification was accepted by the evaluating authority.

Table 4.7: Summary of neurotoxicity studies using propiconazole

STUDY	SPECIES/ STRAIN AND DOSES	NOAEL	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS	REFERENCE/ STUDY NUMBER
Acute neurotoxicity (OECD 424, GLP)	Rats Alpk:APfSD 10/sex/group Dose: 0, 30, 100, 300 mg/kg bw	NOAEL: 100 mg/kg bw/day	Not specified	CGA64250/4839 (2005) FAO, 2019: Additional data
90-Day neurotoxicity (OECD 424, GLP)	Rats Crl:CD(SD) 12/sex/group Dose: 0, 200, 600, 3500 ppm males 0, 200, 600, 1500 ppm females	NOAEL: 3500 ppm (222 mg/kg bw/day) males and 1500 ppm (111 mg/kg bw/day) females	Not specified	CGA06425_51255 (2013) FAO, 2019: Additional data

4.9. Endocrine disrupting properties

At the current time, propiconazole is not considered as having any endocrine disruption potential in any regulatory jurisdiction.

In the EU, the timeline for the renewal of propiconazole pre-dated the introduction of the Commission Delegated Regulation (EU) No. 217/2100 of 4th September 2017 setting out the criteria for the determination of endocrine disrupting properties pursuant to Regulation (EU) No. 528/2012 of the European Parliament and Council (EC, 2017). Therefore, at the time of the renewal, propiconazole was subject to the interim provision of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 (EC, 2009). Pending the adoption of the new criteria, Annex II, Point 3.6.5 states:

"substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2, shall be considered to have endocrine disrupting properties.

In addition, substances such as those that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 2 and which have toxic effects on the endocrine organs, may be considered to have such endocrine disrupting properties."

Following the 2017 ECHA and RAC evaluation of the harmonised classification of propiconazole in accordance with the CLP Regulation, the substance was classified for

reproduction toxicity in Category 1B H360D (May damage the unborn child) but did not meet the criteria for classification for carcinogenicity, in which case the interim provisions of Annex II were not met.

Based on the available data *in vitro* and *in vivo* in mammals, no final conclusion on the endocrine disruption potential of propiconazole was reached as part of EU evaluation of the renewal of propiconazole as an active substance (EFSA, 2017).

Regarding the potential endocrine disruption properties of propiconazole, the 2021 JMPR noted that within the EU legislative framework, endocrine disruption is a hazard identification process with direct risk management consequences, whereas the JMPR included these aspects as part of the risk assessments as a means to understand the mode of action for certain apical effects, if relevant. Referring to the 2004 meeting, the JMPR concluded that the available database on propiconazole was adequate to characterize the potential hazards to fetuses, infants and children (FAO and WHO, 2021).

4.10. Summary of the toxicology profile of propiconazole

The toxicology profile, of propiconazole has been comprehensively reviewed as part of authoritative regulatory evaluations undertaken internationally by the JMPR and in the EU by EFSA and ECHA. Assessments conducted by the JMPR and EFSA have incorporated hazard identification and characterisation to inform human health risk assessments, whereas ECHA and the RAC exclusively identified human health hazards for risk management and communication purposes in the EU.

Propiconazole has low acute dermal and inhalation toxicity and is not a skin or an eye irritant. The substance has moderate acute oral toxicity and requires classification in GHS Cat 4. H302 (Harmful if swallowed) and is a skin sensitiser, requiring classification in GHS Cat 1. H317 (May cause an allergic skin reaction). Propiconazole is not genotoxic based on the findings of a standard battery of *in vitro* and *in vivo* studies, is not neurotoxic and has not been considered as having endocrine disruption potential.

In studies of the repeated dose toxicity of propiconazole conducted in rodents via the oral, dermal and inhalation routes, decreased body-weight gain, frequently linked to reduced food consumption has been consistently observed in short- and long-term repeated dose toxicity studies and also in studies of developmental and reproductive toxicity. The liver was the primary target organ for toxicity attributable to propiconazole. In rats, erythrocyte parameters were reduced and a range of clinical chemistry changes were seen, however, with the exception of reduced chloride and cholesterol concentrations, there was no consistent pattern between sexes and studies, and results were generally within the physiological range. The sub-chronic toxicity of propiconazole in dogs was primarily characterised by local irritation of the gastrointestinal tracts and no signs of systemic toxicity were observed.

In a 2-year dietary study in male and female mice, and an 18-month dietary study in male mice, the liver was considered to be the only target organ for the long-term toxicity of propiconazole, characterised by changes in clinical chemistry parameters, decreases in body-weight gain and serum concentration of cholesterol, increases in liver weight, hepatocellular hypertrophy and hepatocellular vacuolation at dietary doses at or above 500 ppm. Treatment-related hepatocarcinogenic effects (hepatocellular tumours at and above 850 ppm, 108 mg/kg bw/day) were specific to male mice and not observed in female mice or in rats. Regulatory evaluations concurred that these tumours were induced via a phenobarbital-type mechanism, and on this basis, propiconazole is unlikely to have carcinogenic potential in humans.

In a two-generation study of reproductive toxicity in rats, propiconazole did not affect fertility, mating or gestation. Consistent with the findings of repeated dose toxicity studies, the liver was the target organ for the toxicity, characterised by hypertrophy and vacuolation in parental animals treated at 500 (35 mg/kg bw/day) and 2500 ppm (175 mg/kg bw/day) and in the progeny of high dose dams. Reproductive effects, consisting of reductions in numbers of delivered pups and viable pups delivered, were observed at 2500 ppm. Offspring effects included reductions in pup weights and litter size.

Three studies of developmental toxicity were conducted in rats and one in rabbits. In the first study in rats, at the highest dose of 300 mg/kg bw per day there was evidence of maternal toxicity and retarded development, but no malformations. In the second study, propiconazole caused developmental delays (incomplete ossification of sternebrae and rudimentary cervical ribs) at a dose of 90 mg/kg bw per day, which also produced a slight, transient reduction in food consumption and body weight gain at the initiation of dosing. The NOAEL was 90 mg/kg bw per day for maternal effects and 30 mg/kg bw per day for developmental effects. A low incidence of cleft palate was observed at 90 mg/kg bw per day (one fetus; 0.3%) and at 360/300 mg/kg bw per day (two fetuses; 0.7%) in the presence of severe maternal toxicity. The maternal toxicity included lethargy, ataxia, salivation and reductions in food consumption and body weight gain at the start of the dosing period.

The cleft palate finding, detected in 2/2064 fetuses of treated animals at 300 mg/kg bw per day, in the presence of severe maternal toxicity, versus none in the 2122 fetuses of controls, was also seen at a low incidence in rats in an extensive study that specifically investigated the palate and jaw at a single dose of 300 mg/kg bw per day. Marked maternal toxicity was observed throughout the treatment period, included reductions in food consumption and body-weight gain, ataxia, coma, lethargy and prostration, and three treatment-related deaths among 189 treated dams.

Propiconazole was not teratogenic in rabbits. The NOAEL for fetal effects was 250 mg/kg bw per day on the basis of an increased incidence of the formation of 13^{th} ribs at 400 mg/kg bw per day in the presence of maternal body-weight loss, signs of toxicity and abortions. The NOAEL for maternal toxicity was 100 mg/kg bw per day on the basis of reduced food consumption and body weight loss at 250 mg/kg bw per day.

In the EU, propiconazole has been classified for reproduction toxicity in Category 1B, H360D (May damage the unborn child) in accordance with the CLP Regulation – a hazard identification process intended for the communication of risk management measures throughout the chemical supply chain. Risk assessments conducted as part of the evaluation performed internationally, by the JMPR, and within the EU regulatory jurisdiction have included the relevant developmental hazard as part of the hazard characterisation, as indicated in the derivation of human health reference values discussed in Section 5.

5. Derivation of human health reference values

Following the evaluation of the mammalian toxicology and hazard profile of propiconazole, the agreed health-based reference values adopted by authoritative bodies for use in regulatory risk assessments are summarised in Table 5.1 and discussed further in the sections below.

This section also presents the rationale for selecting reference values for propiconazole to inform the human health risk assessments submitted as part of the derogation application to support the safe use of the products: PRINCIPLE 250 EC, Bumper 250 EC and Propin 250 EC (emulsifiable concentrate (EC) formulations containing 250 g/L propiconazole).

Table 5.1: Summary of health-based reference values derived for human health risk assessment

Reference endpoint	Derived value	Source	Based on endpoint:
ADI	**0-0.07 mg/kg bw/day**	JMPR (FAO and WHO, 2004)	Based on the NOAEL of 7 mg/kg bw/day for parental and offspring toxicity from the two-generation study, UF = 100
	0.04 mg/kg bw/day	EFSA (2017)	Based on the NOAEL of 3.6 mg/kg bw/day from a 2-yeat rat chronic toxicity and carcinogenicity study, UF = 100 (rounded)
Acute RfD	**0.3 mg/kg bw/day**	JMPR (FAO and WHO, 2004)	Based on the NOAEL of 30 mg/kg bw/day for developmental toxicity from the rat prenatal developmental toxicity study, UF = 100
	0.1 mg/kg bw	EFSA (2017)	Based on the NOAEL of 30 mg/kg bw/day for developmental toxicity from the rat prenatal developmental toxicity study, UF = 300
AOEL	Not relevant	JMPR (FAO and WHO, 2004)	-
	0.1 mg/kg bw/day	EFSA (2017)	Based on the parental NOAEL of 8.4 mg/kg bw/day from the rat two-generation study, UF = 100 (rounded)
AAOEL	Not relevant	JMPR (FAO and WHO, 2004)	-
	0.1 mg/kg bw	EFSA (2017)	Based on the NOAEL of 30 mg/kg bw/day from the rat prenatal developmental toxicity study, UF = 300

5.1. Reference values for dietary risk assessments

Following a periodic review in 2004, the JMPR established an Acceptable Daily Intake (ADI) of **0-0.07 mg/kg bw** for propiconazole based on the NOAEL of 7 mg/kg bw/day for parental toxicity (reduced body weight gain in dams and hepatotoxicity) from a two-generation study of reproductive toxicity and the application of an overall uncertainty factor (UF) of 100 (i.e.: 10 to account for interspecies variability and 10 to account for intraspecies variability) The ADI was considered to cover all other end-points, as supported by NOAELs of 11 mg/kg bw/day in a 24-month study in mice, and 18 mg/kg bw/day in a 2-year study in rats and sufficiently protective against the local effects seen in the gastrointestinal tract in dogs (NOAEL, 1.9 mg/kg bw/day), which were considered to be concentration dependent and hence would merit a safety factor of 25 (FAO and WHO, 2004).

The JMPR established an acute reference dose (ARfD) of **0.3 mg/kg bw** based on the NOAEL of 30 mg/kg bw/day from a rat developmental toxicity study, applying a total UF of 100. The NOAEL was identified on the basis of slight increases in rudimentary ribs and unossified sternebrae at 90 mg/kg bw per day, which could not be discounted and was considered to provide an adequate margin over the maternal toxicity and cleft palate seen at 300 mg/kg bw per day. The JMPR noted that the highest dose tested in dogs was 35 mg/kg bw per day and that the proposed ARfD would be protective for any potentially acute effects observed in dogs (FAO and WHO, 2004).

The EU evaluation of propiconazole concluded on a different interpretation of the same toxicological dataset. At renewal, EFSA maintained the acceptable daily intake (ADI) set

during the first review of **0.04 mg/kg bw/day** (rounded value). The ADI was based on the relevant long-term NOAEL of 3.6 mg/kg bw/day in the 2-year study in rats based on adrenal toxicity observed at 18.1 mg/kg bw/day and the application of a total UF of 100.

Based on the re-assessment of the toxicological profile of propiconazole during the renewal evaluation, the existing ARfD established by the European Commission, (EC, 2003) of 0.3 mg/kg bw set on the basis of developmental toxicity in rats was revised. During the peer review, the experts agreed to maintain the same point of departure i.e. the NOAEL of 30 mg/kg bw per day for developmental toxicity observed at 90 mg/kg bw/day in the developmental toxicity study in rats. While a standard UF of 100 had been applied during the first review, an additional UF of 3 was applied to the standard UF of 100 (i.e.: total UF of 300) to provide a margin of safety of 900 relative to the lowest observable adverse effect level (LOAEL) for developmental toxicity in rats. The resulting ARfD was determined to be **0.1 mg/kg bw.**

In the 2021 JMPR, the respective experts from the FAO and the WHO scrutinised EFSA's concerns and conclusions on certain aspects of the toxicological profile of propiconazole made following the evaluation of the renewal of the substance as a plant protection active substance in the EU (FAO and WHO, 2021). The JMPR concluded that based on the information presented in the EU documentation, the concerns identified, including those pertaining to the interpretation of the toxicity data, were not substantiated and did not therefore merit any review of propiconazole in advance of the normal periodic review.

Regarding the EU's interpretation of the critical toxicological effects and points of departure (POD) for deriving the ADI of 0.04 mg/kg bw/day using the NOAEL of 3.6 mg/kg bw/day from a two-year study of chronic toxicity and carcinogenicity, the JMPR noted that the NOAEL was based on slight (< 5%) reductions in adrenal weights in males and slight (< 10%) reductions in body weight gain in females at some time points, but not over the entire duration of the study. The JMPR considered such slight reductions in adrenal weight and body weight gains, in the absence of any related findings, as not adverse.

Regarding the EU's derivation of an ARfD of 0.1 mg/kg bw from the same NOAEL of 30 mg/kg bw/day from the rat developmental toxicity study, considered as the same POD as the JMPR but applying a safety factor of 300 to maintain a margin of 900 to the LOAEL for developmental effects (90 mg/kg bw per day), the JMPR considered that the margin between the ARfD of 0.3 mg/kg bw and the LOAEL for the severe effect of cleft palate and maternal toxicity at 300 mg/kg bw per day was adequate. The JMPR did not consider that the application of an additional UF of 3 was required.

Consequently, the health-based reference values established by the JMPR in 2004 are still considered to be valid for assessing the dietary risks associated with the use of propiconazole and have been used recently by the JMPR in this regard. (FAO and WHO, 2024).

Based on these considerations, the JMPR ADI and ARfD are considered to be relevant and adequately protective health-based reference values to inform the dietary risk assessments submitted in support of the derogation application.

5.2. Reference values for non-dietary risk assessments

Since the focus of the JMPR evaluation is the assessment of dietary risks arising from potential exposures to pesticide residues, the JMPR does not derive health-based reference values for non-dietary risk assessments and therefore the reference values established during the EU evaluation of propiconazole have been considered.

During the renewal evaluation of propiconazole, EFSA maintained the systemic Acceptable Operator Exposure Level (AOEL) set during the first review of **0.1 mg/kg bw/day**, based on parental toxicity observed in the two-generation study in rats. The AOEL is based on the

relevant parental NOAEL of 8.4 mg/kg bw/day in the two-generation study in rats based on liver toxicity observed at higher doses. An uncertainty factor of 100 was applied. No correction factor for oral absorption was applied to derive the AOEL. The resulting value for the AOEL was determined to be 0.08 mg/bw/day, rounded by EFSA to 0.1 mg/kg bw/day.

At renewal, an Acute Acceptable Operator Exposure Level (AAOEL) of **0.1 mg/kg bw** was established on the same basis as the ARfD. No correction factor for oral absorption was applied to derive the AAOEL.

Taking into account that the 2004 JMPR evaluation of propiconazole made a comparable interpretation of the relevant critical effects in the two-generation reproductive toxicity study (i.e.: parental toxicity and liver effects), the EU AOEL and AAOEL values have been used to inform the non-dietary risk assessments submitted in support of the derogation application.

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7. Supported products

Company	**Product**	**Registration number**
ICA International Chemicals (Pty) Ltd	Principle 250 EC	L10533
Sharda International Africa (Pty) Ltd	Propin 250 EC	L10487
Adama South Africa (Pty) Ltd	Bumper 250 EC	L6034